FOURTH EDITION

TEXTBOOK OF NATURAL MEDICINE

Joseph E. Pizzorno | Michael T. Murray

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TEXTBOOK OF NATURAL MEDICINE

Edited by

Joseph E. Pizzorno, ND
Editor in Chief
Integrative Medicine: A Clinician's Journal
Eagan, Minnesota;
President Emeritus
Bastyr University
Kenmore, Washington;
Chair
Science Board
Bioclinical Naturals
Burnaby, British Columbia

Michael T. Murray, ND
Director of Product Development and Education
Natural Factors Nutritional Products, Inc.
Everett, Washington;
President
Dr. Murray Natural Living, Inc.
Paradise Valley, Arizona

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3251 Riverport Lane
St. Louis, Missouri 63043

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To Dr. John Bastyr and all the natural healers of the past and future who bring the "healing power of nature" to all the people of the world. Dr. Bastyr, the namesake for Bastyr University, exemplified the ideal physician/healer/teacher we endeavor to become in our professional lives.

We pass on a few of his words of wisdom to all who strive to provide the best of health care and healing: "Always touch your patients—let them know you care," and "Always read at least one research article or learn a new remedy before you retire at night."

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Contributors

Kathy Abascal, BS, JD, RH(AHG)
Vashon, Washington

Yaser Abdelhamid, ND, LAc, MS, BS, BA
President
Integrative Natural Health Strategies, LLC
Westlake, Ohio

Zemphira Alavidze, PhD
The Eliava Institute
Tbilisi, Republic of Georgia
Tbilisi State Medical University Central Clinic
Tbilisi, Republic of Georgia

Jason Allen, ND, MPH
Clinical Research Assistant Professor
Bastyr University
Kenmore, Washington;
Staff Physician, Seattle Integrative Medicine
PhD Student (Toxicology), University of Washington
Seattle, Washington

Lise Alschuler, ND, FABNO
Vice President of Quality and Education
Emerson Ecologics
Bedford, New Hampshire;
Independent Practitioner
Naturopathic Specialists
Scottsdale, Arizona

Steve Austin, ND
Columnist
Emerson Ecologics Update
Emerson Ecologics
Bedford, New Hampshire

Jeff Baker, ND, DHANP, CCH
Homeopathic Family Practice
Makawao, Hawaii

Peter W. Bennett, ND, RAc
Naturopathic Physician
Meditrine Naturopathic Medical Clinic
Langley, British Columbia, Canada;
Adjunct Faculty
Boucher Institute of Naturopathic Medicine
New Westminster, British Columbia, Canada

Bob G. Blasdel, BS
Graduate Teaching Associate
Department of Microbiology
The Ohio State University
Columbus, Ohio;
Graduate Research Associate
Laboratory of Phage Biology
The Evergreen State College
Olympia, Washington

Peter B. Bongiorno, ND, LAc
Co-Director
InnerSourceHealth
New York, New York

Dennis N. Bourdette, MD, FAAN
Chairman and Roy and Eulalia Swank Family Research Professor
Department of Neurology
Oregon Health & Science University
Portland, Oregon

Rachelle S. Bradley, ND
Naturopathic Physician
Heartland Naturopathic Clinic
Omaha, Nebraska

J. Alexander Bralley, PhD
CEO
Metametrix, Inc.
Clinical Laboratory Division
Duluth, Georgia

Kate Broderick, JD, ND, LAc
Owner
Evolution Natural Medicine
Seattle, Washington

Carlo Calabrese, ND, MPH
Executive Director
Naturopathic Physicians Research Institute
Portland, Oregon

Alan Christianson, ND
Private Practice
Integrative Health
Scottsdale, Arizona

Anthony J. Cichoke, Jr., MA, DC, DACBN, PhD
Author, Researcher, and Lecturer
Fellow of the International Association for the Study of Pain
Medizinische-Enzym-Forschungsgesellschaft (Medical Enzyme Research Society)
Portland, Oregon

George W. Cody, JD, MA
Consultant
Capital Projects and Land Use
Natural Medicine HPI
Kenmore, Washington

Kevin L. Conroy, ND
Owner
Port Angeles Natural Health PLLC
Port Angeles, Washington

Walter J. Crinnion, BS, ND
Professor and Chair
Environmental Medicine
Southwest College of Naturopathic Medicine
Tempe, Arizona

T. Michael Culp, MA, NMD
Director and Chief Medical Officer
The Natural Health & Wellness Centre, Ltd.
London, England

Peter J. D'Adamo, ND, MIFHI
Distinguished Professor, Clinical Sciences
Center of Excellence in Generative Medicine
University of Bridgeport
Bridgeport, Connecticut

Zora DeGrandpre, MS, ND
Hazel Dell Natural Health Clinic
Vancouver, Washington

Rhonda Dorren, BScPharm
Calgary, Alberta, Canada

Mark Dreher, PhD
President and Chief Scientific Officer
Nutrition Science Solutions, LLC
Wimberley, Texas

John R. Endres, ND
Chief Scientific Officer
AIBMR Life Sciences, Inc.
Puyallup, Washington

Geovanni Espinosa, ND, LAc
Director
Integrative Urology Center
New York Langone Medical Center
New York, New York

Cathryn M. Flanagan, ND
Naturopathic Physician
Natural Family Health Care
Old Saybrook, Connecticut

Alan R. Gaby, MD
Author and Lecturer
Concord, New Hampshire

Leo Galland, MD, FACP, FACN
Director
Foundation for Integrated Medicine
New York, New York

Susan A. Gaylord, PhD
Associate Professor, Department of Physical Medicine and Rehabilitation
Director, Program on Integrative Medicine
University of North Carolina School of Medicine
Chapel Hill, North Carolina

Andrea Girman, MD, MPH
Director of Medical Education
Genova Diagnostics
Asheville, North Carolina

Alan Goldhamer, DC
Director
TrueNorth Health Center
Santa Rosa, California

Mark D. Groven, ND
Director Physical Rehabilitation
Physical Medicine
Graham Rehabilitation and Wellness Center
Seattle, Washington

Patrick Hanaway, MD
Chief Medical Officer
Genova Diagnostics;
Co-founder and Owner
Family to Family
Asheville, North Carolina

Heidi Hascall, MA
Program Administrator and Senior Research Associate
Health Policy Research Northwest
Eugene, Oregon

Jason Hawrelak, ND, BNat(Hons), PhD
Goulds Naturopathica
Hobart, Tasmania, Australia

Leah Hechtman, M Sci Med (RHHG), BHSc (Naturopathy), ND
Director, The Natural Health and Fertility Centre;
President, National Herbalists Association of Australia (NHAA);
PhD Candidate: Department of Obstetrics, Gynecology and Neonatology
Faculty of Medicine
University of Sydney
Sydney, New South Wales, Australia

Stephen Helms, NMD
Salt Lake City and Park City, Utah

Wendy Hodsdon, ND
Portland Alternative Medicine, LLC
Adjunct Faculty
National College of Natural Medicine
Portland, Oregon

Tori Hudson, ND
Clinical Professor
National College of Natural Medicine
Portland, Oregon;
Clinical Professor Bastyr University
Seattle, Washington;
Medical Director
A Woman's Time;
Program Director
Institute of Women's Health and Integrative Medicine
Portland, Oregon

Corene Humphreys, BHSc, ND, DipMedHerb, Dip Hom
Director and Owner
Medical Research and Development
Nutritional Medicine Ltd.;
Faculty
Wellpark College of Natural Therapies;
Member
Naturopaths of New Zealand Inc.
Auckland, New Zealand;
Member
Institute of Functional Medicine
Gig Harbor, Washington;
Member
Natural Health Council (NZ) Inc.
Auckland, New Zealand

Aimee Huyck, ND, PT
Private Practice
Mountlake Terrace, Washington;
Adjunct Faculty
Bastyr University
Kenmore, Washington

Tim Irving, DC, MS, LMT
Faculty
Physical Medicine Department;
Curriculum Coordinator
Nutrition Department
National College of Natural Medicine;
Owner
Optimum Function
Portland, Oregon

Mary James, ND
Senior Health Educator
Medical Education
Genova Diagnostics
Asheville, North Carolina;
Research Fellow
Optimal Health & Prevention Research Foundation
San Diego, California;
Senior Editor
Alternative Medicine Review
Dover, Idaho

Kelly Jennings, ND, MSOM, LAc
Private Practice
Urban Wellness Group, LLC
Portland, Oregon

Herb Joiner-Bey, ND
Nutrition Instructor
Seattle School of Homepathy
Edmonds, Washington;
Medical Science Consultant
Barlean's Organic Oils
Ferndale, Washington

David S. Jones, MD, FABFP
President and Director of Medical Education
Institute for Functional Medicine
Gig Harbor, Oregon

Tina Kaczor, ND, FABNO
Senior Medical Editor
Natural Medicine Journal;
Owner/Clinician
Clinic of Natural Medicine
Eugene, Oregon

Parris M. Kidd, BSc, PhD
Biomedical Consultant
PMK Biomedical
El Cerrito, California

Richard Kitaeff, MA, ND, DiplAc, LAc
Director
New Health Medical Center
Edmonds, Washington;
Acupuncture Pain Specialist
Northwest Hospital
Seattle, Washington;
Clinical Affiliate Faculty
Bastyr University
Kenmore, Washington

Thomas A. Kruzel, BA, MT, ND
Medical Director
Rockwood Natural Medicine Clinic
Scottsdale, Arizona

Sarah J. Kuhl, MD
Physician–Scientist VA Northern California and Contra
Costa Regional Medical Center
Martinez, California

Elizabeth Kutter, PhD
Professor Emeritas
Lab of Phage Biology
The Evergreen State College
Olympia, Washington

Andrew Lange, ND
Naturopathic Medicine
Boulder, Colorado

Rick Liva, RPh, ND
Managing Physician
The Connecticut Center for Health
Middletown, Connecticut;
Director of Quality and Chief Medical Officer
Vital Nutrients
Middletown, Connecticut

Pina LoGiudice, ND, LAc
Co-Director
InnerSource Health
Huntington, New York

Richard S. Lord, BS, PhD
Chief Science Officer
Clinical Laboratory Division
Metametrix, Inc.
Duluth, Georgia;
Professor, Clinical Biochemistry
Nutrition Institute
University of Bridgeport
Bridgeport, Connecticut

John C. Lowe, MA, DC
Director of Research
Fibromyalgia Research Foundation
Juno Beach, Florida

Michael Lyon, BSc, MD
Adjunct Professor
Food, Nutrition and Health Program
University of British Columbia
Vancouver, British Columbia, Canada

Douglas "Duffy" Mackay, ND
Vice President
Scientific and Regulatory Affairs
Council for Responsible Nutrition
Washington, DC

Robert M. Martinez, DC, ND
Private Practice
Kirkland, Washington

L. Charles Masur, MD
Scientific Support Physician
Scientific Support Department
Doctor's Data Inc.
St. Charles, Illinois

Steven C. Milkis, ND
Clinical Faculty
School of Naturopathic Medicine
Bastyr University
Seattle, Washington

Laurie K. Mischley, ND
Clinical Research Assistant Professor
Bastyr University Research Institute
Kenmore, Washington;
Physician, Naturopathic Neurology
Seattle Integrative Medicine
Seattle, Washington

Gaetano Morello, BSc, ND
Private Practice
Naturopathic Medicine
Complement Health Care
West Vancouver, British Columbia, Canada;
Scientific Advisory Board
Scientific and Educational Affairs
Schwabe North America
Green Bay, Wisconsin

Gerard Mullin, MD
Associate Professor of Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland

Stephen P. Myers, ND, BMed, PhD
Professor
NatMed-Research
Health and Wellbeing Research Cluster
School of Health and Human Sciences
Southern Cross University
Lismore, New South Wales, Australia

Paul J. Nicolai, ND
Portland, Oregon

Mark H. Nolting, ND, LAc, DiplAc, DNBAO
Senior Medical Director CAM
Healthways
Sterling, Virginia

Melissa Palmer, MD
Clinical Professor of Medicine
Hepatology
New York University
New York, New York;
Director of Hepatology
New York University Hepatology Associates
New York University
Plainview, New York

Cristiana Paul, MS Nutrition
Independent Consultant: nutrition researcher, formulator, writer, clinician
Los Angeles, California

Lara Pizzorno, MDiv, MA, LMT
Senior Medical Writer, Editor, and Researcher
Integrative Medicine Consultants, LLC
Seattle, Washington;
Editor
Longevity Medicine Review
Petaluma, California;
Senior Medical Editor
Salugenecists, Inc.
Seattle, Washington

Dirk Powell, BS, ND
Adjunct Professor
Naturopathic Medicine
Bastyr University
Bothell, Washington

David Quig, PhD
Vice President
Scientific Support
Doctor's Data, Inc.
St. Charles, Illinois

Sheila Quinn
Freelance Medical Writing and Editing Services
Gig Harbor, Washington

Irfan Qureshi, ND
Chief Regulatory Officer
Vitamin Research Products
Carson City, Nevada;
Vice President
VMN Research
Enumclaw, Washington

Ronald G. Reichert, BA, ND
Director of Scientific Affairs
Canadian Centre for Functional Medicine
Coquitlam, British Columbia, Canada

Paul Reilly, ND, LAc, FABNO
National Director of Naturopathic Medicine
Cancer Treatment Centers of America
Renton, Washington

Corey Resnick, ND
President
Integrative Health & Nutrition, Inc.
Lake Oswego, Oregon;
Medical Advisory Board
Integrative Therapeutics, Inc.
Green Bay, Wisconsin

Sally J. Rockwell, CCN, PhD
Owner
Diet Design
Shoreline, Washington

Robert A. Ronzio, PhD
Emeritus Certified Nutrition Specialist
Executive Director, Insight Learning Institute
Austin, Texas

Sam Russo, ND, LAc
Private Practice
Vermont Naturopathic Clinic
South Burlington, Vermont

Angela Sadlon, ND
Tahoma Clinic
Renton, Washington

Trevor K. Salloum, BA, ND
Kelowna, British Columbia, Canada

Alexander G. Schauss, PhD, FACN
Senior Director of Research
Natural and Medicinal Products Research
AIBMR Life Sciences, Inc.
Puyallup, Washington

Lynne Shinto, ND, MPH
Associate Professor
Neurology
Oregon Health & Science University
Portland, Oregon

Barbara Siminovich-Blok, ND, LAc
Health Services Manager
Physician and Acupuncturist
North American Pharmacal
Wilton, Connecticut

Pamela Snider, ND
Executive and Senior Editor
Foundations of Naturopathic Medicine Project
North Bend, Washington;
Associate Professor
National College of Natural Medicine
Portland, Oregon;
Adjunct Professor
Bastyr University
Seattle, Washington

Virender Sodhi, MD, ND
Private Practice
Ayurvedic and Naturopathic Medical Clinic
Bellevue, Washington;
Faculty
School of Naturopathic Medicine
Bastyr University
Kenmore, Washington

Nick Soloway, LMT, DC, LAc
Helena, Montana

Nancy Sudak, MD
American Board of Integrative Holistic Medicine
Duluth, Minnesota

Jade Teta, ND, CSCS
Owner and Founder
Metabolic Effect Inc.
Winston-Salem, North Carolina

Keoni Teta, ND, LAc, CSCS
Co-Owner and Founder
The Naturopathic Health Clinic of North Carolina;
Co-Owner and Founder
Metabolic Effect
Winston-Salem, North Carolina

Sherry Torkos, BScPharm
Pharmacist and Author
Fort Erie, Ontario, Canada

Jessica Tran, ND
Private Practice
Wellness Integrative
Irvine, California

Michael Traub, ND, DHANP, FABNO
Medical Director
Lokahi Healing Center
Kailua Kona, Hawaii;
Consulting Staff
Department of Medicine
North Hawaii Community Hospital
Kamuela, Hawaii;
Adjunct Faculty
Center for Spirituality and Healing
University of Minnesota
Minneapolis, Minnesota;
Adjunct Faculty
Postgraduate Medical Education
National College of Natural Medicine
Portland, Oregon

Terry Willard, CIH, PhD
Director
Herbal
Wild Rose College of Natural Healing
Calgary, Alberta, Canada

Michelle M. Wong, MD
Manakai O Malama Integrative Healthcare and Rehabilitation Center
Honolulu, Hawaii

Vijayshree Yadav, MD, MCR
Assistant Professor
Neurology
Oregon Health & Science University
Portland, Oregon

Eric L. Yarnell, ND, RH(AHG)
Associate Professor
Botanical Medicine
Bastyr University;
Chief Medical Officer
Northwest Naturopathic Urology
Seattle, Washington;
President
Heron Botanicals
Poulsbo, Washington;
Chief Financial Officer
Healing Mountain Publishing
Wenatchee, Washington

Gregory T. Yasuda, ND, LMP
Adjunct Faculty
Naturopathic Medicine
Bastyr University
Kenmore, Washington

Jared L. Zeff, ND, LAc
Medical Director
Private Practice
Salmon Creek Clinic
Vancouver, Washington;
Professor and Adjunct Faculty
Bastyr University
Kenmore, Washington;
Senior Editor
Foundations of Naturopathic Medicine Textbook Project
Seattle, Washington;
Chairman
International Educational Project
Foundations of Naturopathic Medicine
Seattle, Washington

Ira D. Zunin, MD, MPH, MBA
Assistant Clinical Professor
Department of Integrative Medicine
John A. Burns School of Medicine
University of Hawaii at Manoa
Honolulu, Hawaii;
Medical Director
Manakai O Malama Integrative Healthcare Group and Rehabilitation Center
Honolulu, Hawaii

Heather Zwickey, PhD
Dean of Research and Professor of Immunology
Director of Helfgott Research Institute
National College of Natural Medicine;
Adjunct Associate Professor
Department of Neurology
Oregon Health & Science University
Portland, Oregon

Preface

In addition to updating all the content and research, the fourth edition of the *Textbook of Natural Medicine* (which has now been in publication since 1985) brings several new features: new chapters, a new utilization guide, comprised into one volume. The new chapters include topics such as female infertility, medicinal mushrooms, natural products and quality control, pregnancy health, Unani medicine, and vitamin K. In addition to new chapters, some chapters have been renamed for better consistency and some have been moved to Sections which we felt were more appropriate. To facilitate utilization, we have provided alphabetical tabs to help searching for specific diseases. Closely related diseases have been placed in a single chapter—for example depression, dysthymia, manic phase, and seasonal affective disorder are all located in the Affective Disorders chapter—so becoming familiar with these groupings is essential for finding specific diseases. There are twelve appendices that provide additional resources for the clinician. Finally, for the first time in over two decades the *Textbook of Natural Medicine* is back to a single volume. We worked with authors to make their writing more succinct and eliminate unnecessary content. We also reduced the length of Section VI by removing duplication of content from Section V in the therapeutics portion of the chapters. We hope you will be as pleased with the latest edition as we are.

Joseph E. Pizzorno
Michael T. Murray

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Preface to the Third Edition

The scientific support for the philosophical and therapeutic foundation of natural medicine has evolved remarkably over the past 35 years. Concepts that were once considered "quaint" at best are now recognized as fundamental to good health and the prevention and treatment of disease. This textbook, with its roughly 10,000 citations to peer-reviewed research literature, provides well-documented standards of practice for natural medicine. Based on a sound combination of philosophy and clinical studies, this work provides the astute practitioner with a reliable informational resource to provide health care that identifies and controls the underlying causes of disease, is supportive of the body's own healing processes, and is considerate of each patient's unique biochemistry.

This textbook is composed of six sections, each focused on a fundamental aspect of the practice of natural medicine. "Philosophy of Natural Medicine" covers the history and conceptual basis of natural medicine. "Supplementary Diagnostic Procedures" provides a primer on diagnostic procedures not commonly taught in conventional medical schools. Diet analysis, food allergy testing, immune function assessment, fatty acid profiling, and hair mineral analysis are examples of these analytical procedures. The next section, "Therapeutic Modalities," provides a descriptive, practical, scientific, and historical review of the common modalities of natural medicine, including botanical medicine, nutritional therapy, therapeutic fasting, exercise therapy, hydrotherapy, counseling, acupuncture, homeopathy, and soft tissue manipulation. "Syndromes and Special Topics" considers underlying issues relevant to many diseases. "Pharmacology of Natural Medicines" covers the pharmacognosy, pharmacology, and clinical indications for the most commonly prescribed botanical medicines, special nutrients, and other natural agents. "Specific Health Problems" provides an in-depth natural medicine approach to more than 70 specific diseases and conditions. The comprehensive therapeutic rationales are well documented and based on the pathophysiology and causes of each condition.

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 Sheila Quinn
 Leo Galland, MD, FACP, FACN
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SECTION 1

PHILOSOPHY OF NATURAL MEDICINE

Nature is doing her best each moment to make us well. She exists for no other end. Do not resist. With the least inclination to be well, we should not be sick.

—Henry David Thoreau

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One of the features of the various schools of natural medicine that differentiates them from conventional (allopathic) medicine is their strong philosophical foundation. The basic philosophical premise of naturopathic medicine, for example, is that there is an inherent healing power in nature and in every human being. We believe that a primary role of the physician is to bring out or enhance this innate healing power within his or her patients.

In many ways, this was the most difficult section of the textbook to write, since no comprehensive history of the social, political, and philosophical development of naturopathic medicine had ever been written, and even in the halcyon years of the 1920s and 1930s, the profession was never able to agree upon a concise philosophy. This situation has now changed.

We provide here a well-documented chapter detailing the roots of American naturopathy. After a century of maturation, the profession has now widely agreed to a comprehensive definition, set of principles, and system of case analysis that provide a systematic guide for the application of these concepts in a clinical setting.

The seven fundamental principles of naturopathic medicine are as follows:

1. The healing power of nature (*vis medicatrix naturae*)
2. First do no harm (*primum non nocere*)
3. Find the cause (*tolle causam*)
4. Treat the whole person
5. Preventive medicine
6. Wellness
7. Doctor as teacher

These principles translate into the following questions the practitioner applies when analyzing a case:

- What is the first cause; what is contributing now?
- How is the body trying to heal itself?
- What is the minimum level of intervention needed to facilitate the self-healing process?
- What are the patient's underlying functional weaknesses?
- What education does the patient need to understand why he or she is sick and how to become healthier?
- How does the patient's physical disease relate to his or her psychological and spiritual health?

We have further expanded on the philosophical basis of naturopathic medicine by having these concepts addressed by several authors whose backgrounds allow each of them a unique and, we believe, complementary insight into some of the fundamental questions of the goals of health care. Although the dominant school of medicine has essentially ignored these issues, we believe that the true physician cannot function without a sound philosophical basis to guide his or her actions. Without a more than superficial understanding of health and disease, the physician is more likely to function as a technician, temporarily alleviating symptoms while allowing the real disease to progress past the point of recovery.

CHAPTER 1

Eastern Origins of Integrative Medicine and Modern Applications

Ira D. Zunin, MD, MPH, MBA and Michelle M. Wong, MD

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INTRODUCTION

Emaho, the Tibetan word for "wondrous," aptly describes the history of healing. The healing art of medicine is neither fixed in one theory of disease nor has its origins in a single body of perceptions. Its roots reveal rich and fascinating strands to its heritage. Each strand has developed potent theories and recommendations that inform prevention, illness, and treatment. These differences profoundly influence the vision and values among the members of a given culture—how to live well and how to address illness and health. Specifically, the contrasts in Eastern and Western approaches have been like strangers from afar, and now as of the twenty-first century, have become increasingly aware of each other in the evolving field of integrative medicine. Each has its advantages and limitations. Recognizing and skillfully combining the best of both approaches is an ongoing challenge and a noteworthy, positive advance for humanity.

In the past 20 years, medicine in the West has begun to diligently examine and resume its inclusion of indigenous traditions in medical practice. The term "integrative medicine" emerged in the early 1990s to describe a paradigm shift in modern medicine. Integrative medicine believes that drawing from multiple traditions better serves people, rather than using only one medical system. At the core of the integrative medicine movement in the West is how to examine indigenous healing modalities with scientific rigor for safety and efficacy, while retaining respect for their history and culture. With its emphasis on quality research evidence, integrative medicine modalities have gained further acceptance in the West, while having spawned a resurgence of indigenous medicines in their countries of origin.

Eastern healing traditions have made some of the greatest advances in integration with modern medicine. In this chapter, the authors briefly review the historical origins of Eastern and Western traditions and the contrast in their philosophies and examine some Eastern healing traditions more closely to better understand the application of Eastern healing modalities to modern medicine. Please note that the following is only an introduction to healing traditions that have had some success in practice with Western medicine. The authors encourage readers to actively engage in learning about other healing traditions specific to their local community.

Terminology

As the field of integrative medicine evolves, so does its terminology. "Modern medicine" in this chapter is used to describe the most mainstream medicine practiced and determined by the evolving scientific method, and "complementary and alternative medicine" (CAM) is used to describe practices that are not as well defined by the scientific method. Theories of medicine can also be grouped based on geographic origin: Western, originating from Greco-Roman philosophy, and Eastern, originating from Asian-Pacific philosophy. The term modern medicine implies fluidity, and it is fitting to use such terminology during the current period of expanding medical boundaries.

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COMPARISON OF EASTERN AND WESTERN MEDICINE: ORIGINS AND PHILOSOPHIES

Historical Origins

The foundation of several Eastern healing traditions inextricably embraces the philosophies of early Eastern thought, those of Buddhism, Taoism, and Hinduism. These philosophies still provide the underpinnings for many contemporary Eastern cultures, allowing Eastern indigenous healing traditions to maintain widespread acceptance and practice. Several unique but related traditions developed in the East before the Christian era and are still heavily practiced today as discrete systems, including Chinese medicine, Ayurveda (traditional Indian medicine), and Tibetan medicine. Other Eastern traditions enjoy moderate practice in their areas of origin, including Persian medicine, medicine as set forth in the Dead Sea Scrolls, and folk shamanism and animism. Chinese Ayurveda, and Tibetan medicine will be more closely examined and compared later in this chapter, along with their current transformations in the West.

In contrast, modern medicine in the West developed quite independently from religious thought. It was, and continues to be, shaped by science. Modern scientific thought evolved from the Greek philosophers beginning with Euclid around 300 BC and later Plato, Socrates, and Aristotle. The mathematic theories of these Greek philosophers set the foundation for Renaissance scientists more than 1500 years later, who further developed the scientific method. The scientific method, which describes a constant process of empirical observation, logical reasoning, and skepticism to discern knowledge, is still the thought process used today to validate modern medicine.

It was not until later in the twentieth century, however, that the scientific method became the mainstay of modern medicine. In the early nineteenth century, modern medicine was pluralistic in nature as "professional care was mostly provided by botanical healers and midwives, supplemented by surgeons, barber-surgeons, apothecaries, and uncounted cancer doctors, bonesetters, inoculators, abortionists, and sellers of nostrums."[1] During much of this same period, the profession of naturopathy flourished to the benefit of many. At this time, the medical profession was still in its early stages in the United States. By the early to mid-twentieth century, medicine was much more narrowly defined through the scientific method. In the past 20 years, however, medicine in the United States has experienced another shift, arguably a shift again to the medical pluralism from more than 100 years ago. This raises the question: is this merely historical pattern or the birth of a unique era?

If modern medicine is experiencing yet another paradigm shift, the culture will necessarily move beyond the older ethos of the scientific method that defined its previous paradigm. Master Hong succinctly commented on this point, "What this [Qi Gong] master possesses isn't magic. It is just science that has not yet been examined."[2] In the twenty-first century, the culture of medicine is once again embracing its diverse options for health care, shifting yet again toward pluralism and reflecting the social landscape of a new generation. What is happening invites all healers to enlarge their ideas of disease and health and to welcome an expanded and deeper perspective.

Philosophies in Contrast

"Vive la différence." The differences in Eastern and Western medical traditions stem directly from their foundational differences in world views. Judith Farqhuar described these essential differences in world views as "the difference between a world of fixed objects and a world of transforming effects. Like the solid inertial world of modern natural science traditions, the … transformative world of Chinese medicine seems to exist prior to all argument, observation, and intervention. Perhaps with a certain discomfort, Western readers must acknowledge that 'their' abstractions about such things make as much sense as 'ours'."[3]

One of the most obvious and far reaching differences between Eastern and Western medical traditions is the concept of inter- and intra-personal relationships. Stemming from the Socratic model and Cartesian dualism, Western medicine heavily delineates between mind and body, between doctor and patient, and between healthy and diseased. In contrast, medicine originating in the East finds little distinction in these areas. Instead, it views continuity and balance as vital to health. Illness is defined by imbalances of patterns that should naturally be in harmony. Multiple aspects of the being, including the mind, body, and spirit, are integral to this harmony. In contrast, illness in modern Western medicine is described by a specific pathology, caused by discrete foreign pollutants, and often cured by another foreign element.

In its extreme, the patient is an accident attached to the disease under treatment.

The fundamental concepts of Eastern healing traditions are deeply embedded in the philosophies of their cultures. Consequently, they are perceptions, ideas, and values shared by most society members. Although health is integral to one's everyday life in Eastern societies, it is only one part of Western society. Likewise, health is defined in the East as a unity of individual, environmental, and societal factors. Although the Western definition of health has moved toward encompassing the physical, mental, social, and spiritual, each is still defined as a separate entity. In modern medical communities, divisions between physical and mental health and social work, are still at large, with these departments often not acting in concert.

These distinct differences shape the patient–doctor relationship. In Eastern traditions, a unique balance of these factors is critical to diagnosis and treatment of a patient's disharmony rather than disease. Physicians in Western medicine often look beyond the patient–doctor relationship to an external body of knowledge to diagnose and treat, guided by categories of symptoms. A general comparison of Eastern and Western concepts with regard to health is shown in Table 1-1.

Overview and Comparison of Eastern Traditions

As mentioned, although several indigenous healing traditions in the East have been preserved, Chinese, Ayurvedic, and Tibetan medicine remain among the most heavily practiced traditions in

TABLE 1-1 **Comparison of Western and Eastern Concepts**

	WESTERN	EASTERN
World views	Reductionist	Holistic
Mechanism of disorder	Pathologic mechanism	Imbalance of harmonies
Foundational structure	Logic, mathematics	Eastern religions and philosophies
Patient–doctor relationship	Access external body of knowledge for diagnosis and treatment	Unique balance critical to diagnosis and treatment

TABLE 1-2 **Comparison of Tibetan, Ayurvedic, and Chinese Medicine**

	TIBETAN	AYURVEDA	CHINESE
Health and disease	Defined by balance or imbalance of states		
Fundamental textures	3 humors: wind, bile, phlegm	3 humors (doshas): air, fire, water principles	Qi, blood, Shen
Principle of opposites	Hot/cold	Hot/cold	Yin/yang
5 Elements	Air, water, fire, ether, earth	Ether, water, fire, earth, air	Air, water, fire, metal, earth
Diagnostics	Pulse (most important), urine, tongue, morphology		
Treatment modalities	Behavioral (lifestyle, meditation), diet, herbals, external treatment	Dietary alterations, yoga, exercise, herbal formulas, surgical techniques	Acupuncture, herbals, Qi gong (acupuncture, massage)
Origin			
• Religious	Intimately related to Buddhist philosophy but stands on its own	Intimately related to Hindu philosophy but stands on its own	No formal tie to Taoism or Buddhism
• Text	*Gyu-zhi* (Tibetan rGyud-bzhi)	*Rig Veda* (second millennium BC) 800 BC	*Nei Jing* 2598 BC
Recent history (post-Newtonian, within past century)	Transformation by Chinese invasion	Enjoyed the greatest continuity	Transformation by Cultural Revolution

their respective regions. All three traditions stem largely from similar philosophical foundations; thus in all, health and disease are seen as inextricably interrelated. They play integral parts in the delicate balance of harmony and disharmony. Table 1-2 provides a comparison of these three traditions.

Origins

Tibetan medicine and Ayurvedic medicine have similar historical origins, since Ayurveda is the root of Tibetan medicine. Ayurvedic origins are found as early as the second millennium BC in the *Rig Veda*, with its second classical stage in the Brahmanic period in 800 BC, where it continued as an unbroken lineage until the Moslem conquest of India in the thirteenth century. During that time in the sixth century BC, the historical Buddha, Shakyamuni, was born in India, and after achieving Enlightenment under a Bodhi tree in Bodhgaya and delivering the teachings of the Four Noble Truths, Buddhism was born.*

The Tibetan medical tradition offers that the Buddha, often called the "Great Physician," taught the medical texts himself, including the *Gyu-zhi*, the most important Tibetan medical text. The Sanskrit version of the *Gyu-zhi*, however, was probably not written until around 400 AD.[4] Although some scholars may debate whether the historical Buddha's teachings are the precise origin of Tibetan and, thus, Ayurvedic medicine, Buddhism's influence on these two healing traditions is unquestionable.

Like Ayurveda, the origins of Chinese medicine date back to at least the second millennium BC, to the era of the great Yellow Emperor, Huangdi (2698–2598 BC). The classic medical text written during his reign is *Huangdi Nei Jing (The Yellow Emperor's Inner Canon)*. Yet perhaps of more influence to Chinese medicine known today is the *Nan Jing (The Classic of Difficult Issues)*, written around the first or second century AD. As Nolting notes in Chapter 31 on "Acupuncture" in this edition, the *Nei Jing* deals more with "demonological medicine and religious healing," whereas the *Nan Jing* developed Chinese medicine as an original system, with well-defined and organized principles, diagnostics, and therapeutics.[5]

Chinese medicine also witnessed various transformations, most notably its recent evolution into Traditional Chinese Medicine (TCM), the modern form of Chinese medicine practiced in China and worldwide. Influenced by the advent of modern science, Chinese medicine was required during the 1950s to establish increased legitimacy in the face of the new Marxist ideology, which emphasized "natural science" and delegitimized Confucian influences. Initially, the People's Republic of China denounced folk, demonic, and Buddhist temple medicine.[6] However, in 1951, Mao Zedong revived and then canonized portions of the tradition with his "Chinese medicine is a great treasure-house" speech.[7] In Mao's Cultural Revolution, Chinese medicine was transformed to TCM and embraced as a means to preserve the "spirit of a nation." The "new medicine" movement highlighted traditional medicine's ability to arouse one's own bodily defenses against illness while excluding metaphysical ideologies. TCM thus embodied one general theory of Chinese medicine and discouraged diverse readings and interpretations by practitioners and students.

Of the three traditions, Tibetan medicine enjoyed the most continuity in lineage until the Chinese invasion in 1959. With the Moslem invasion of India in the thirteenth century, much of the Ayurvedic medical system was destroyed, along with many Buddhist texts. Fortunately, by the seventh century AD, Ayurvedic medicine had traveled to Tibet and was safely preserved in the Himalayan Mountains. Once in Tibet, Buddhism and its medicine first adapted to the indigenous shamanic religious culture, Bon, whose greatest contribution to the Tibetan medical system was its knowledge of the indigenous medical herbs of the sub-Himalayan plateaus. With King Strongtsan Gampo's formal introduction of Buddhism to Tibet in the early seventh century, the influence of Buddhism on its medicine flourished. This continued up until the Chinese invasion in 1959.

Despite its isolation in practice, Tibetan medicine shares several principles with other Eastern healing traditions. Its strongest ties are with Chinese medicine to the north and Ayurvedic medicine to the south. Eastern traditions of healing are undoubtedly intertwined in a rich tapestry, stemming partly from an extraordinary

*Lineage refers to the descendants of a common ancestor considered to be the founder of the line.

meeting of healers. During the seventh century, the Tibetan King Gampo held the world's first recorded international medical conference. Noted physicians from India, China, Greece, Nepal, Persia, and Mongolia dialogued in a cross-cultural exchange, and texts from each medical tradition were translated.

Fundamental Philosophies: Tools to Assess Balance

The notion that ill health stems from the imbalance of certain fundamental forces or "textures" stands at the core of many Eastern healing traditions. Although the traditions may vary as to which fundamental forces, textures, or elements are involved in diagnosis and treatment, certain philosophies are shared. In these, the five elements, fundamental textures, and principles of opposites govern the universe. The five-element theory is the most common approach used to diagnose and restore health. The five elements are commonly understood to define, control, and at the same time be governed by a constellation of internal and external phenomena. These phenomena include human emotions, human senses, body organs, and climate.

Humoral pathology, central to Ayurvedic, Tibetan, Persian, and Greek systems, is the core principle that unifies the mind with the body and the individual with his environment. It defines the balance or imbalance of the textures that influence one's state of health. These humors define an array of biological, physiopathologic, and psychological phenomena related to the body, the mind, and the environment. In both Tibetan and Ayurvedic medicine, three humors, or primary qualities, maintain aspects of health. In Tibetan medicine, they are *Vayu* (Tibetan *Rlung*), *Pitta* (Tibetan *Khrid*), and *Kapha* (Tibetan *Bad-kan*), translated as "wind," "bile," and "phlegm," respectively. Yet the English translation is imprecise and limits the meanings of wind, bile, and phlegm principles, which further describe the mind, energy, and inert matter. Analogies can be drawn using conventional physics. Wind can be compared with kinetic energy, bile with caloric energy, and phlegm with mass energy. With reference to personality, those governed by air tend to be wiry and impulsive; bile types are muscular and quick to anger; and those ruled by phlegm are normally heavy set and tend to avoid conflict. Additionally, the humors are the products of the three delusions, which are the root cause of all suffering in the Buddhist tradition: phlegm, a product of ignorance, bile from anger, and wind from attachment. Understanding the humors as products of the three delusions underlines the interrelationship between Buddhism as a spiritual practice and the healing professions.

In Ayurvedic medicine, these humors are the three *Doshas*, known as *Vat* (or air principle), *Pit* (or fire principle), and *Kaph* (or water principle), and they carry specific actions. *Vat* is the bodily air principle and governs movement; *Pit* is the bodily fire principle that controls metabolism; and *Kaph* is the biological water principle that provides physical structure. These principles are also associated with the metabolic activities of anabolism, catabolism, and metabolism. In addition, they are associated with certain personalities and certain physical characteristics of dry or oily, light or heavy, and hot or cold. For a more complete discussion of the *Doshas* and their related properties and functions, see Chapter 32.

Chinese medicine encompasses a similar principle that certain fundamental qualities must be in balance to achieve a healthy state. These fundamental textures are the universal Qi, Blood *(xue),* Essence *(jing),* and Spirit *(shen).* Like the humors of Tibetan and Ayurvedic medicine, Qi is universal and encompasses and connects all animate phenomena internally (body, mind, organs, senses) and externally (organism to environment). Qi generates change both on a small scale and in the larger picture of Yin and Yang, those opposite forces, for example, of light and dark, female and male, that embody all organisms. Qi has five major functions: movement, protection, harmonious transformation, stability and retention, and warming of the body. The definition of blood in Chinese medicine goes beyond the physical concept of blood in Western medicine, since it is the Yin complement to the clinical Yang Qi, functioning to nourish, circulate, and moisten the body. Essence is specific to organic life and slowly perpetuates life forward. Although Qi is the fluid movement of ordinary time, Essence spans a lifetime and embodies all characteristics involved with birth, maturation, and death. Lastly, Spirit is unique to human life but is beyond mind-consciousness. It is what prompts humanity and relationships with one's self and other humans, and it examines all facets of humanity—moral, social, mental, physical, and emotional.

Although the concept of Yin and Yang is at the core of Chinese medicine, principles of opposites to achieve balance and optimal health are central to all three traditions. The Tibetan and Ayurvedic systems employ "hot" and "cold" to depict opposites. These fundamental opposites, fundamental textures, and five elements are intricately related to one another, providing a holistic framework in which to consider health and illness.

Diagnostics and Treatments

In accordance with its foundational philosophies, diagnostics in Eastern traditions take into account the person as a whole. The patient's physiologic characteristics, mental dispositions, and other personal, social, economic, and environmental details are assessed. In addition, diagnosis includes the following examinations: general physical, pulse, urine, tongue, eyes, skin, and ears.

The core principle in treatment is to restore the person's health to equilibrium through several behavioral, lifestyle, diet, manual, and medicinal treatment approaches. Treatment methods in the Tibetan tradition are arranged in a hierarchy of usage: (1) behavioral practices (lifestyle, meditation), (2) diet, (3) herbal medicines, and (4) external treatments (acupuncture, massage, moxa, and surgery). Treatment therapies in Ayurveda include dietary alterations, yoga, exercise, herbal formulas, and surgical techniques. Ayurveda places special emphasis on diet as a modality, since it considers the human body a mental and physical product of the food consumed. Main treatment methods in Chinese medicine include acupuncture, herbal medicine, and sometimes Qi Gong.



MODERN APPLICATIONS: THE AGE OF INTEGRATION

[The interpreter's] task is rather to seize the vital conception of the art-work, to blend it with his own ego and the views of his period, and thus to imbue it with life and effectiveness. His artistry is a product of its mental culture. It develops and changes with the evolution of artistic requirements. His formative and emotional powers are derived from the spirit of the epoch to which he belongs.

Much that charmed former generations has no effect in ours; so much is part and parcel of its passing. Only what is exalted over time and place remains as eternal gain; and here, again, another generation finds new treasures that earlier ones passed by unheeding. This is the unfailing criterion of true greatness, that its creations continually beget ever-new, ever-changing values, that they bring to each successive generation new revelations.

—Max Spicker, 1912

As the social landscape changes, the culture of medicine continually redefines what is considered "conventional." Numerous recent studies have shown that since the early 1990s, consumers have been demanding alternatives to modern care.[8] Only since then has integrated medicine, including naturopathy, penetrated the Ivory Tower and research institutions in the United States. Driven by scientific advancement and a need for increased knowledge, this movement toward more pluralistic medicine has now brought us beyond the age of information and into the "age of integration."

With the current plethora of health information, it is becoming more apparent that optimal healing is not the property of any one tradition or system. Integrative clinics that incorporate multiple healing systems now thrive throughout the country and at major academic medical institutions. Employers and managed care agencies are beginning to offer coverage for acupuncture, chiropractic, naturopathy, and massage services. The Academic Consortium for Integrative Medicine has been formed among top-ranked medical schools to integrate CAM into their curricula. The National Institutes of Health has devoted an institute just for CAM with a budget of over $130 million.* Some medical residencies now include CAM in their training, and fellowships in integrative medicine now exist.

Despite the recent explosion of integrative medicine entering research, education, and clinical arenas, several barriers still limit the growth of integrative medicine in the United States. The most pressing and present barrier to clinical integration is reimbursement. To persuade insurers to cover the costs of CAM therapies, research evidence built on rigorous clinical trials and data that demonstrate cost efficacy of these modalities are necessary.

Perhaps an even greater barrier to integration is the challenge of how to establish safe and effective practices for these modalities, while carefully preserving the lineage of indigenous traditions. To examine this issue, the authors outline the birth and evolution of indigenous traditions as medical professions in the United States and later provide units on clinical practice, risk management, professional communications, practice management, and research that serve as essential tools for integration.

The current dilemma in the development of these CAM professions is how to perpetuate lineages during this integration with other health care professions, while not lowering standards for CAM practitioners. This present boom in alternative health care has resulted in the current state of integrative medicine: a confusing situation with too many practitioners offering a wide range of skills but leaving consumers without tools to decipher which are the most effective or true to tradition.

The middle path must be taken by raising the bar for practice standards. If the bar is too low, traditions will no longer be protected and they will not be as efficacious in practice. Consequently, practitioners may not be appreciated by either patients or traditional providers. If the bar is too high, few will find access and few will be able to practice. Either way, invaluable traditions may be lost.

The Birth and Evolution of a Medical Profession in the United States: Complementary and Alternative Medicine Professions

In the last years of the twentieth century, the United States witnessed the beginning transformations of indigenous healing traditions into CAM professions. After the counter-culture years of the 1960s and 1970s that challenged institutionalized medicine, interest in "natural healing" practices surged. As a result, chiropractic care and naturopathy were the first traditions to become formalized in modern medicine. Since then, Chinese medicine—via acupuncture—has made the largest entrance into health care in the United States, with more than 50 TCM and acupuncture schools in the United States and Canada accredited by the Accreditation Commission for Acupuncture and Oriental Medicine (ACAOM), adoption of licensure laws in the majority of states, and an increasing number of insurers offering coverage. A far second to Chinese medicine has been the development of Ayurvedic and Tibetan medicine, which are still in the early phases of their evolution as professions in the United States.

Every medical tradition, even current scientific-based modern medicine, began at the margin and progressed through a similar cycle to become an established practice or profession. Currently, CAM modalities are finding similar challenges as they endure this evolution toward becoming established professions. Typically, in stage 1, lone practitioners of the tradition arrive in the United States and provide informal workshops to the public and interested health care providers. These CAM practitioners practice their traditions informally. Stage 2 develops only after public and provider acceptance of safety and efficacy. Stage 2 marks the development of professional education and associations, provides standards for school accreditation and credentialing, and, ultimately, licensure by state boards. With regulation through professional associations, third-party payers become amenable to insurance reimbursement for CAM treatments. Finally, stage 3 results in set state and national standards for the profession, including education, practice, and methods to evaluate safety and efficacy, as well as widespread acceptance and practice. In this current era, the accomplishment of stage 3 is inherently dependent on the respectful and appropriate blending of these CAM traditions with the dominant medical paradigm based in science.

At this time in the United States, the professions of naturopathy, chiropractic, acupuncture, and massage are in early stage 3 of their professional and legislative developments, where accredited schools in all these fields have been undoubtedly established and licensure is being governed by state boards. For instance, acupuncture currently has two established organizations that help to set standards for training and practice: the ACAOM and the National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM). ACAOM is recognized by the U.S. Department of Education to accredit first professional master's degree and master's level programs in acupuncture and Oriental medicine and is currently petitioning to begin accrediting postgraduate, clinical doctoral programs. Acupuncturists are currently licensed according to state boards, but licensure laws vary from state to state. Many states recognize NCCAOM certification as a national standard, and thus practitioners can earn licensure with NCCAOM certification in these states. Acupuncture, as practiced by over 5000 medical doctors in the United States, is currently the fastest growing medical specialty. The American Academy for Medical Acupuncture now offers specialty board certification in the field. Nevertheless, although there is now some insurance coverage for modalities like acupuncture, barriers such as standardization in education, practice, and research still exist.

TOOLS FOR INTEGRATION

As providers of CAM services join professional networks and become increasingly integrated into conventional health delivery, the CAM professions gain both credibility and exposure.

*Monetary figure from National Institutes of Health, Office of Budget website at http://officeofbudget.od.nih.gov/br.html for fiscal year 2012.

Integration brings with it a new set of responsibilities. Utilization is growing and evolving so quickly that the educational institutions preparing CAM providers for licensure are hard pressed to keep up with the trend. As a result, CAM provider education often does not fully prepare its graduates to meet the growing expectations of the public, the medical community, or the legal system. Providers must gain competency in "tools for integration" that lead to a new set of skills for clinical practice, risk management, professional communications, practice management, and research. These tools include, but are not limited to, those listed in Box 1-1.

The emerging field of integrative medicine has arrived at the end of the beginning. It is no longer simply a vision of what could be. Billions of dollars are now spent out of pocket for several hundred million visits to integrative providers and for herbs and nutraceuticals each year. The majority of medical schools now offer some form of CAM education for physicians in training. Yet until now, the consumer has carried the day. As physicians move forward into the twenty-first century, they are ready to enter the beginning of the middle. The transition is rapidly underway, and clinical models for integration and quality studies demonstrating efficacy and cost offsets are imperative to its success.

In practice, it is also increasingly necessary to build bridges between the indigenous community, evolving CAM professions, and established medical institutions. Researchers, academicians, and health care professionals from multiple backgrounds need to understand the challenges in integration to provide optimal health with wisdom for this generation and the next. Only through partnership can the best medicine be offered and this evolution in the culture of health care be assisted.

BOX 1-1 **Tools for Integration**

Clinical
Prevention and identification of medical emergencies in the CAM clinic
Prevention and appropriate medical responses to adverse reactions of CAM therapies
Recommendations for interdisciplinary care of common complaints
Guidelines for selected scope of practice issues
Herbs as nutraceuticals

Risk Management
Malpractice
Informed consent
Expert testimony
Charting
Regulatory issues
Insurance

Professional Communications
Patient presentations
Referral protocols
Operations
Human resources
Patient relations
Using information technology

Research
A survey of conventional research tools
Customizing conventional research tools to study CAM
Evaluating research publications
Using research findings
Performing original research

CAM, Complementary and alternative medicine.

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CHAPTER 2

Functional Medicine: A Twenty-First Century Model of Patient Care and Medical Education

David S. Jones, MD, FABFP, Sheila Quinn, and Leo Galland, MD, FACP, FACN

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In this chapter, the basic principles, constructs, and methodology of functional medicine are reviewed. It is not the purpose of this chapter to recapitulate the range and depth of the science underlying functional medicine; books and monographs covering that material in great detail are already available for the interested clinician and for use in health professional schools (see Bibliography at the end of the chapter). The purpose is to describe how functional medicine is organized to deliver personalized systems medicine and is equipped to respond to the challenge of treating complex chronic disease more effectively.

WHAT IS FUNCTIONAL MEDICINE?

Functional medicine encompasses a dynamic approach to assessing, preventing, and treating complex chronic disease. It helps clinicians of all disciplines identify and ameliorate dysfunctions in the physiology and biochemistry of the human body as a primary method of improving patient health. This model of practice emphasizes that chronic disease is almost always preceded by a period of declining function in one or more of the body's physiologic organizing systems. Returning patients to health requires reversing (or substantially improving) the specific dysfunctions that contributed to the disease state. Those dysfunctions are, for each of us, the result of lifelong interactions among our environment, our lifestyle choices, and our genetic predispositions. Each patient, therefore, represents a unique, complex, and interwoven set of influences on intrinsic functionality that, over time, set the stage for the development of disease or the maintenance of health. To manage the complexity inherent in this approach, functional medicine has adopted practical models for obtaining and evaluating clinical information that leads to individualized patient-centered therapies.

Historically, the word "functional" was used somewhat pejoratively in medicine. It implied a disability associated with either a geriatric or psychiatric problem. The authors suggest, however, that this is a very limited definition of an extremely useful word. Medicine has not really produced an efficient method for identifying and assessing changes in basic physiologic processes that produce symptoms of increasing duration, intensity, and frequency, although it is known that such alterations in function often represent the first signs of conditions that, at a later stage, become pathophysiologically definable diseases. By broadening the use of functional to encompass this view, functional medicine becomes the science and art of detecting and reversing alterations in function that clearly move a patient toward chronic disease over the course of a lifetime.

One way to conceptualize where functional medicine falls in the continuum of health and health care is to examine the functional medicine "tree." In its approach to complex chronic disease, functional medicine encompasses the whole domain represented by the graphic shown in Figure 2-1, but first addresses the patient's core clinical imbalances (found in the functional physiologic organizing systems), the fundamental lifestyle factors that contribute to chronic disease, and the antecedents, triggers, and mediators that initiate and maintain the disease state. Diagnosis, of course, is part of the functional medicine model, but the emphasis is on understanding and improving the functional core of the human being as the starting point for intervention.

Functional medicine clinicians focus on restoring balance to the dysfunctional systems by strengthening the fundamental physiologic processes that underlie them and by adjusting the environmental and lifestyle inputs that nurture or



FIGURE 2-1 The continuum of health and health care: the functional medicine tree. (Courtesy of the Institute for Functional Medicine.)

impair them. This approach leads to therapies that focus on restoring health and function, rather than simply controlling signs and symptoms.

Principles

Seven basic principles characterize the functional medicine paradigm:

- Acknowledging the biochemical individuality of each human being, based on the concepts of genetic and environmental uniqueness
- Incorporating a patient-centered rather than a disease-centered approach to treatment
- Seeking a dynamic balance among the internal and external factors in a patient's body, mind, and spirit
- Addressing the web-like interconnections of internal physiologic factors
- Identifying health as a positive vitality—not merely the absence of disease—and emphasizing those factors that encourage a vigorous physiology
- Promoting organ reserve as a means of enhancing the health span, not just the life span, of each patient
- Staying abreast of emerging research—a science-using approach

Lifestyle and Environmental Factors

The building blocks of life, as well as the primary influences on them, are found at the base of the functional medicine tree graphic (see Figure 2-1). When we talk about influencing gene expression, we are interested in the interaction between lifestyle and environment in the broadest sense and any genetic predispositions with which a person may have been born—including the epigenome.* Many environmental factors that affect genetic expression are (or appear to be) a matter of choice (such as diet and exercise); others are very difficult for the individual patient to alter or escape (air

*Epigenetics—the study of how environmental factors can affect gene expression without altering the actual DNA sequence and how these changes can be inherited through generations.

and water quality, toxic exposures); and still others may be the result of unavoidable accidents (trauma, exposure to harmful microorganisms). Some factors that may appear modifiable are heavily influenced by the patient's economic status—if you are poor, for example, it may be impossible to choose more healthful food, decrease stress in the workplace and at home, or take the time to exercise and rest properly. Existing health status is also a powerful influence on the patient's ability to alter environmental input. If you have chronic pain, exercise may be extremely difficult; if you are depressed, self-activation is a major challenge.

The influence of these lifestyle and environment factors on the human organism is indisputable,[1,2] and they are often powerful agents in the battle for health. Ignoring them in favor of the quick fix of writing a prescription—whether for pharmaceutical agents, nutraceuticals, or botanicals—means the cause of the underlying dysfunction may be obscured but not eliminated. In general terms, the following factors should be considered when working to reverse dysfunction or disease and restore health:

- Diet (type, quality, and quantity of food; food preparation; calories, fats, proteins, carbohydrates)
- Nutrients (both dietary and supplemental)
- Air and water
- Microorganisms (and the general condition of the soil in which food is grown)
- Physical exercise
- Trauma
- Psychosocial and spiritual factors, such as meaning and purpose, relationships, work, community, economic status, stress, and belief systems
- Xenobiotics
- Radiation

Fundamental Physiologic Processes

There are certain physiologic processes that are necessary to life. These are the "upstream" processes that can go awry and create "downstream" dysfunctions that eventually become disease entities. Functional medicine requires that clinicians consider these in evaluating patients, so that interventions can target the most fundamental level possible. These processes are:

1. Communication
 - Outside the cell
 - Inside the cell
2. Bioenergetics/energy transformation
3. Replication/repair/maintenance/structural integrity
4. Elimination of waste
5. Protection/defense
6. Transport/circulation

These fundamental physiologic processes are usually taught early in health professions curricula, where they are appropriately presented as the foundation of modern, scientific patient care. Unfortunately, subsequent training in the clinical sciences often fails to fully integrate knowledge of the functional mechanisms of disease with therapeutics and prevention, emphasizing organ system diagnosis instead.[3] Focusing predominantly on organ system diagnosis without examining the underlying physiology that produced the patient's signs, symptoms, and disease often leads to managing patient care by matching diagnosis to pharmacology. The job of the health care provider then becomes a technical exercise in finding the drug or procedure that best fits the diagnosis (not necessarily the patient), leading to a significant curtailment of critical thinking pathways: "Medicine, it seems, has little regard for a complete description of how myriad pathways result in any clinical state."[4]

Even more important, pharmacologic treatments (and even natural remedies) are often prescribed without careful consideration of their physiologic effects across all organ systems, physiologic processes, and genetic variations.[5] Pharmaceutical companies exploit this weakness. We do not see drug advertisements that urge the practitioner to carefully consider the impact of all other drugs being taken by the patient before prescribing a new one! The marketing of drugs to specific specialty niches, and the use of sound bite sales pitches that suggest discrete effects, skews health care thinking toward this narrow, linear logic, as notably exemplified by the cyclooxygenase-2 inhibitor drugs that were so wildly successful on their introduction, only to be subsequently withdrawn or substantially narrowed in use due to collateral damage.[6,7]

Core Clinical Imbalances

The functional medicine approach to assessment, both before and after diagnosis, charts a course using different navigational assumptions. Every health condition instigates a quest for information centered on understanding when and how the specific biological system(s) under examination spun out of control to begin manifesting dysfunction and/or disease. Analyzing all the elements of the patient's story, the signs and symptoms, and the laboratory assessment through a matrix focused on functionality requires analytic thinking and a willingness on the part of the clinician to reflect deeply on underlying biochemistry and physiology. The foundational principles of how the human organism functions—and how its systems communicate and interact—are essential to the process of linking ideas about multifactorial causation with the perceptible effects called disease or dysfunction.

To assist clinicians in this process, functional medicine identified and organized a set of core clinical imbalances that are linked to the fundamental physiologic processes (organizing systems). These serve to marry the mechanisms of disease with the manifestations and diagnoses of disease. Many common underlying pathways of disease are reflected in these clinical imbalances. The following list of imbalanced systems and processes is not definitive, but some of the most common examples are provided. We recommend that the organizing systems be considered in the order as shown in the following:

Assimilation Imbalances
- Digestion
- Absorption
- Microbiota/gastrointestinal
- Respiration

Defense and Repair Imbalances
- Immune system
- Inflammatory processes
- Infection and microbiota

Energy Imbalances
- Energy regulation
- Mitochondrial function

Biotransformation and Elimination Imbalances
- Toxicity
- Detoxification

Communication Imbalances
- Endocrine
- Neurotransmitter
- Immune messengers
- Cognition

Structural Integrity Imbalances
- From the subcellular membranes
- To the musculoskeletal system

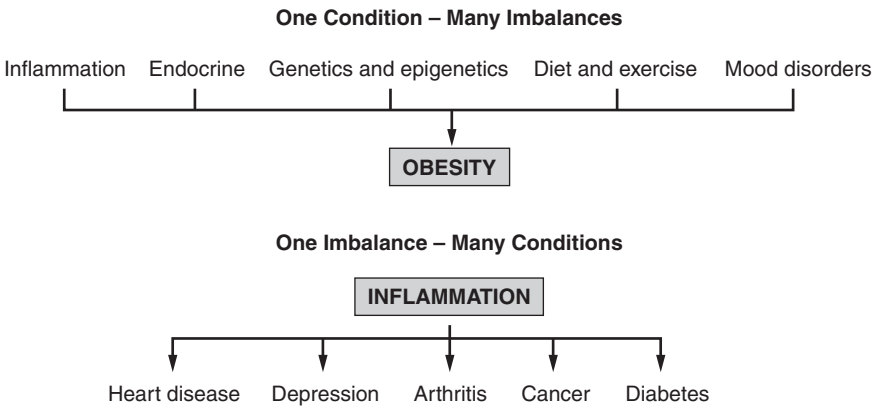


FIGURE 2-2 Core clinical imbalances—multiple influences. (Courtesy of the Institute for Functional Medicine.)

Using this construct, it becomes much clearer that one disease and/or condition may have multiple causes (i.e., multiple clinical imbalances), just as one fundamental imbalance may be at the root of many seemingly disparate conditions (Figure 2-2).

The most important precept to remember about functional medicine is that restoring balance—in the patient's lifestyle and/or environment and in the body's fundamental physiologic processes—is the key to restoring health.

Antecedents, Triggers, and Mediators*

What modern science has taught us about the genesis of disease can be represented by three words: triggers, mediators, and antecedents. Triggers are discrete entities or events that provoke disease or its symptoms. Microbes are an example. The greatest scientific discovery of the nineteenth century was the microbial etiology of the major epidemic diseases. Triggers are usually insufficient in and of themselves for disease formation; however, host response is an essential component.

It is, therefore, the functional medicine practitioner's job to know not just the patient's ailments or diagnoses, but the physical and social environment in which sickness occurs, the dietary habits of the person who is sick (present diet and pre-illness diet), his or her beliefs about the illness, the impact of illness on social and psychological function, factors that aggravate or ameliorate symptoms, and factors that predispose to illness or facilitate recovery. This information is necessary for establishing a functional treatment plan.

Identifying the biochemical mediators that underlie host responses was the most productive field of biomedical research during the second half of the twentieth century. Mediators, as the word implies, do not cause disease. They are intermediaries that contribute to the manifestation and/or continuation of disease. Antecedents are factors that predispose to acute or chronic illness. For a person who is ill, antecedents form the illness diathesis. From the perspective of prevention, they are risk factors. Knowledge of antecedents provides a rational structure for the organization of preventive medicine and public health.

Medical genomics seeks to better understand disease by identifying the phenotypic expression of disease-related genes and their products. The application of genomic science to clinical medicine requires the integration of antecedents (genes and the factors controlling their expression) with mediators (the downstream products of gene activation). Mediators, triggers, and antecedents are not only key biomedical concepts, they are also important psychosocial concepts. In person-centered diagnosis, the mediators, triggers, and antecedents for each person's illness form the focus of clinical investigation.

Antecedents and the Origins of Illness

Understanding the antecedents of illness helps the physician understand the unique characteristics of each patient as they relate to his or her current health status. Antecedents may be thought of as congenital or developmental. The most important congenital factor is gender: women and men differ sharply in susceptibility to many disorders. The most important developmental factor is age; what ails children is rarely the same as what ails the elderly. Beyond these obvious factors lies a diversity as complex as the genetic differences and separate life experiences that distinguish one person from another.

Triggers and the Provocation of Illness

A trigger is anything that initiates an acute illness or the emergence of symptoms. The distinction between a trigger and a precipitating event is relative, not absolute; the distinction helps organize the patient's story. As a general rule, triggers only provoke illness as long as the person is exposed to them (or for a short while afterward), whereas a precipitating event initiates a change in health status that persists long after the exposure ends.

Common triggers include physical or psychic trauma, microbes, drugs, allergens, foods (or even the act of eating or drinking), environmental toxins, temperature change, stressful life events, adverse social interactions, and powerful memories. For some conditions, the trigger is such an essential part of our concept of the disease that the two cannot be separated; the disease is either named after the trigger (e.g., strep throat) or the absence of the trigger negates the diagnosis (e.g., concussion cannot occur without head trauma). For chronic ailments like asthma, arthritis, or migraine headaches, multiple interacting triggers may be present. All triggers, however, exert their effects through the activation of host-derived mediators. In closed-head trauma, for example, activation of *N*-methyl-D-aspartic acid receptors, induction of nitric oxide synthase, and liberation of free intraneuronal calcium determine the late effects. Intravenous magnesium at the time of trauma attenuates severity by altering the mediator response.[8,9] Sensitivity to different triggers often varies among persons with similar ailments. A prime task of the functional practitioner is to help patients identify important triggers for their ailments and develop strategies for eliminating them or diminishing their virulence.

*This section was excerpted and adapted from Galland L. Patient-centered care: antecedents, triggers, and mediators. In *Textbook of Functional Medicine,* Institute of Functional Medicine, Gig Harbor, WA, Ch. 8.

BOX 2-1 **Common Illness Mediators**

Biochemical Hormones
Neurotransmitters
Neuropeptides
Cytokines
Free radicals
Transcription factors

Subatomic
Ions
Electrons
Electrical and magnetic fields

Cognitive/Emotional
Fear of pain or loss
Feelings or personal beliefs about illness
Poor self-esteem, low perceived self-efficacy
Learned helplessness
Lack of relevant health information

Social/Cultural
Reinforcement for staying sick
Behavioral conditioning
Lack of resources due to social isolation or poverty
The nature of the sick role and the doctor/patient relationship

Mediators and the Formation of Illness

A mediator is anything that produces symptoms or damages tissues of the body, including certain behaviors. Mediators vary in form and substance. They may be biochemical (e.g., prostanoids and cytokines), ionic (e.g., hydrogen ions), social (e.g., reinforcement for staying ill), psychological (e.g., fear), or cultural (e.g., beliefs about the nature of illness). A list of common mediators is presented in Box 2-1. Illness in any single person usually involves multiple interacting mediators. Biochemical, psychosocial, and cultural mediators interact continuously in the formation of illness.

CONSTRUCTING THE MODEL

Assessment

Combining the principles, lifestyle and environment factors, fundamental physiologic processes, antecedents, triggers, mediators, and core clinical imbalances creates a new information gathering and sorting architecture for clinical practice—in effect a new heuristic* to serve the practice of functional medicine. This new model includes an explicit emphasis on principles and mechanisms that infuse meaning into the diagnosis and deepen the clinician's understanding of the often overlapping ways things go wrong. Any methodology for constructing a coherent story and an effective therapeutic plan in the context of complex chronic illness must be flexible and adaptive. Like an accordion file that compresses and expands upon demand, the amount and kind of data collected will necessarily change in accordance with the patient's situation and the clinician's time and ability to piece together the underlying threads of dysfunction.

*Heuristics are rules of thumb—ways of thinking or acting—that develop through experimentation and enable more efficient and effective processing of data.

The conventional assessment process involving the Chief Complaint, History of Present Illness, and Past Medical History sections must be expanded (Figure 2-3) to include a thorough investigation of antecedents, triggers, and mediators, and a systematic evaluation of any imbalances within the fundamental organizing systems. Personalized medical care without this expanded investigation falls short.

The Functional Medicine Matrix Model

Distilling the data from the expanded history, physical examination, and laboratory findings into a narrative story line that includes antecedents, triggers, and mediators can be challenging. Key to developing a thorough narrative is organizing the story using the Functional Medicine Matrix Model form (Figure 2-4).

The matrix form helps organize and prioritize information and also clarifies the level of present understanding, thus illuminating where further investigation is needed. For example:

- Indicators of inflammation on the matrix might lead the clinician to request tests for specific inflammatory markers (such as highly sensitive C-reactive protein, interleukin levels, and/or homocysteine).
- Essential fatty acid levels, methylation pathway abnormalities, and organic acid metabolites help determine adequacy of dietary and nutrient intakes.
- Markers of detoxification (glucuronidation and sulfation, cytochrome P450 enzyme heterogeneity) can determine functional capacity for molecular biotransformation.
- Neurotransmitters and their metabolites (vanilmandelate, homovanillate, 5-hydroxyindoleacetate, quinolinate) and hormone cascades (gonadal and adrenal) have obvious utility in exploring messenger molecule balance.
- Computed tomographic scans, magnetic resonance imaging (MRI), or plain x-rays extend the view of the patient's structural dysfunctions. The use of bone scans, dual energy x-ray absorptiometry scans, or bone resorption markers[10,11] can be useful in further exploring the web-like interactions of the matrix.
- Newer, useful technologies such as functional MRIs, single-photon emission computed tomography or positron emission tomographic scans offer more comprehensive assessment of metabolic function within organ systems.

It is the process of completing a comprehensive history and physical using the expanded functional medicine heuristic and then charting these findings on the matrix that best directs the choice of laboratory work and successful treatment.

Therapies should be chosen for their potential impact on the most significant imbalances of the particular patient. A completed matrix form facilitates review of common pathways, mechanisms, and mediators of disease and helps clinicians select points of leverage for treatment strategies. However, even with the matrix as an aid to synthesizing and prioritizing information, it can be very useful to consider the impact of each variable at five different levels.

1. Whole body interventions: Because the human organism is a complex adaptive system, with countless points of access, interventions at one level will affect points of activity in other areas as well. For example, improving the patient's sleep beneficially influences the immune response, melatonin levels, and T-cell lymphocyte levels and helps decrease oxidative stress. Exercise reduces stress, improves insulin sensitivity, and improves detoxification. Reducing stress (and/or improving stress management) reduces cortisol levels, improves sleep, improves emotional well being, and reduces the risk of heart

Chief Complaint (CC)
History of Present Illness (HPI)
Past Medical History (PMH)
– Explore antecedents, triggers, and mediators of CC, HPI, and PMH
Family Medical History
– Genetic predispositions?
Review of Organ Systems (ROS)
Medication and Supplement History
Dietary History
Social, Lifestyle, Exercise History
Physical Examination (PE)
Laboratory and Imaging Evaluations
Explore Core Clinical Imbalances:
Assimilation Imbalances
Digestion
Absorption
Microbiota/GI
Respiration
Defense and Repair Imbalances
Immune system
Inflammatory processes
Infection and microbiota
Energy Imbalances
Energy regulation
Mitochondrial function
Biotransformation and Elimination Imbalances
Toxicity
Detoxification
Communication Imbalances
Endocrine
Neurotransmitter
Immune messengers
Cognition
Structural Integrity Imbalances
From the subcellular membranes to the musculoskeletal system
Initial Assessment:
– Enter data on Matrix form; look for common themes
– Review underlying mechanisms of disease
– Recapitulate patient's story
– Organ system-based diagnosis
– Functional medicine assessment: underlying mechanisms of disease; genetic and environmental influences
Treatment Plan:
– Individualized
– Dietary, lifestyle, environmental
– Nutritional, botanical, psychosocial, energetic, spiritual
– May include pharmaceuticals and/or procedures

FIGURE 2-3 Expanding the accordion file: the functional medicine assessment heuristic. (Courtesy of the Institute for Functional Medicine.)

disease. Changing the diet has myriad effects on health, from reducing inflammation to reversing coronary artery disease.

2. Organ system interventions: These interventions are used more frequently in the acute presentation of illness. Examples include splinting; draining lesions; repairing lacerations; reducing fractures, pneumothoraxes, hernias, or obstructions; or removing a stone to reestablish whole organ function. There are many interventions that improve organ function. For example, bronchodilators improve air exchange, thereby decreasing hypoxia, reducing oxidative stress, and improving metabolic function and oxygenation in a patient with reactive airway disease.
3. Metabolic or cellular interventions: Cellular health can be addressed by insuring the adequacy of macronutrients, essential amino acids, vitamins, and cofactor minerals in the diet (or, if necessary, from supplementation). An individual's metabolic enzyme polymorphisms can profoundly affect his or her nutrient requirements. For example, adding conjugated linoleic acid to the diet can alter the peroxisome proliferator activated receptor system, affect body weight, and modulate the inflammatory response.[12-14] However, in a person who is diabetic or insulin resistant, adding conjugated linoleic acid may induce hyperproinsulinemia, which is detrimental.[15,16] Altering the types and proportions of carbohydrates in the diet may increase insulin sensitivity, reduce insulin secretion, and fundamentally alter metabolism in the insulin-resistant patient. Supporting liver detoxification pathways with supplemental glycine and *N*-acetylcysteine improves the endogenous production of adequate glutathione, an essential antioxidant in the central nervous system and gastrointestinal tract.
4. Subcellular/mitochondrial interventions: There are many examples of nutrients that support mitochondrial function.[17,18]

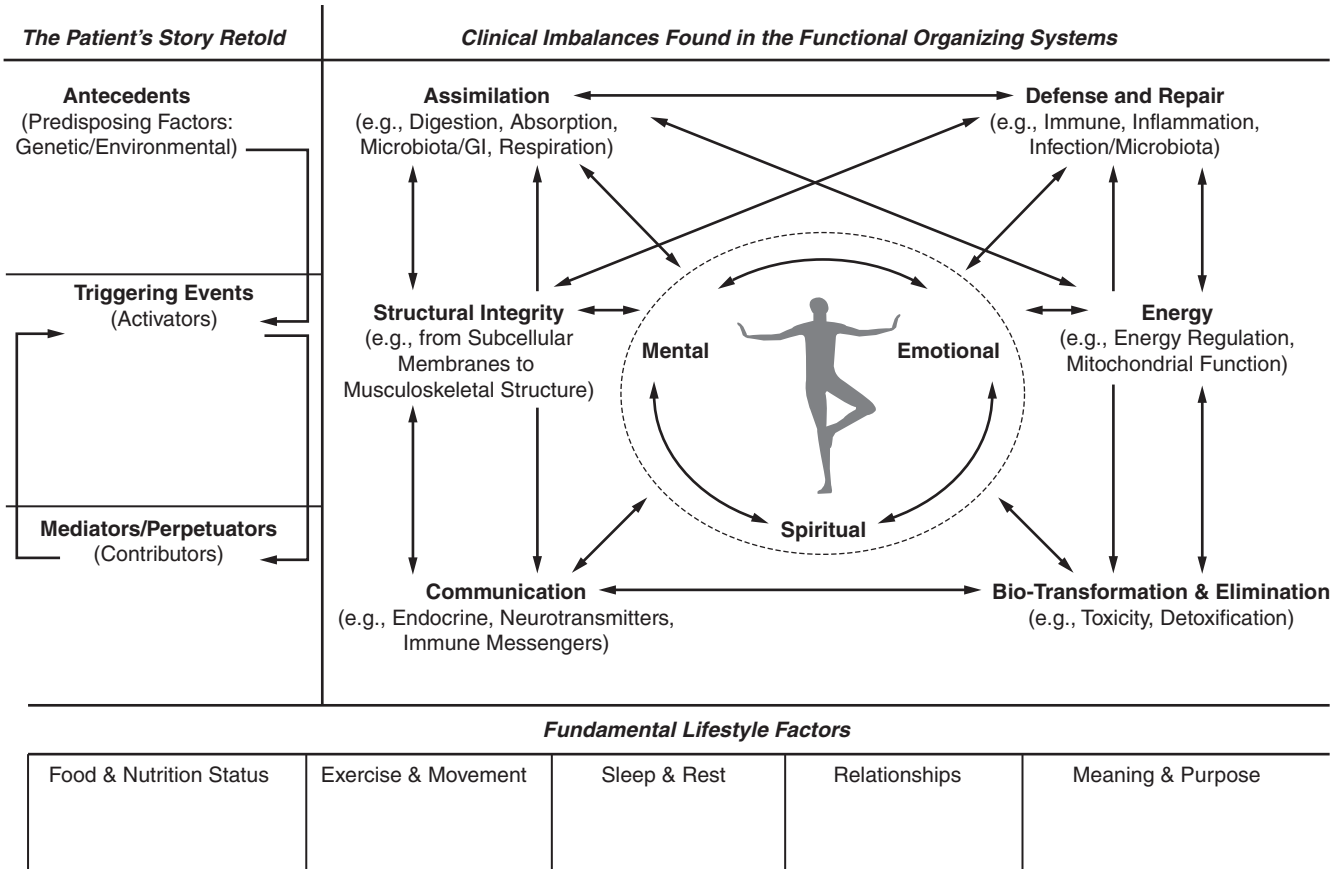


FIGURE 2-4 The functional medicine matrix model. (Courtesy of the Institute for Functional Medicine.)

Inadequate iron intake causes oxidants to leak from mitochondria, damaging mitochondrial function and mitochondrial DNA. Making sure there is sufficient iron helps alleviate this problem. Inadequate zinc intake (found in more than 10% of the U.S. population) causes oxidation and DNA damage in human cells.[18] Ensuring the adequacy of antioxidants and cofactors for the at-risk individual must be considered in each part of the matrix. Carnitine, for example, is required as a carrier for the transport of fatty acids from the cytosol into the mitochondria, improving the efficiency of β-oxidation of fatty acids and resultant adenosine triphosphate production. In patients who have lost significant weight, carnitine undernutrition can result in fatty acids undergoing ω-oxidation, a far less efficient form of metabolism.[19] Patients with low carnitine may also respond to riboflavin supplementation.[19]

5. Subcellular/gene expression interventions: Many compounds interact at the gene level to alter cellular response, thereby affecting health and healing. Any intervention that alters nuclear factor-κB entering the nucleus, binding to DNA, and activating genes that encode inflammatory modulators, such as interleukin-6 (and thus C-reactive protein), cyclooxygenase-2, interleukin-1, lipoxygenase, inducible nitric oxide synthase, tumor necrosis factor-α, or a number of adhesion molecules, will impact many disease conditions.[20,21] There are many ways to alter the environmental triggers for nuclear factor-κB, including lowering oxidative stress, altering emotional stress, and consuming adequate phytonutrients, antioxidants, alpha-lipoic acid, eicosapentaenoic acid, docosahexaenoic acid, and γ-linoleic acid.[20] Adequate vitamin A allows the appropriate interaction of vitamin A-retinoic acid with more than 370 genes.[22] Vitamin D in its most active form intercalates with a retinol protein and the DNA exon and modulates many aspects of metabolism, including cell division in both healthy and cancerous breast, colon, prostate, and skin tissue.[23] Vitamin D has key roles in controlling inflammation, calcium homeostasis, bone metabolism, cardiovascular and endocrine physiology, and healing.[23]

Experience using this model, along with improved pattern recognition skills, will often lessen the need for extensive laboratory assessments. However, there will always be certain clinical conundrums that simply cannot be assessed without objective data and, for most patients, there may be an irreducible minimum of laboratory assessments required to accumulate information. For example, in the clinical workup of autistic spectrum disorders in children, heavy metal exposure and toxicity may play an important role. Heavy metal body burden cannot be sensibly assessed without laboratory studies. In most initial workups, laboratory and imaging technologies can be reserved for those complex cases in which the initial interventions prove insufficient to the task of functional explication. When clinical acumen and educated steps in both assessments and therapeutic trials do not yield expected improvement, laboratory testing often provides rewarding information. This is frequently the context for focused genomic testing.

The Healing Partnership

No discussion of the functional medicine model would be complete without mention of the therapeutic relationship. Partnerships are formed to achieve an objective. For example, a business partnership forms to engage in commercial transactions for

financial gain; a marriage partnership forms to build a caring, supportive, home-centered environment. A healing partnership forms to heal the patient through the integrated application of both the art of medicine (insight driven) and the science of medicine (evidence driven). An effective partnership requires that trust and rapport be established. Patients must feel comfortable telling their stories and revealing intimate information and significant events.

In the twentieth century, contemporary medicine, traditionally considered a healing profession, evolved away from the role of healing the sick to that of curing disease through modern science. Research into this transition revealed that healing was traditionally associated with themes of wholeness, narrative, and spirituality. Professionals and patients alike report healing as an intensely personal, subjective experience involving a reconciliation of meaning for an individual and a perception of wholeness. The biomedical model as currently configured no longer encompasses these characteristics.

Contemporary medicine considers the wholeness of healing to be beyond its orthodoxy—the domain of the nonscientific and nonmedical.[24] We disagree. To grasp the profound importance of the healing partnership to the creation of a system of medicine adequate to the demands of the twenty-first century, an emerging body of relevant research was reviewed.[25-27] As Louise Acheson, MD, MS, Associate Editor for the *Annals of Family Practice*, articulated recently in that journal[28].

> *It is challenging to research this ineffable process called healing…. Hsu and colleagues asked focus groups of nurses, physicians, medical assistants, and randomly selected patients to define healing and describe what facilitates or impedes it.[30] The groups arrived at surprisingly convergent definitions: "Healing is a dynamic process of recovering from a trauma or illness by working toward realistic goals, restoring function, and regaining a personal sense of balance and peace." They heard from diverse participants that "healing is a journey" and "relationships are essential to healing."*

Research into the role of healing in the medical environment recently generated some thoughtful and robust investigations. Scott et al's[25] research into the healing relationship found very similar descriptions to those of Hsu et al.[29] The participants in the study[26] articulated aspects of the healing partnership as:

1. Valuing and creating a nonjudgmental emotional bond
2. Appreciating power and consciously managing clinician power in ways that would most benefit the patient
3. Abiding and displaying a commitment to caring for patients over time

Three relational outcomes result from these processes: trust, hope, and a sense of being known. Clinician competencies that facilitate these processes are self-confidence, emotional self-management, mindfulness, and knowledge.[26] In this rich soil, the healing partnership flourishes.

The characteristics of a conventional therapeutic encounter are fundamentally different from a healing partnership, and each emerges from specific emphases in training. In the therapeutic encounter, the relationship forms to assess and treat a medical problem using (usually) an organ system structure, a differential diagnosis process, and a treatment toolbox focused on pharmacology and medical procedures. The therapeutic encounter pares down the information flow between physician and patient to the minimum needed to identify the organ system domain of most probable dysfunction, followed by a sorting system search (the differential diagnosis heuristic). The purpose of this relationship is to arrive at the most probable diagnosis as quickly as possible and select an intervention based on probable efficacy. The relationship is a left-brain–guided conversation controlled by the clinician and characterized by algorithmic processing and statistical thinking.[30,31]

The functional medicine healing partnership forms with a related but broader purpose: to help the patient heal by identifying the underlying mechanisms and influences that initiated and continue to mediate the patient's illness(es). This type of relationship emphasizes a shared responsibility for identifying the causes of the patient's condition and achieving insight about enduring solutions. The healing partnership is critical to the delivery of personalized systems medicine and to manage the uncertainty (choices under risk) inherent in clinical practice. In the healing partnership, the appropriate utilization and integration of left-brain and right-brain functions are found.

In language, we have the fullest expression of the integration of left- and right-brain function. Language is so complex that the brain has to process it in different ways simultaneously—both denotatively and connotatively. For complexity and nuance to emerge in language, the left brain needs to see the trees and the right brain helps us see and understand the forest.[32,33]

The starting point for creating a healing partnership is the patient's experience. People, not diseases, can heal. Mindful integration of brain function is at the heart of a healing partnership. Some of the basic steps for establishing a healing partnership include:

1. Allowing patients to express, without interruption,[*] their story about why they have come to see you. The manner in which the patient frames the initial complaints often presages later insight into the root causes. Any interruption in this early stage of narrative moves the patient back into left-brain processing and away from insight.[34]
2. After focusing on the main complaint, encouraging the patient's narrative regarding their present illness(es). Clarifications can be elicited by further open-ended questioning (e.g., "tell me more about that"; "what else do you think might be going on?"). During this portion of the interview, there is a switching back and forth between right- and left-brain functions.
 - During this conversation, signs and symptoms of the present illness are distributed by the practitioner into the Functional Medicine Matrix Model form as previously described.
 - Analysis of the data thus collected proceeds by assessing probable underlying causes—based on evidence about common underlying mechanisms of disease—and ongoing mediators of the disease.
3. Next, conveying to the patient in the simplest terms possible that to achieve lasting solutions to the problem(s) for which he and/or she has come seeking help, a few fundamental questions must be asked and answered to understand the problem in the context of the patient's personal life. This framing of the interview process moves the endeavor from a left-brain compilation to a narrative that encourages insight—based on complex pattern recognition—about the root causes of the problem.
4. At this stage, control is shared with the patient: "Without your help, we cannot understand your medical problem in the

[*]Research focused on the therapeutic encounter has repeatedly found that clinicians interrupt the patient's flow of conversation within the first 18 seconds or less, often denying the patient an opportunity to finish. (Beckman DB, et al. The effect of physician behavior on the collection of data. Ann Intern Med. 1984;101:692-696.)

depth and breadth you deserve." Implementing this shared investigation can be facilitated by certain approaches:

a) For determining antecedent conditions, the following questions are useful:
 - When was the last time you felt well? When were you free of this problem?
 - What were the circumstances surrounding the appearance of the problem?
 - Have similar problems appeared in family members?

b) For triggers, the following question is critical:
 - What conditions, activities, or events seemed to initiate the problem? (Microbes and stressful personal events are examples, but illustrate quite different categories of triggers. Triggers by themselves are usually insufficient for disease formation, so triggers must be viewed within the context of the antecedent conditions.)

c) Mediators of the problem are influences that help perpetuate it.
 - There can be specific mediators of diseases in the patient's activities, lifestyle, and environment. Many diverse factors can affect the host's response to stressors.
 - Any of the core clinical imbalances, discussed previously and shown on the Functional Medicine Matrix Model, can transform what might have been a temporary change in homeostasis into a chronic allostatic condition.

It helps at this juncture to emphasize again that the following issues are elemental in forming a healing partnership:

- Only the patient can inform the partnership about the conditions that provided the soil from which the problem(s) under examination emerged. The patient literally owns the keys to the joint deliberation that can provide insight about the process of achieving a healing outcome.
- The professional brings experience, wisdom, tools, and techniques and works to create the context for a healing insight to emerge.
- The patient's information, input, mindful pursuit of insight, and engagement become "the horse before the cart." The cart carries the clinician—the person who guides the journey using evidence, experience, and judgment, and who contributes the potential for expert insight.

The crux of the healing partnership is an equal investment of focus by both clinician and patient. They work together to identify the right places to apply leverage for change. Patients must commit to engage both their left-brain skills and their right-brain function to inform and guide the exploration to the next steps in assessment, therapy, understanding, and insight. Clinicians must also engage both the left-brain computational skills and the right-brain pattern-recognition functions that, when used together, can generate insight about the patient's story. An overview of the functional medicine model can be seen in Figure 2-5.

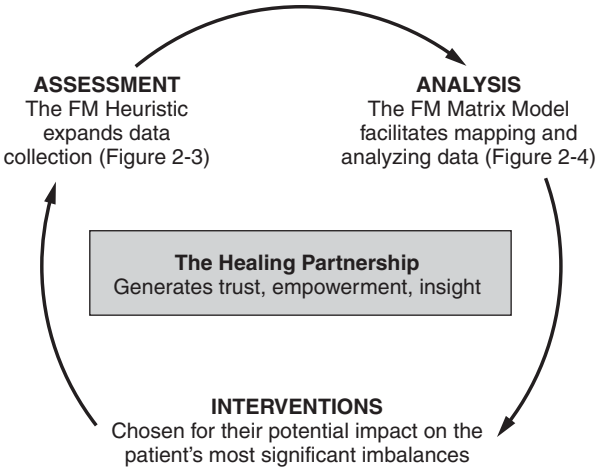


FIGURE 2-5 Overview of the functional medicine (FM) model. (Courtesy of the Institute for Functional Medicine.)

INTEGRATION OF CARE

Functional medicine explicitly recognizes that no single profession can cover all the viable therapeutic options. Interventions and practitioners will differ by training, licensure, specialty focus, and even by beliefs and ethnic heritage. However, all health care disciplines (and all medical specialties) can—to the degree allowed by their training and licensure and assuming a good background in Western medical science—use a functional medicine approach, including integrating the matrix as a basic template for organizing and coupling knowledge and data. Consequently, functional medicine can provide a common language, a flexible architecture, and a unified model to facilitate integrated and integrative care. Regardless of which discipline the clinician has been trained in, developing a network of capable, collaborative practitioners with whom to co-manage challenging patients and to whom referrals can be made for therapies outside the primary clinician's own expertise will enrich patient care and strengthen the clinician–patient relationship.

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CHAPTER 3

A Hierarchy of Healing: The Therapeutic Order

A Unifying Theory of Naturopathic Medicine

Jared L. Zeff, ND, LAc, Pamela Snider, ND, Stephen P. Myers, ND, BMed PhD, and Zora DeGrandpre, MS, ND

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A BRIEF HISTORY OF NATUROPATHIC MEDICINE

In 1900 Benedict Lust "invented" naturopathy, a practice that combined many natural therapies and therapeutic systems under the umbrella of a comprehensive philosophy based upon the European nature cure movement that flourished in the 1800s, the vis medicatrix naturae (healing power of nature) and other vitalistic principles. As such, naturopathic medicine has deep historical roots and represents a lineage of Western natural medicine that can be traced back to the Roman, Greek, Egyptian, and Mesopotamian cultures, and conceptually, to many traditional and indigenous world medicines.

The modern naturopathic profession originated with Lust, and it grew under his tireless efforts. He crisscrossed the United States lecturing and lobbying for legislation to license naturopathy, testifying for naturopaths indicted for practicing medicine without a license, and traveling to many events and conferences to help build the profession. He also wrote extensively to foster and popularize the profession, and through his efforts, the naturopathic profession grew rapidly.[1-3] By the 1940s, naturopathic medicine had developed a number of 4-year medical schools and had achieved licensure in about one third of the United States, the District of Columbia, four Canadian provinces, and a number of other countries.[2,4]

The profession went through a period of decline, marked with internal disunity and paralleled by the rise of biomedicine and the promise of wonder drugs. By 1957, there was only one naturopathic college left. By 1975, only eight states still licensed naturopathic physicians, and by 1979, there were only six. A survey conducted in 1980 revealed that there were only about 175 naturopathic practitioners still licensed and practicing in the United States and Canada.[5] In contrast, in 1951, the number was approximately 3000.[6]

The decline of naturopathic medicine after a rapid rise was due to several factors. By the 1930s, a significant tension developed within the profession regarding naturopathic practice, as did the development of unified standards and the role of experimental, reductionist science as an element of professional development.[7,8] This tension split the profession of naturopathic physicians from within after the death of Lust in the late 1940s, at a time when the profession was subject to both significant external forces and internal leadership challenges. Many naturopathic doctors questioned the capacity for the reductionist scientific paradigm to research naturopathic medicine objectively in its full scope.[7,9,10]

This perception created mistrust of science and research. Science was also frequently used as a bludgeon against naturopathic medicine, and the biases inherent in what became the dominant paradigm of scientific reductionism made a culture of scientific progress in the profession challenging. The discovery of effective antibiotics elevated the standard medical profession to dominant and unquestioned stature by a culture that turned to mechanistic science as an unquestioned authority. The dawning of the atomic age reinforced a fundamental place for science in a society increasingly dominated by scientific discovery. In this culture, standard medicine, with its growing political and economic strength, was able to force the near elimination of naturopathic medicine through the repeal or "sunsetting" of licensure acts.[1,2,11]

In 1956, as the last doctor of naturopathy (ND) program ended (at the Western States College of Chiropractic), several doctors, including Drs. Charles Stone, W. Martin Bleything, and Frank Spaulding, created the National College of Naturopathic Medicine in Portland, OR, to keep the profession alive. However, that school was nearly invisible as the last vestige of a dying profession and rarely

attracted as many as 10 new students a year. The profession was considered dead by its historic adversaries.

The culture of America, dominated by standard medicine since the 1940s, however, began to change by the late 1960s. The promise of science and antibiotics was beginning to seem less than perfect. Chronic disease was increasing in prevalence as acute infection was less predominant, and standard medicine had no "penicillin" for chronic diseases. In the late 1970s, scholars in family medicine proposed a biopsychosocial model of care in response to a prevailing perception of a growing crisis in standard medicine.[12] The publication of Engel's "The Need for a New Medical Model" in April 1977 signaled the founding of the field of family medicine based on a holistic philosophy and paralleled a broader social movement in support of alternative health practices and environmental awareness. Elements of the culture were rebelling against plastics and cheap synthetics, seeking more natural solutions. The publication of Rachael Carson's *Silent Spring* in 1962, an indictment of chemical pesticides and environmental damage, marked a turning point in cultural thinking. In *Silent Spring,* Carson challenged the practices of agricultural scientists and the government and called for a change in the way humankind viewed the natural world.[13] New evidence of the dangers of radiation, synthetic pesticides, and herbicides, as well as environmental degradation from industrial pollution, were creating a new ethic. Organic farming, natural fibers, and other similar possibilities were starting to capture attention. A few began seeking natural alternatives in medicine. By the late 1960s and early 1970s, enrollments at the National College of Naturopathic Medicine began to reach into the 20s. The 1974 class numbered 23 students. In 1975, the National College enrolled a class of 63 students.[14] The profession was experiencing a resurgence.

In 1978, with a desire to create a college based on science-based natural medicine, Joseph E. Pizzorno, ND, LM, and his colleagues, Les Griffith, ND, LM; Bill Mitchell, ND; and Sheila Quinn created the John Bastyr College of Naturopathic Medicine in Seattle, WA. With the creation of Bastyr, named after the eminent naturopathic physician, Dr. John Bartholomew Bastyr (1912–1995), the profession entered a new phase. Not only did this new college double the profession's capacity to produce new doctors, it also firmly placed the profession on the ground of scientific research and validation. "Science-based natural medicine," coined by Dr. Pizzorno, was a major driving force behind the creation and mission of Bastyr. Both Drs. Bastyr and Pizzorno had significant influence and leadership in achieving this focus.

One of Dr. Bastyr's important legacies was to establish a foundation and a model for reconciling the perceived conflict between science and the deeply established healing practices and principles of naturopathic medicine. Kirchfeld and Boyle[3] described his landmark contribution as follows:

> *"Although naturopathic colleges in the early 1900s did include basic sciences training, it was not until Dr. John Bastyr (1912-1995) and his firm, efficient and professional leadership that science and research-based training in natural medicine was inspired to reach its fullest potential. Dr. Bastyr, whose vision was one of 'naturopathy's empirical successes documented and proven by scientific methods,' was himself the prototype of the modern naturopathic doctor, who culls the latest findings from the scientific literature, applies them in ways consistent with naturopathic principles and verifies the results with appropriate studies."*

Bastyr also saw a tremendous expansion in both allopathic and naturopathic medical knowledge, and he played a major role in making sure the best of both were integrated into naturopathic medical education.[3,15]

Bastyr met Lust on two occasions and was closely tied to the nature cure tradition of Kneipp through two influential women: his mother and his mentor, Dr. Elizabeth Peters, who studied with Father Kneipp. He effortlessly integrated the clinical theories and practices of naturopathy with the latest scientific studies and helped create a new and truly original form of modern primary clinical care within naturopathic medicine. He spent the twentieth century preparing the nature cure of the nineteenth century for entry into the twenty-first century.[1,15] Today's philosophical debates within the profession are no longer about science. They tend to center on challenges to the Nature Cure tradition. A current debate, for instance, is about the role of "green allopathy" within the profession: the tendency to use botanical medicine or nutritional supplements as a simple "green drug" or pharmaceutical replacement versus the importance of implementing the full range of healing practices derived from Nature Cure to stimulate health restoration alongside, or instead of, botanical medicine or nutritional supplements. Professional consensus appears strong that the full range of naturopathic healing practices must be retained, strengthened, and engaged in the process of education and scientific research and discovery in the twenty-first century.[16-18]

ORIGINAL PHILOSOPHY AND THEORY

Through the initial 50-year period of professional growth and development (1896–1945), naturopathic medicine had no clear and concise statement of identity. The profession was whatever Lust said it was. He defined "naturopathy" or "nature cure" as both a way of life and a concept of healing that used various natural means of treating human infirmities and disease states. The "natural means" were integrated into naturopathic medicine by Lust and others based on the emerging naturopathic theory of healing and disease etiology. The earliest therapies associated with the term involved a combination of American hygienics and Austro-Germanic nature cure and hydrotherapy. Leaders in this field included Kuhne, Lindlahr, Trall, Kellogg, Holbrook, Tilden, Graham, McFadden, Rikli, Thomson, and others who wrote foundational naturopathic medical treatises or developed naturopathic clinical theory, philosophy, and texts to enhance, agree with, and diverge from Lust's original work.[19-27]

The bulk of professional theory was found in Lust's magazines, *Herald of Health* and *The Naturopath.* These publications displayed the prodigious writings of Lust, but did not contain a comprehensive and definitive statement of either philosophy or clinical theory. Lust often stated that all natural therapies fell under the purview of naturopathy. Several texts were considered as somewhat definitive by various aspects of the profession at different times. These texts included the seven-volume *Natural Therapeutics* by Henry Lindlahr, MD, which was published in the early 1900s. Lindlahr's *Nature Cure* (1913) was considered a seminal work in naturopathic theory, laying the groundwork for a systematic approach to naturopathic treatment and diagnosis. Lindlahr ultimately presented the most coherent naturopathic theory extant, summarized in his *Catechism of Naturopathy,* which presented a five-part therapeutic progression:

1. "Return to Nature"—attend to the basics of diet, dress, exercise, rest, etc.
2. Elementary remedies—water, air, light, electricity
3. Chemical remedies—botanicals, homeopathy, etc.
4. Mechanical remedies—manipulations, massage, etc.
5. Mental/spiritual remedies—prayer, positive thinking, doing good works, etc.[28]

In the 1950s Spitler wrote *Basic Naturopathy, a Textbook*,[9] and Wendel wrote *Standardized Naturopathy.*[10] These texts presented somewhat different approaches; Spitler's text emphasized theory and philosophy, whereas Wendel's text was written, as evidenced by the title, to emphasize the standard naturopathic practices of the day, with an eye toward regulatory practice. In contrast, Kuts-Cheraux's *Naturopathic Materia Medica*, written in the 1950s, was produced to satisfy a statutory demand by the Arizona legislature, but persisted as one of the few extant guides of that era. Practitioners relied on a number of earlier texts, many of which arose from the German hydrotherapy practitioners[29-34] or the Eclectic school of medicine (a refinement and expansion of the earlier "Thomsonian" system of medicine)[35-39] and predated the formal American naturopathic profession (1900). However, by the late 1950s, publications diminished. The profession was generally considered on its last gasp, an anachronism of the pre-antibiotic era.

During the process of winning licensure, naturopathic medicine was defined formally by the various licensure statutes, but these definitions were legal and scope-of-practice definitions, often in conflict with each other, reflecting different standards of practice in different jurisdictions. In 1965, the U.S. Department of Labor's *Dictionary of Occupational Titles*[40] presented the most formal and widespread definition. The definition was not without controversy. as it reflected one of the internally competing views of the profession, primarily, the nature cure perspective:

> *"Diagnoses, treats and cares for patients using a system of practice that bases treatment of physiological function and abnormal conditions on natural laws governing the human body. Utilizes physiological, psychological and mechanical methods such as air, water, light, heat, earth, phytotherapy, food and herbs therapy, psychotherapy, electrotherapy, physiotherapy, minor and orificial therapy, mechanotherapy, naturopathic corrections and manipulations, and natural methods or modalities together with natural medicines, natural processed food and herbs and natural remedies. Excludes major surgery, therapeutic use of x-ray and radium, and the use of drugs, except those assimilable substances containing elements or compounds which are components of body tissues and physiologically compatible to body processes for the maintenance of life."*[40]

This definition did not list drugs or surgery within the scope of modalities available to the profession. It defined the profession by therapeutic modality and was more limited than most of the statutes under which naturopathic physicians practiced,[41] even in 1975, when there were only eight licensing authorities still active.



MODERN NATUROPATHIC CLINICAL THEORY: THE PROCESS OF DEVELOPMENT

> *"Medical philosophy comprises the underlying premises on which a health care system is based. Once a system is acknowledged, it is subject to debate. In Naturopathic medicine, the philosophical debates are a valuable, ongoing process which helps the understanding of health and disease evolve in an orderly and truth-revealing fashion."*
>
> ***—Randall Bradley, ND[42]***

After the profession's decline in the 1950s and 1960s, a rebirth was experienced, more grounded in medical sciences and fueled by a young generation with few teachers. The profession's roots were neglected out of ignorance, for the most part, along with a youthful arrogance. By the early 1980s, it was apparent that attempts to regenerate the progress made by Lust would require the creation of a unified professional organization and all which that entailed: accreditation for schools, national standards in education and licensure, clinical research, and the articulation of a coherent definition of the profession for legislative purposes, as well as for its own internal development. These accomplishments would be necessary to be able to demonstrate the uniqueness and validity of the profession, guide its educational process, and justify its status as a separate and distinct medical profession.

In 1987, the newly formed (1985) American Association of Naturopathic Physicians (AANP) began this task under the leadership of James Sensenig, ND (president) and Cathy Rogers, ND (vice president), appointing a committee to head the creation of a new definition of naturopathic medicine. The "Select Committee on the Definition of Naturopathic Medicine" succeeded in a 3-year project that culminated in the unanimous adoption by AANP's House of Delegates (HOD) of a comprehensive, consensus definition of naturopathic medicine in 1989 at the annual convention held at Rippling River, OR.[43-45] The unique aspect of this definition was its basis in definitive principles, rather than therapeutic modalities, as the defining characteristics of the profession. In passing this resolution, the HOD also asserted that the principles would continue to evolve with the progress of knowledge and should be formally reexamined by the profession as needed, perhaps every 5 years.[43-48]

In September 1996, the AANP HOD passed a resolution to review three proposed principles of practice that had been recommended as additions to the AANP definition of naturopathic medicine originally passed by the HOD in 1989. These three new proposed principles were rejected, and the AANP HOD reconfirmed the 1989 AANP definition unanimously in 2000. The results of a profession-wide survey conducted from 1996 to 1998 on these three new proposed principles demonstrated that although there was lively input, the profession agreed strongly that the original definition was accurate and should remain intact. The HOD recommended that the discussion be moved to the academic community involved in clinical theory, research, and practice for pursuit through scholarly dialogue.[49-53] This formed the basis for further efforts to articulate a clinical theory. AANP members stated in 1987–1989 during the definition process: "These principles are the skeleton, the core of naturopathic theory. There will be more growth from this foundation."[45] By 1997, this growth in modern clinical theory was evident.

The first statement of such a theory was published in the AANP's *Journal of Naturopathic Medicine* in 1997 in an article titled "The Process of Healing, a Unifying Theory of Naturopathic Medicine."[54] This article contained three fundamental concepts that were presented as an organizing theory for the many therapeutic systems and modalities used within the profession and were based on the principles articulated in the consensus AANP definition of naturopathic medicine. The first of these was the characterization of disease as a process rather than a pathologic entity. The second was the focus on the determinants of health rather than on pathology. The third was the concept of a therapeutic hierarchy.

This article also signaled the emergence of a growing dialogue among physicians, faculty, leaders, and scholars of naturopathic philosophy concerning theory in naturopathic medicine. The hope and dialogue sparked by this article was the natural next step of a profession redefining itself both in the light of today's advances in health care and with respect to the foundations of philosophy at the traditional heart of naturopathic medicine. This dialogue naturally followed the discussions of the definition

process and created a vehicle for emerging models and concepts to be built on the bones of the principles. The essence and inherent concepts of traditional naturopathic philosophy were carried in the hearts and minds of a new generation of naturopathic physicians into the twenty-first century—these modern naturopathic students and naturopathic physicians began to gather to articulate, redefine, and reunify the heart of the medicine.

This new dialogue was formally launched in 1996, when the AANP Convention opened with the plenary session: "Towards a Unifying Theory of Naturopathic Medicine" with four naturopathic physicians presenting facets of emerging modern naturopathic theory. The session closed with an open microphone. The impassioned and powerful comments of the naturopathic profession throughout the United States and Canada engaged in the vital process of deepening and clarifying its unifying theory. Dr. Zeff presented "The Process of Healing: The Hierarchy of Therapeutics"; Dr. Mitchell presented "The Physics of Adjacency, Intention, Naturopathic Medicine, and Gaia"; Dr. Sensenig presented "Back to the Future: Reintroducing Vitalism as a New Paradigm"; and Dr. Snider announced the Integration Project, inviting the profession to engage in it by "sharing a beautiful and inspiring anguish—the labor pains of naturopathic theory in the twenty-first century. We know what we have done, and we know there is much more…The foundation is laid. We are ready now for development and integration."[55]

Days later, in September 1996, the Consortium of Naturopathic Medical Colleges (now the American Association of Naturopathic Medical Colleges [AANMC]) formally adopted and launched the Integration Project, an initiative to integrate naturopathic theory and philosophy throughout all divisions of all naturopathic college curricula, from basic sciences to clinical training. A key element of the project engaged the further development and refinement of naturopathic theory. The project was co-chaired by Drs. Snider and Zeff from 1996 to 2003. Steering members from all North American naturopathic colleges participated and contributed.[45] Methods included professional and scholarly research, expert teams, symposiums, and training. The result was the fostering of systematic inquiry among academicians, clinicians, and researchers concerning the underlying theory of naturopathic medicine, bringing the fruits of this work and inquiry into the classroom and into scientific discussion.[56]

The Integration Project sustained both formal and informal dialogue since its inception in 1996, which continues today. The work has engaged faculty and scholars of naturopathic philosophy in the United States, Canada, and Australia. It has also engaged institutional leaders and practicing doctors and faculty in all areas of the profession. Why? Naturopathic philosophy is deeply felt as the "commons" of naturopathic medicine: a place where the profession meets—one that is owned by all naturopathic physicians—that reflects, holds, and deepens the heart of naturopathic medicine. Naturopathic philosophy is the foundation and heart of naturopathic medicine. It remains valid by evolving with the progress of knowledge, the progress of science, and the progress of the human spirit. It is for this reason medicine is seen as an art as well as a science. Because naturopathic philosophy engages the intuitively felt mission of nature doctors, it is vital that the profession periodically gathers to renew and revitalize progress regarding its unifying foundations.

The Integration Project sparked a wide range of activities in all six ND colleges, resulting in all-college retreats to share tools, retreats for training of non-ND faculty in naturopathic philosophy, integration of a basic sciences curriculum, expert teams revision of core competencies across departments ranging from nutrition to case management and counseling, development of clinical tools and seminars for clinic faculty, creation of new courses, and the integration of important research questions derived from naturopathic philosophy into research studies and initiatives.[57] The latest effort is the Foundations of Naturopathic Medicine Project (textbook and symposia series, www.foundationsproject.com) and its development and presentation of the educational module on Emunctorology, an essentially naturopathic science, during 2009 and 2010. This is a joint effort of faculty from several of our schools, led by Drs. Thom Kruzel and Stephen Myers.

North American core competencies for naturopathic philosophy and clinical theory were developed by faculty representing all accredited ND colleges in a landmark AANMC retreat in 2000. The AANMC's Dean's Council formally adopted these competencies in 2000 and recommended that they be integrated throughout curricula in all ND colleges. These national core competencies included the process of healing theory, Lindlahr's model, and the hierarchy of therapeutics (the therapeutic order).[58,59]

Finally, many meetings with scholars and teachers of naturopathic theory and other faculty and leaders—formal and informal—resulted in the further development and refinement of the hierarchy of therapeutics developed by Dr. Zeff in 1997.

Drs. Snider and Zeff and naturopathic theory faculty worked closely with other naturopathic faculty from AANMC colleges in a series of revisions. Drs. Snider and Zeff collaborated in 1998 to develop the hierarchy of therapeutics into the therapeutic order. The therapeutic order was subsequently explored and refined through a series of faculty retreats and meetings, as well as through experience with students and through student feedback. A key finding of the clinical faculty at Bastyr University was the emphasis on the principle "holism: treat the whole person" and respect for the patient's own unique healing order and his or her values as a context for applying the therapeutic order to clinical decision making.[60] The therapeutic order, or hierarchy of healing, is now incorporated into ND college curricula throughout the United States, Canada, Australia, and New Zealand. For example, an important international outgrowth of the profession's development of theory is the adoption of the unified *"Working Definition of Naturopathic Nutrition"* in June 2003 by the Australian naturopathic profession (Box 3-1). The 3-year project, fostered by Dr. Stephen Myers, brought together nutrition faculty from naturopathic medicine colleges throughout Australia. The project was co-hosted by the Naturopathy and Nutrition panel, an independent group of naturopaths and nutrition educators whose mission is to foster and support the development of the science, teaching, and practice of naturopathic nutrition, and the School of Natural and Complementary Medicine at Southern Cross University. The definition evolved over two retreats attended by more than 40 faculty members involved in teaching nutrition as part of a naturopathic medicine education. It commenced as a general agreement within the group that there was a real and distinct difference between conventional nutritional concepts and naturopathic nutritional theory. General agreement was that the distinction between the two had to date been poorly defined and had been the source of dissonance between the naturopathic and science faculty within the colleges. The obvious next step was to define that difference to ensure that nutrition curriculum within naturopathic medicine colleges reflected the core elements of naturopathic nutrition. At the second retreat held in June 2003, the working definition was adopted with a recommendation that it be widely circulated within the naturopathic medicine profession to commence a dialogue aimed at both appropriate revision and broad adoption. This process created a much-needed consensus definition on naturopathic nutrition. This definition is based on the AANP defining principles and incorporates the therapeutic order theory.

BOX 3-1 **Working Definition of Naturopathic Nutrition**

Preamble

Naturopathic medicine is a distinct system of primary health care—an art, science, philosophy and practice of diagnosis, as well as treatment and prevention of illness. Naturopathic medicine is distinguished by the principles that underlie and determine its practice. These principles include the healing power of nature (vis medicatrix naturae), identification and treatment of the causes (tolle causam), the promise to first do no harm (primum non nocere), doctor as teacher (docere), treatment of the whole person, and emphasis on prevention. These principles give rise to a practice that emphasizes the individual and empowers him or her to greater responsibility in personal health care and maintenance.

Definition

Naturopathic nutrition is the practice of nutrition in the context of naturopathic medicine.

Naturopathic nutrition integrates both scientific nutrition and the principles of naturopathic medicine into a distinct approach to nutritional practice.

Core components of naturopathic nutrition are:

- A respect for the traditional and empirical naturopathic approach to nutritional knowledge
- The value of food as medicine
- An understanding that whole foods are greater than the sum of their parts and recognition that they have vitality (properties beyond physiochemical constituents)
- Individuals have unique interactions with their nutritional environments

Practice

In the context of the definition, and with respect to the therapeutic order, the practice of naturopathic nutrition may include the appropriate use of the following:

- Behavioral and lifestyle counseling
- Diet therapy (including health maintenance, therapeutic diets, and dietary modification)
- Food selection, preparation, and medicinal cooking
- Therapeutic application of foods with specific functions
- Traditional approaches to detoxification
- Therapeutic fasting strategies
- Nutritional supplementation

Data from Snider P, Payne S. Making naturopathic curriculum more naturopathic: agendas, minutes, 1999-2001. Clinic faculty task force on integration. Faculty development retreat, Bastyr University, 1999.

A THEORY OF NATUROPATHIC MEDICINE

Standard medicine, or biomedicine, has a simple and elegant paradigm. Simply stated, it is "the diagnosis and treatment of disease." In practice, this statement contains several assumptions. One assumption is that illness can be understood in terms of discrete diseases (i.e., human illnesses can be divided into identifiable entities, such as measles or specific forms of cancer, etc.). The next assumption is that "cure" is the elimination of the disease entity. The third assumption is that this is accomplished by the evidence-based application of pharmaceuticals, surgeries, or similar treatments to eliminate, palliate, or suppress the entity and its symptomatic expressions. These are so obvious that they are not commonly considered. They form the background thinking in medical decision making: identify and treat the disease.

The elegance of this model, and the science behind it, has taken medicine to its highest point in history as a reliable vehicle to ease human illness, and its application has saved countless lives. The understanding of the physician, at least about the nature of pathology, has never been as complete. However, illness has a near-infinite capacity to baffle the physician. New diseases arise, such as human immunodeficiency virus/acquired immune deficiency syndrome, and shifts occur in disease focus, such as the shift between 1900 and 2000 from acute infection to chronic illness as the predominant cause of death.[61]

Beyond these obvious changes, even with the current depth of understanding, the standard medical world often lacks the ability to effectively understand and cure chronic disease, and treatment tends to become a task of the management of symptoms and the attempt to reduce long-term damage and other consequences, rather than actual cure of the illness. So, even representing an apex of human achievement as it does, modern medicine is not without its weaknesses. Its greatest weakness is probably this inability to cure chronic illness as easily as it once cured pneumonia with penicillin or tuberculosis with streptomycin. Compounding the problem is the growing prevalence of antibiotic-resistant infections.[62,63] Part of the reason for the failures within modern medical science is its mechanistic basis. Breaking the body down to its constituent parts has led to a fundamental ignorance of and disrespect for the wholeness of the individual, the natural laws of physiology governing health and healing, and particularly for all things spiritual (the transpersonal domains). Inherent in the dictum—diagnose and treat the disease—is the general neglect of the larger understanding that disease is a process conducted by and within an intelligent organism that is constantly attempting to heal itself, with disease manifestations often expressions of this self-healing endeavor. As noted by Pizzorno et al,[64] this intelligent organism strives for optimal function and health. Human beings "…are natural organisms, our genomes developed and expressed in the natural world. The patterns and processes inherent in nature are inherent in us. We exist as a part of complex patterns of matter, energy, and spirit. Nature doctors have observed the natural processes of these patterns in health and disease and determined that there is an inherent drive toward health that lives within the patterns and processes of nature."

The uniqueness of naturopathic medicine is not in its therapeutic modalities or the "natural" alternatives to the drugs and surgeries of standard medicine. It is in the clinical theory that governs the selection and application of these modalities, captured in the unifying definition adopted in 1989 and expressed more specifically in the continuing articulation of clinical theory. That is, it is the way the naturopathic physician thinks about illness and healing.

The first element of this theory is based upon the first defining principle: vis medicatrix naturae. It is based on the understanding that disease can be seen as a process, as well as an entity. One can analyze the process of illness and derive some understanding. However, to do this, one needs to examine the assumptions underlying this concept. The governing assumptions of standard medicine are principally that diseases are entities, and that drugs and surgery can eliminate these entities from the suffering person. These are not the governing assumptions of naturopathic medicine.

ILLNESS AND HEALING AS PROCESS

Naturopathic medicine can be characterized by a different model than "identify and treat the disease." "The restoration of health" would be a better characterization. Naturopathic physicians adopted the following elegantly brief definition of naturopathic

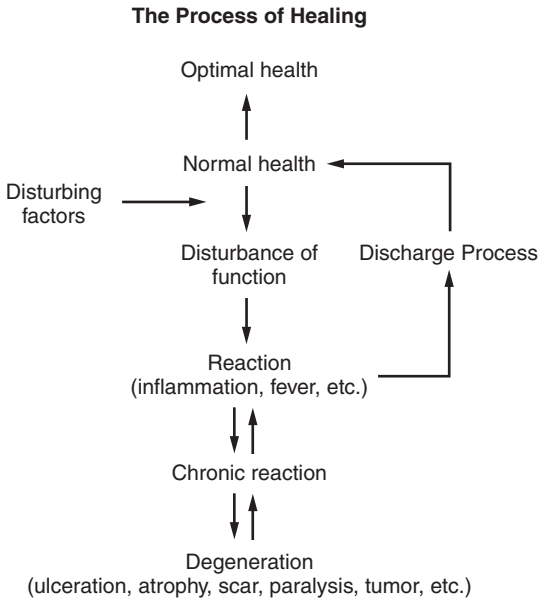


FIGURE 3-1 The process of healing (used by permission Jared L. Zeff, ND).

medicine in 1989 in an AANP position paper: "Naturopathic physicians treat disease by restoring health."[44] Immediately a significant difference is made clear: standard medicine is disease based; naturopathic medicine is health based. Although naturopathic medical students study pathology with the same intensity and depth as standard medical students, as well as its concomitant diagnoses, the naturopathic medical student learns to apply that information in a different context. In standard medicine, pathology and diagnosis are the basis for the discernment of the disease "entity" that afflicts the patient, the first of the two steps of identifying and destroying the entity of affliction. In naturopathic medicine, however, disease is seen much more as a process than as an entity. Rather than viewing the ill patient as experiencing a "disease," the naturopathic physician views the ill person as functioning within a process of disturbance and recovery, in the context of nature and natural systems. Various factors disturb normal health. If the physician can identify these disturbances and moderate them (or at least some of them), the illness and its effects abate, at least to some extent, if not totally. As disturbances are removed, the body can improve in function, and in doing so, health naturally improves. The natural tendency of the body is to maintain itself in as normal a state of health as is possible—this is the basis of homeostatic principles.[65] The role of the physician facilitates this self-healing process.

The obvious first task of the naturopathic physician, therefore, is to determine what is disturbing the health so that these causative elements may be ameliorated. Disease is the process whereby the intelligent body reacts to disturbing elements. It employs such processes as inflammation and fever to help restore its health. In general, one can graph this process simply, as in Figure 3-1.

The Naturopathic Model in Acute Illness

One can see "illness-as-process" most easily in the common cold. Within standard medical understanding, the common cold is caused by a virus, from among a family of pathologic viruses, which can infect a person. The immune system responds, developing appropriate antibodies, which eventually neutralize the virus. There is no "cure" yet discovered, except time. Medications are used to ameliorate the symptomatic experience: aspirin or acetaminophen for fever, antihistamines to dry the mucus discharge, etc. These measures are not cures; they reduce the symptomatic expression of the "cold" but often lengthen the process. In naturopathic medicine, the cold is seen not as a disease entity, but as part of a fundamental process whereby the body restores itself to health.

If the virus were the sole cause of the common cold, then everyone who came into contact with sufficient dose of the virus would get the cold. Obviously, this does not happen. Susceptibility factors include immune competence, fatigue, vitality, genetics, and other host factors.[66] The virus enters a milieu in which all these factors affect the process. Once the virus enters the system, and if it overcomes resistance factors (Box 3-2), one begins to see disturbance of function, as illustrated in Figure 3-1. One does not feel quite right. One may begin to get a sore throat, the first inflammatory reaction, occurring at the point of entry of the virus into the body. The immune factors described may overcome the virus at this point, may be insufficient, or may be suppressed. All of this is mutable to some extent and is affected by host factors, such as nutritional status and fatigue, and can be influenced by taking immune tonics, vitamin C, and other supplements.

To the individual with the condition, the "cold" may proceed into a general state of fatigue and inflammation, possibly fever followed by mucus discharge, cough, and other symptoms, as the body processes and responds to the virus and its effects; eventually the body overcomes it and eliminates the results.

In the naturopathic model, the virus is not understood so much to be a separate disease entity, but a general and fundamental process of disturbance and recovery within the living body. It is a method whereby the body restores itself after a sufficient amount of disturbance accumulates within the system. This is why the cold has no "cure." It is the cure for what ails the body. In the naturopathic model of health, it is the support of this "adaptive response"—the restoration of balance that is the central point—through which the process is the "cure" (Box 3-3).

BOX 3-2 Scientific Considerations: The Immune Response and Resistance Factors

Once inside the body, the rhinovirus binds to cellular receptors (primarily the intercellular adhesion molecule-1 [ICAM-1]) or to the low-density lipoprotein (LDL) receptor. The viral particles are then internalized and begin to take over the cellular machinery to produce intact virions.[66,67] At this stage, the body can sometimes mount an adequate defense via cell-mediated immunity to overcome the viral incursion. If we have been previously exposed to the virus, the body's humoral immune response will rapidly produce antibodies to the viral protein, which can also lead to eradication of the microbe. These two immune responses explain why some individuals may develop the full condition, whereas others will shake off the exposure within a few hours. If the viral load overcomes the body's innate defenses, the virus replicates unabated. In the process of replication, the virus not only disrupts the cellular mechanisms, but damages them as well by infecting the surface epithelium, as well as the macrophages[68] and fibroblasts.[69] Naturopathic physicians are interested in the factors that lead to greater immune competence and health restoration through the process of healing and the health practices that support it. French physiologist Claude Bernard (1813–1878) said that the inner terrain or "milieu interieur" was the cause of disease, and not the microbes; this concept underpins the naturopathic approach.

BOX 3-3 Scientific Considerations: Consequences of Suppressing the Body's Response

Current research shows that future pathologies may be linked to "suppression" of early rhinovirus infection. These include childhood asthma, adult asthma, and chronic obstructive pulmonary disease (COPD).[70,71] Individuals with asthma are known to have subtle deficiencies in production of type I and type III interferon (IFN),[72,73] indicating that for some asthma patients, early exposure to the rhinovirus predisposes them to asthma, and that the suppression of the normal response may be critical in the future development of asthma. With these effects in mind, the naturopathic physician does not look solely at the virus as a pathogenic entity, but also seeks to determine how the patient responds to the virus, thereby determining the most reasonable approach to aiding the patient's natural responses and moderating the patient's long-term health strategies. Suppression of the body's natural responses is avoided. The long-term use of corticosteroids is a prime example of suppression and its consequences.[74,75]

BOX 3-4 Scientific Considerations: The Role of Environment in Chronic Illness

Environmental and lifestyle disturbances are a profound driver in the naturopathic model of health. The scientific evidence is now irrefutable that the national and global burden of chronic disease is highly dependent on modifiable behavioral factors. In a recent study of the causes of death, it was found that tobacco, poor diet and lack of physical activity, alcohol and drug use, toxic agents, and vehicular and firearm incidents were the leading actual causes of death.[79] Other factors included frank malnutrition (as opposed to poor nutrition), unsafe sexual practices, and poor sanitation.[80,81] It has been definitively shown, for example, that diet and lifestyle changes can prevent some forms of diabetes[82,83] and other chronic diseases[84,85] that are leading causes of death in the United States.[79,82,83]

The Naturopathic Model in Chronic Illness

Chronic illness arises, in general, when any or all of three factors occur:

1. The disturbing factors persist, such as a chronically improper diet, which continues to burden the body cumulatively, as the digestive processes slowly weaken under the stress of the improper or inadequate diet.
2. The reactive potential is blocked or suppressed, usually by drugs, which interfere with the capacity of the body to process and remove its disturbances.
3. The vitality of the system is insufficient, or has become too overwhelmed, to mount a significant and sufficient reaction.

As these three factors prevent a sufficient reactive purge of disturbances, the body slides into a chronic, weakened reactive state with possible episodes of intermittent reaction, and is perceived to be in a persistent chronic illness. Ultimately, as function is sufficiently disturbed, structures or functions are damaged, and chronic inflammation becomes ulceration or scar tissue formation. In terms of the allostatic model, the balance has been disrupted, and there is no more adaptive potential. Atrophy, paralysis, or even tumor formation[76–78] may occur. All of this is the body manifestly doing the best it can for itself in the presence of persistent disturbing factors and with respect to the limitations and range of vitality influenced by the constitution, psycho-emotional/spiritual state, genotype of the person, and his or her surrounding environment (Boxes 3-4 and 3-5).

BOX 3-5 Scientific Considerations: Chronic Illness and the Adaptive Response

Regarding the responses of an overwhelmed or chronically disturbed organism, it has been argued recently that the anemia of chronic disease is an adaptive biological response rather than a harmful disorder and is associated with a number of chronic states.[86] Citing a number of studies, it was also argued that it was the treatment of the anemia of chronic disease among critically ill patients and those with renal failure and cancer (e.g., breast cancer and head and neck cancers) that was associated with the greater mortality. The U.S. Food and Drug Administration issued a warning against the use of erythropoiesis-stimulating agents in those cancer patients not undergoing chemotherapy or radiation therapy.[87]

States where the normal compensatory mechanisms become overwhelmed or suppressed (reducing the reactive potential of the body) include states of chronic oxidative stress[88] and inflammatory processes.[89,90] It is not, however, solely a matter of an overwhelmed or chronically disturbed organism that is critical to the process of disease progression. Adaptive responses are also of vital importance to the development of chronic disease. Research has shown that these evolutionarily preserved adaptive mechanisms of physical activity, insulin sensitivity, and fat storage are essential in the prevention of chronic disease states.[84,85] In the development of type 2 diabetes, for example, there is increasing evidence that it is the individual's maladaptation to lack of physical activity that appears to lead to decreased insulin sensitivity and increased fat storage, which can then lead to a plethora of chronic diseases, many characterized by states of chronic inflammation[91] and oxidative stress. Continuing basic and clinical studies indicate that many of the processes currently regarded in mainstream medicine as harmful have been evolutionarily retained to provide an adaptive advantage.[92,93] The Harvard Health Letter recently published an article describing inflammation as part of the "Unifying Theory of Disease"[94] giving support to the argument that inflammation is crucial in both health and disease and that chronic diseases arise when the inflammatory process occurs without appropriate control. The allostatic model also provides a theoretical basis for naturopathic clinical theory. The allostatic model describes the process of achieving stability (homeostasis) through changes in the homeostatic "set points" or control boundaries.[95-98] Homeostasis, the maintenance of stability in biochemical and physiologic processes, is essential for life—and allostasis, the "re-setting" of the homeostatic "set points", is essential for the maintenance of homeostasis. As it develops through the various iterations of researchers and clinicians, the model emphasizes the need to look beyond the current linear-reductionist model of disease and toward a more wholistic and balanced approach to disease conditions.

The adaptive response of the organism to insult or frank structural damage is a concept that also has support outside naturopathic medicine. For example, Schnaper et al[99] described a conceptual framework for progressive kidney disease where the initial disease develops through an injury of some nature that provokes a cellular response as an adaptation to the original injury. Where this cellular response is effective, no progressive kidney disease may ensue. If, however, there is a maladaptation, these attempts at self-repair may lead to progressive loss of nephrons and chronic kidney disease.

Reversal of this overwhelmed condition is rarely accomplished by medicating the pathologic state. This often results in the control of symptoms but with the persistence of the illness, while ideally controlling its more dangerous aspects using higher force interventions such as pharmaceutical drugs and surgical intervention. Reversal is more likely accomplished by identifying and ameliorating the disturbance, and as necessary, strengthening or

supporting the reactive potential. The first step in this process is to identify and reduce disturbing factors.

THE DETERMINANTS OF HEALTH

To reduce the disturbance, one must identify the disturbance. In standard medicine, the first step is to identify the pathology, which is then treated. In naturopathic medicine, one must come to understand what is disturbing the health. To do this, the physician needs to understand what determines health in the first place. The physician can then evaluate the patient in these terms and come to understand what is disturbing the natural state of health. Such a list could be created by any doctor, certainly any naturopathic physician. The authors propose using the list in Box 3-6.

Some of these determinants have been discussed—those modifiable behavioral factors such as drug and alcohol use, poor diet or frank malnutrition, lack of physical exercise, environmental and socioeconomic factors, and unsafe sexual practices.[79-81,100] (Box 3-7). Many of these behavioral factors have major psychological and spiritual components, and the effect can be increased stress on both the individual and the family, with all its attendant consequences.[100-102] The naturopathic physician evaluates the patient with these areas in mind, looking for aspects of disturbance, first in the spirit, and most generally in diet, digestion, and stress in its various aspects. In this evaluation, the naturopathic physician brings to bear a body of knowledge somewhat unique to naturopathic medicine to evaluate not solely in terms of pathologic entity, but in terms of normal function and subclinical functional disturbance (Box 3-8). By locating areas of abnormal function or disturbance, the naturopathic physician acts or recommends ways to ameliorate the disturbance.

As disturbing factors or insults to the system are reduced, the natural tendency of the system is to improve and optimize its function, directing the system back toward normalcy, or homeostasis. In more conventional medical terms, this is one of the fundamental concepts of the allostatic model.[95-98,101] In naturopathic thinking, this is the removal of the obstacles to cure, which allows the emerging action of the vis medicatrix naturae, the vital force, the healing power of nature. This is the first step in the hierarchy of healing and what naturopathic physicians may call the overarching model in the clinical theory (the process of healing) of naturopathic medicine: the therapeutic order. This process can be seen in the naturopathic model of healing in Figure 3-1.

THERAPEUTIC ORDER

The therapeutic order is a natural hierarchy of therapeutic intervention based on, or dictated by, observations of the nature of the healing process from ancient times through the present.[112] "Therapeutic orders" also exist in traditional Chinese, Tibetan, Ayurvedic, and Unani medicine theories. It is a natural ordering of the modalities of naturopathic medicine and their application. The concept is somewhat plastic, in that one must evaluate the unique needs, and even the unique healing requirements, of the specific patient or situation.[113] However, in general, the nature of healing dictates a general approach to treatment. In general, this order is listed in Box 3-9.

An analogy for the therapeutic order in Australian standard medicine is what is called the "softer option" model of patient care.[118] This model recognizes that, given a choice, the patient will generally choose the softer option, provided that this does not limit a harder option, if the softer option fails. By way of example, given a choice between an antibiotic and amputation for a minor cut finger, most people would choose the softer option. Expanding this range of choice to an herbal cream, antiseptic (herbal or nonherbal) and a Band-Aid, an antibiotic, or amputation, we develop a therapeutic order ranging from the softest option (the least force) to the hardest option (the higher force intervention). The therapeutic order can be seen as a progression of therapeutic interventions that begin with this "softer option."

BOX 3-6 **Naturopathic Medicine Determinants of Health**
Factors That Influence Health

Inborn Determinants
Genetic make-up (genotype)
Intrauterine/congenital factors
 Intrauterine influences: maternal nutrition, health, & lifestyle
 Maternal exposures: drugs, toxins, illnesses, viruses, psycho-emotional
Constitution: determines susceptibility

Disturbances/Disturbing Factors
Illnesses: Pathobiography
Medical Interventions (or lack of)
Physical and emotional exposures, stresses and trauma
Toxic and harmful substances
Trauma (physical/emotional)
Toxemia
Addictions
Environmental disturbances, stress: environmental, physical, emotional

How We Live - Hygienic, Lifestyle, Psycho-emotional, Spiritual, Socioeconomic & Environmental Factors

Spirit
Spiritual life/practice
Self-assessment
Relationship to larger universe *(trust, consciousness, compassion)*

Exposure to Nature/ Environment
Fresh air
Clean water
Natural light
Geography and ecosystem
Exposure to natural systems, wild places, cycles

Diet, Nutrition, and Digestion
Unadulterated food
Optimal nutrition

Rest and Exercise
Rest and sleep
Recreation
Exercise and movement
Breath
Vital Force, vital reserve, energy
Structural integrity

Socio-economic factors
Loving and being loved
Meaningful work
Culture
Community
Government/public policy
Environment
Income and economic
Health care (quality and access)
Education

From Snider P, Zeff J, Myers S, DeGrandpre Z, et al. Course syllabus: NM5114, Naturopathic Clinical Theory. Seattle: Bastyr University, 1997-2012.

BOX 3-7 Scientific Considerations: Subclinical Inflammation and Chronic Illness

It is becoming increasingly evident that many chronic diseases may have a long subclinical phase, most involving the inflammatory process. As mentioned, a chronic, subclinical inflammatory state has been linked to a number of disorders, including insulin resistance,[104] obesity,[105] vascular disease,[106-109] hypertension,[110] and aging.[111]

BOX 3-8 Scientific Considerations: Determinants of Health within Public and Community Health Concerns

There exists increasing consensus that Crohn's disease and ulcerative colitis result from the combined effects of four important factors, none of which are individually sufficient to cause the disease. These four factors are the global changes in the environment, alterations in the microbiome of the intestine, multiple genetic factors, and aberrations or maladaptations in both the innate and adaptive immune systems.[114-117] These four factors, considered to be vital to the development and the increased rates of irritable bowel disease, are quite similar to the Determinant of Health described in Box 3-6. This serves as a further example of the growing appreciation for the similarities (with important differences) between naturopathic medicine and public and community health.

Acute and Chronic Concerns

As discussed previously, there is an inherent drive toward health that is observable within the patterns and processes of nature. The drive is not perfect. There are times when unguided, unassisted, or unstopped, the drive goes astray, causing preventable harm or even death in patients; the constructive healing intention[119] becomes destructive pathology. The ND is trained to know, respect, and work with this drive in both acute and chronic illness, using the therapeutic order, and to know when to wait or do nothing, act preventively, assist, amplify, palliate, intervene, manipulate, control, or even suppress using the principle of the least force.[120] Acute and chronic concerns are both addressed and managed using the therapeutic order.[121] Acute concerns are addressed first to avoid further damage, risk, or harm to the patient. The point of entry for assessment and therapy is dependent on each patient's need for effective, safe care, healing, and prevention of suffering and degeneration.[64,121]

Naturopathic physicians avoid suppression of symptoms in acute circumstances unless necessary for patients' well-being and safety. Instead, wherever possible, therapies for acute concerns use the least force (minimizing toxic side effects, suppression of natural functions, and physiologic burdens) available to intervene effectively, healing or palliating as needed. The full range of modalities from nutrition to homeopathy, botanical and physical medicine, hydrotherapy, counseling, prescriptive medication, and surgery are available to the patient as the naturopathic physician works to apply the least force in providing effective preventive, acute, and chronic care.[121]

Establish the Conditions for Health

Identify and Remove Disturbing Factors

If one understands health to be the natural state and "disturbance" the original culprit, then identifying and reducing disturbance is the obvious first step, unless there is immediate danger to life or limb, in which case acting to reduce suffering and preserve life or limb is paramount. In most chronic disease, neither is immediately threatened. This understanding dictates the primary treatment goal the physician must attend to: the identification and amelioration of those factors disturbing health, especially factors that most disturb health (inappropriate diet, excessive stress, and spiritual disharmony). To understand what disturbs health, one must understand what determines health. The naturopathic physician evaluates a patient with reference to the determinants of health to discover wherein the patient's health is disturbed. In this step, the physician is essentially removing the obstacles to cure and allowing the vis medicatrix naturae to do its work.

Among these many possibilities, in general, the most significant are attitude diet, digestion, psychological and other stressers, and what might be called "spiritual integrity." Humans have a transpersonal dimension and can be seen as spiritual beings. Spirit here is not defined by religion or belief in a deity or deities; it is that component of the individual that gives rise to their inner compass, their "joie de vivre" and their internal meaning of life, their core beliefs, and their values. Perceived in this way, it can be seen that many people in society are experiencing "spiritual crises."[86] Although the general purview of the physician is the body, that instrument cannot be separated from the spirit that animates it. If the spirit is disturbed, the body cannot be fundamentally healthy. Hahnemann, the brilliant and insightful founder of homeopathy, instructed physicians to attend to the spirit.[122] Disturbance in the spirit permeates the body and eventuates in physical manifestation. Physicians are responsible

BOX 3-9 The Therapeutic Order: Hierarchy of Healing

1. **Establish the conditions for health**
 - Identify and remove disturbing factors
 - Institute a more healthful regimen
2. **Stimulate the healing power of nature *(vis medicatrix naturae):* the self-healing processes**
3. **Address weakened or damaged systems or organs**
 - Strengthen the immune system
 - Decrease toxicity
 - Normalize inflammatory function
 - Optimize metabolic function
 - Balance regulatory systems
 - Enhance regeneration
 - Harmonize with your life force[1]
4. **Correct structural integrity**
5. **Address pathology: Use specific natural substances, modalities, or interventions**
6. **Address pathology: Use specific pharmacologic or synthetic substances**
7. **Suppress or surgically remove pathology**

The actual therapeutic order may change, depending on the individual patient's needs for safe and effective care. The needs of the patient are primary in determining the appropriate approach to therapy.

Acute and chronic concerns are both addressed using the therapeutic order.[121] Acute concerns are addressed first to avoid further damage, risk, or harm to the patient. The point of entry for assessment and therapy is dependent on each patient's need for effective, safe care, healing, and prevention of suffering or degeneration.[1,121]

From Zeff J, Snider P. Course syllabus: NM5131, Naturopathic clinical theory. Seattle: Bastyr University, 1997-2005.

for perceiving such disturbances and addressing them. At colleges of naturopathic medicine in Australia, the United Kingdom, and North America, faculty work with naturopathic medicine students to develop their ability to perceive the spiritual nature of an individual as a foundational skill in addressing the spiritual crises or fundamental needs that have a profound effect on health and well-being. Using this definition, both atheists and agnostics can be seen to have a spiritual aspect. This definition also removes spirituality from religiosity in a way that does not denigrate any individual religious belief a patient may hold, allowing the naturopathic clinician to explore this aspect of the individual.

One of the oldest concepts in naturopathic medicine is the concept of toxemia. Toxemia is the generation and accumulation of metabolic wastes and exogenous toxins within the body. These toxins may be the results of maldigestive processes, intermediate metabolites, environmental xenobiotics, colon bacterial metabolites, etc. These toxins become irritants within the body, resulting in the inflammation of tissues and the ultimate interference with normal biochemical processes.[123] The maldigestive and dysbiotic[124,125] origin of these internally and externally derived toxins is the result of an inappropriate diet, broad spectrum antibiotics, and the effects of excessive stress on digestion.[126] Eating a diet that cannot be easily digested or that is out of appropriate nutrient balance for the individual results in the creation of metabolic toxins in the intestines.[124,125-127] Stress, causing the excessive secretion of cortisol and adrenalin, results in the decrease of blood flow to the digestive process, among other effects,[95-98,101] which decreases the efficient functioning of digestion and increases the tendency toward maldigestion, dysbiosis, and toxemia. Physicians can now easily measure the degree of toxemia in various ways (urinary indican or phenol[127]). The older concept of toxemia,[129,130] with scientific advances in its understanding[121,129] (Box 3-10), may now be productively combined with understanding of the newer concept of allostasis[95-98] and the historical[119,130] and re-emerging discussion on the inflammatory component of many, if not most, chronic diseases.* Spiritual disharmony, inappropriate diet, digestive disturbance, stress, and toxemia (leading to inflammation) are considered primary causes of chronic illness and must be addressed if healing is to occur. Beyond these, other disturbing factors must be discerned and addressed, whichever pertain to the individual patient.

Institute a Healthier Regimen

As a corollary of the first, once physicians have determined major contributing factors to illness, they construct a healthier regimen for the patient. Some disturbing factors can be eliminated, like inappropriate dietary elements.[82,83] Others are a matter of different choices or living differently.† The basics to consider are appropriate diet, appropriate rest and exercise, stress moderation, a healthy environment, and a good spiritual connection.

If this model is correct, these measures alone should result in enhanced health. The problem arises in knowing how to do these things. What is an appropriate diet? This is an area of considerable controversy. Physicians think about diet in many different ways. The goal of dietary improvement is to reduce the symptomatic consequences of the patient's diet and provide optimal nutrition to the patient. The point here, regardless of how this is done, is that it is central and essential for fundamental health improvement. If the diet is not correct, if digestion is not appropriate, if nutrition is not adequate, the patient cannot maximally improve, and the scene is potentially set for chronic inflammatory conditions and the re-setting of the adaptive allostatic and homeostatic set points. If the diet and digestion are appropriate, the basis for improvement in other areas is enhanced.

*References 104-106, 110, 111, 131-138.
†References 84, 85, 89, 90, 92, 94.

BOX 3-10 Scientific Considerations: Toxemia Today

Using conventional medical terminology, environmental, dietary, and lifestyle derived disorders are termed idiopathic environmental intolerances, multiple chemical sensitivities,[127,128,132,133] or sometimes oxidative stress disorders.[134-138] The terminology may be different, but it describes the same symptomatology. Environmental toxins accumulate, and chronic inflammation increases. These exogenous and endogenous toxins and the lack of exercise stress the system further. The ketogenic diet to control epilepsy may be considered one example of the successful application of diet to control symptoms.[103]

The same is true with these other fundamental elements, to which Lindlahr referred in the first element of his catechism, "return to nature": exercise, rest, dress, etc.[28] These have been expanded in the "determinants of health." They create the basis for improvement. What this really means is to change the "terrain," the conditions in which the disease has formed—not only to change but to improve the conditions so that there is less basis for the disease. Hahnemann addresses this on the first page of his *Organon of Medicine*.[122] He identified four tasks for the physician: to understand the true nature of illness, "what is to be cured"; to understand the healing potential of medicines; to understand obstacles to recovery and how to remove them; and to understand the elements that derange health and how to correct them so that recovery may be permanent.[122] Changing and improving the terrain in which the disease developed is the obvious first step in bringing about improvement. This sets up the basis for the following elements to have the most beneficial effects.

Stimulate the Self-Healing Mechanisms

A certain percentage of patients improve sufficiently simply by removing disturbing factors and establishing a healthier regimen. Most require more work. Once the patient is prepared, once the terrain is beginning to clear of disturbing factors, then one begins to apply stimulation to the self-healing mechanisms. The basis of this approach is the underlying recognition of the vis medicatrix naturae, the tendency of the body to be self-healing, the wisdom and intelligence within the system that constantly tends toward the healthiest expression of function, and the healing "forces" in the natural environment (air, water, light, etc.). The body heals itself. The physician can help create the circumstances to promote this. Then, as necessary, the physician stimulates the system. This also requires that attention be given to the patient's emotional state of mind, because the psychological condition of the patient is often of major importance.[140,141]

One of the best ways to do this is through constitutional hydrotherapy, as developed by Otis G. Carroll, ND, early in the past century. This procedure is simple, involving the placement of hot and then cold towels on the trunk and back, in specific sequence (depending on the patient), usually accompanied by a sine wave stimulation of the digestive tract. This is a dynamic treatment, simple, inexpensive, and universally applicable. It helps recover digestive function, stimulates toxin elimination, "cleans the blood," enhances immune function, and has several other effects. It moves the system along toward a healthier state.[142] Exercise

often achieves similar results. Many naturopathic modalities can be used to stimulate the overall vital force.

More specific approaches to stimulation, although general in effect, are applied differently to each patient and have a less general effect than those previously mentioned. Homeopathy and acupuncture[143-145] are often the primary methods of such stimulation. They add little to the system; they are not gross chemical treatments. They work with what is there, stimulating a reaction, stimulating function, and correcting disturbed patterns.

Each method helps move the system out of its disturbed state and, with the reduction of encumbrance, helps move it toward health.

Finally, exposure to the patterns, rhythms, and forces of nature is a traditional part of naturopathic medicine and the tradition of nature doctors throughout the world. As previously noted, "We exist as part of complex patterns of matter, energy, and spirit,"[1] and the natural progression of these patterns and the drive toward health inherent in them, is a natural ally for the physician. Exposure to appropriate rhythms, patterns, and forces of nature strengthens vitality and stimulates the healing power of nature.

Support Weakened or Damaged Systems or Organs

Some systems or functions require more than stimulation to improve. Some organs are weakened or damaged (e.g., adrenal fatigue after prolonged stress), and some systems are blocked or congested (e.g., the hepatic detoxification pathways) and require extra help. This is where naturopathic physicians use their vast natural medicinary. Botanical medicines can affect any system or organ, enhancing its function, improving its circulation, providing specific nutrition, and stimulating repair. Glandular substances can be applied to a similar purpose. Plus, there are the growing number of evidence-based "nutraceuticals"—biological compounds that enhance metabolic pathways and provide substance for metabolic function.[146-157]

Naturopathic physicians can also apply specific homeopathic medications, usually in the lower potencies, which act nutritively and can stimulate specific organs or functions. This method, generally referred to as drainage, can be used to stimulate detoxification of specific substances from the body in general or of specific organ systems or tissues. Dr. Pizzorno's work in *Total Wellness*,[158] the work of "functional medicine" leader Jeffrey Bland, PhD, and the *Textbook of Functional Medicine* by Jones[120] exemplify the clinical strategies applied at this level of the therapeutic order. These strategies are used to restore optimal function to an entire physiologic system (immune, cardiovascular, detoxification, life force, endocrine).[158]

One can also use specific exercises to stimulate or enhance organ health. Some systems of Yoga and Qi Gong are organ specific. Specific applications of hydrotherapy and other physiotherapy systems can be applied to enhance the function of organs or tissues.

It has been the clinical experience of many naturopathic physicians that these methods, combined with an appropriate diet and a healthier regimen, along with constitutional hydrotherapy, appropriate homeopathy, and acupuncture, bring most health problems back to normal, without negative consequence, rapidly, efficiently, and permanently.

Address Structural Integrity

Many structural problems result from generalized stress of some kind on internal systems. For example, mid-back misalignment or discomfort (T1–T12) is often found associated with a history of underlying stress on the digestive organs, the enervation of which originates at those spinal segments. One can manipulate the vertebra back into proper alignment or massage contracted musculature, but until one corrects the underlying functional disturbance, there will be a tendency to repeated structural misalignment. In some circumstances, the singular problem may be simply structural disintegrity. One may have fallen or been hit in some fashion and simply needs the neck manipulated back into proper alignment and the surrounding soft tissue relaxed. There may be no dietary error or other disturbance aside from the original injury, and correction requires only simple manipulation or therapeutic massage. This is an example of the flexibility of the therapeutic order concept. In this case, first-order therapeutics manipulate the cervical spine or relax chronically contracted muscles. Usually, however, the problem of structure is part of the larger problem, and such intervention becomes a fourth-order therapeutic.[64]

Reintegrating structure can occur in many ways, one of which is the method of "bone cracking" known to the ancient Greeks and Chinese and probably all other ancient healing cultures. However, there are nonforce manipulative systems that include many modalities of therapeutic massage. Some systems of exercise are designed to reintegrate and maintain normal structural relationships. Any of these might be appropriate to a specific patient. By approaching the problem in the context of the therapeutic order, one can expect structural corrections to be required only occasionally and for the results to be more or less permanent.

Address Pathology: Use Specific Natural Substances, Modalities, or Interventions

Having gone through the first four steps of this therapeutic hierarchy, most patients improve. The improvement is based on the sound footing of the underlying correction or removal of fundamental causative elements. It is also based on the intrinsic nature of the body to heal itself using the least possible force. Most pathology improves or disappears under these circumstances. Sometimes it is necessary to address pathology. This may be the case because the particular pathology may be threatening to life or limb. Acting on this threat is imperative. It can be done often with naturopathic means, directed specifically against the pathology. Biochemical or genetic individuality also can demand an emphasis at this level of intervention.

One of the major conflicts in naturopathic medicine is that some practitioners find it expedient to diagnose and treat pathology (the standard medical model) rather than pursue a naturopathic model of practice. This approach tends to be less satisfying and less productive of the most elegant outcomes and the long-term continued health of the patient. It also reduces the capacity of the physician to treat, such as in cases where there is no evidence-based treatment for the pathology in question, or where there is no clear diagnosis (i.e., no distinct pathology to treat). This approach is increasingly referred to as "green allopathy." However, the vast body of knowledge that naturopathic education presents in this arena makes such an approach seductive, especially in a culture that more or less expects, supports, reinforces, and pays for an "allopathic" approach to diagnosis and treatment.

It is easy to do this. The culture is accustomed to this model and often expects to encounter this in the naturopathic physician's office. In some states, such as Oregon, Washington, and Arizona, where the naturopathic formulary includes most antibiotics and many pharmaceutical drugs, one can practice almost without distinction from a medical doctor. The typical naturopathic formulary is often sufficient to prescribe on a strictly pathologic basis.

The problem with this is that it is generally not as effective, especially in the treatment of chronic disease. The value of naturopathic medicine in our culture is not that naturopathic physicians can function almost like medical doctors, with a "natural" formulary instead of drugs. It is that they offer a fundamentally different approach, one based on the restoration of health rather than the treatment of disease.

Given all of this, it still may be useful to directly address the pathologic entity or its etiology.[159-163] When treating an antibiotic-resistant infection, for example, it may be useful to apply botanical medicines with specific antibiotic properties, along with immune tonics and the more fundamental steps of this therapeutic hierarchy. In difficult cases, such as many cancers, using agents that have specific, pathology-based therapeutics may be an essential element of comprehensive treatment. The naturopathic formulary provides a vast and increasing number of such options. One advantage of such treatment is that, in general, when applied by a knowledgeable practitioner, it rarely adds more burden or toxicity to the system. Naturopathic pathology-based treatments still follow the dictum "do no harm."

Address Pathology: Use Specific Pharmacologic or Synthetic Substances

About 800,000 medical doctors and osteopathic physicians in the United States are trained in the science of pathologic-based treatment, using pharmaceuticals and surgery, etc. There are times when such an approach is necessary to preserve life, limb, or function. Although some naturopathic physicians, by training and by statute, may prescribe pharmaceuticals or perform minor office procedures and surgeries, naturopathic physicians may also refer patients in need of such services to appropriate medical doctors or osteopaths. In a growing number of states, NDs can legally provide an expanding range of prescription drugs. Although this is an important tool for the naturopathic primary caregiver, this privilege requires enhanced responsibility for the ND to prescribe those substances only as needed—and to thoroughly rely on applying the least force appropriate to effect recovery and protect patient safety. Both Dr. Lust (at the end of his life) and Dr. Bastyr recognized the need for NDs to have the ability to access, as needed, prescriptive medications and perform minor office procedures to function as primary caregivers. However, both admonished that the philosophy and principles of the medicine guide their judicious use—only as truly needed, based on the least force necessary to restore the patient to health.

Naturopathic physicians are well trained in this regard and respect the necessity and utility of standard medical practice in appropriate situations. Some disagreement exists regarding which situations may be appropriate. The AANP developed position papers to resolve some of these questions.

In general, although recognizing the necessity of such treatment, most naturopathic physicians also recognize that such treatment often carries consequences that also must be addressed.

Suppress Pathology

Sometimes it is necessary when there is risk of harm to the patient's health or tissue, or to relieve suffering, to suppress pathology. Medical doctors are especially trained in this art and have powerful and effective tools with which to do this. Unfortunately, suppression, because it does not fundamentally remove or address essential causative factors (such as dietary error) often results in the development of other, often deeper disturbance or pathology. Because much pathologic expression is the result of the actual self-healing mechanisms (e.g., inflammation), suppressive measures are, in general, anti–vis medicatrix naturae. The result of suppression is that the fundamental disturbing factors are still at play within the person, still disrupting function to some extent, whereas the suppression reduces the symptomatic expression and resolution of disturbance. One simple example of this is the over use of corticosteroidal anti-inflammatory and antihistaminic drugs in the treatment of acute asthma. This usually effectively opens the airways. However, prolonged use weakens the patient. If the treatment persists, the patient becomes immune compromised and osteoporotic and can develop psychological disorders. These symptoms are part of the long-term effects of steroids.[74] It may necessarily maintain breathing, but the long-term cost to the organism is high.

Suppression, although it may be life saving, often has serious consequences. With standard medical methods of care, cure of chronic illness is often elusive. This is the benefit of the naturopathic approach: by taking a nonsuppressive course of action, based on sound physiologic principles, one can often restore health without recourse to the potential damage of suppression. Naturopathic physicians, although recognizing the occasional necessity of suppressive approaches, in general avoid suppression, which is a primary way in which physicians can inflict harm, even with the best of intentions.

THEORY IN NATUROPATHIC MEDICINE

This therapeutic hierarchy is based on the observation of the nature of healing and the inherent order of the healing process. It is part of a unifying theory of naturopathic medicine, an outgrowth of the principles that underlie naturopathic thinking. It provides the physician with instructions that order the many therapeutic modalities used by the practice.

The consensus definition of naturopathic medicine, adopted by the AANP in 1989, is a statement of identity, distinguishing naturopathic medicine from other systems of medical thought. Contained within it is a set of instructions regarding the practice of the medicine. The three concepts discussed here—"disease as process," "the determinants of health," and "the therapeutic order"—are an articulation of these instructions. They are presented as a clinical theory of naturopathic medicine. They have been crystallized, as is the definition, from the observation by nature doctors throughout time and across many traditions of the nature of health, disease, and healing. They provide the physician with instructions. These instructions include a procedure for thinking about human illness in such a way that one can approach its cure in an ordered fashion by understanding its process as an expression of the vis medicatrix naturae. It provides the framework for truly evaluating the patient as a whole being: spiritual, mental/emotional, and physical, rather than as a category of pathology. Plus, it provides the physician a system for organizing and efficiently integrating the vast therapeutic array provided in naturopathic medicine. Ultimately, it satisfies Hahnemann's observation of the ideal role of medicine, that "the highest ideal of cure is rapid, gentle and permanent restoration of the health … in the shortest, most reliable and most harmless way, upon easily comprehensible principles."[122] The roots of the observations that form this theory are traceable through the mid- and early-twentieth century, to the traditional theory of nineteenth-century European nature cure, and to the roots and theories of traditional world

medicines. Hippocrates' writings on the vis medicatrix naturae form a foundation that historically underpins the development of this theory.[164,165]

Finally, it is observable across many traditional world medicines that various healing orders are described. Such structures hold implications for public and community health priorities and suggest the reprioritization of health care priorities and financing. Implications for public policy and the growing national disease debt invite exploration.

Although this presentation is not comprehensive, the attempt has been made to demonstrate these roots, at least in some of their major articulations. The work presented here is a continuation of this historical process, which ultimately is driven by the true mission of the physician: to ease suffering and to preserve life.

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CHAPTER 4

The History of Naturopathic Medicine: The Emergence and Evolution of an American School of Healing

George W. Cody, JD, MA and Heidi Hascall, MA

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INTRODUCTION

Naturopathy, as a generally used term, emerged in America from the writings and promotion of Benedict Lust. Naturopathy, or "nature cure," is both a way of life and a concept of healing that employs various natural means of treating human infirmities and disease states. The earliest mechanisms of healing associated with the term, as used by Lust, involved a combination of hygienics and hydropathy (hydrotherapy). The term itself was coined in 1895 by Dr. John Scheel of New York City to describe his method of health care. However, earlier forerunners of these concepts already existed in the history of natural healing, both in America and in the Austro-Germanic European core.

Lust came to this country from Germany in the 1890s as a disciple of Father Sebastian Kneipp, a Dominican priest, and as an emissary dispatched by Father Kneipp to bring hydrotherapy to America. Lust purchased the term "naturopathy" from Scheel in 1902 to describe the eclectic compilation of doctrines of natural healing that he envisioned to be the future of natural medicine. In January 1902, Lust, who had been publishing the *Kneipp Water Cure Monthly* and its German language counterpart in New York since 1896, changed the name of the journal to *The Naturopath and Herald of Health* and evoked the dawn of a new health care era with the following editorial:

> *Naturopathy is a hybrid word. It is purposely so. No single tongue could distinguish a system whose origin, scope and purpose is universal—broad as the world, deep as love, high as heaven. Naturopathy was not born of a sudden or a happen-so. Its progenitors have for eons been projecting thoughts and ideas and ideals whose culminations are crystallized in the new Therapy. Connaro, doling out his few fixed ounces of food and drink each day in his determined exemplification of Dietotherapy; Priessnitz, agonizing, despised and dejected through the long years of Hydropathy's travail; the Woerishofen priest, laboring lovingly in his little parish home for the thousands who journeyed Germany over for the Kneipp cure; Kuhne, living vicariously and dying a martyr for the sake of Serotherapy; A.T. Still, studying and struggling and enduring for his faith in Osteopathy; Bernarr Macfadden, fired by the will to make Physical Culture popular; Helen Willmans, threading the mazes of Mental Science, and finally emerging triumphant; Orrison Sweet Maraden, throbbing in sympathy with human faults and failures, and longing to realize Success to all mankind—these and hosts of others have brought into being single systems whose focal features are perpetuated in Naturopathy.*
>
> *Jesus Christ—I say it reverently—knew the possibility of physical immortality. He believed in bodily beauty; He founded Mental Healing; He perfected Spirit-power. And Naturopathy will include ultimately the supreme forces that made the Man of Galilee omnipotent.*
>
> *The scope of Naturopathy is from the first kiss of the new-found lovers to the burying of the centenarian whose birth was the symbol of their perfected one-ness. It includes ideally every life-phase of the id, the embryo, the foetus, the birth, the babe, the child, the youth, the man, the lover, the husband, the father, the patriarch, the soul.*
>
> *We believe in strong, pure, beautiful bodies thrilling perpetually with the glorious power of radiating health. We want every man, woman and child in this great land to know and embody and feel the truths of right living that mean conscious mastery.*

We plead for the renouncing of poisons from the coffee, white flour, glucose, lard, and like venom of the American table to patent medicines, tobacco, liquor and the other inevitable recourse of perverted appetite. We long for the time when an eight-hour day may enable every worker to stop existing long enough to live; when the spirit of universal brotherhood shall animate business and society and the church; when every American may have a little cottage of his own, and a bit of ground where he may combine Aerotherapy, Heliotherapy, Geotherapy, Aristophagy and nature's other forces with home and peace and happiness and things forbidden to flat-dwellers; when people may stop doing and thinking and being for others and be for themselves; when true love and divine marriage and pre-natal culture and controlled parenthood may fill this world with germ-gods instead of humanized animals.

In a word, Naturopathy stands for the reconciling, harmonizing and unifying of nature, humanity and God.

Fundamentally therapeutic because men need healing; elementally educational because men need teaching; ultimately inspirational because men need empowering, it encompasses the realm of human progress and destiny.

Perhaps a word of appreciation is due Mr. John H. Scheel, who first used the term "Naturopathic" in connection with his Sanitarium "Badekur," and who has courteously allowed us to share the name. It was chosen out of some 150 submitted, as most comprehensive and enduring. All our present plans are looking forward some five or ten or fifty years when Naturopathy shall be the greatest system in the world.

Actually the present development of Naturopathy is pitifully inadequate, and we shall from time to time present plans and ask suggestions for the surpassing achievement of our world-wide purpose. Dietetics, Physical Culture and Hydropathy are the measures upon which Naturopathy is to build; mental culture is the means, and soul-selfhood is the motive.

If the infinite immensity of plan, plea and purpose of this particular magazine and movement were told you, you would simply smile in your condescendingly superior way and straightway forget. Not having learned as yet what a brain and imagination and a will can do, you consider Naturopathy an ordinarily innocuous affair, with a lukewarm purpose back of it, and an ebbing future ahead of it. Such is the character of the average wishy-washy health movement and tumultuous wave of reform.

Your incredulous smile would not discomfit us—we do not importune your belief, or your help, or your money. Wherein we differ from the orthodox self-labeled reformer, who cries for sympathy and cringes for shekels.

We need money most persistently—a million dollars could be used to advantage in a single branch of the work already definitely planned and awaiting materialization; and we need co-operation in a hundred different ways. But these are not the things we expect or deem best.

Criticism, fair, full and unsparing is the one thing of value you can give this paper. Let me explain. Change is the keynote of this January issue—in form, title, make-up. If it please you, your subscription and a word to your still-benighted friends is ample appreciation. But if you don't like it, say so. Tell us wherein the paper is inefficient or redundant or ill-advised, how it will more nearly fit into your personal needs, what we can do to make it the broadest, deepest, truest, most inspiring of the mighty host of printed powers. The most salient letter of less than 300 words will be printed in full, and we shall ask to present the writer with a subscription-receipt for life.

By to-morrow you will probably have forgotten this request; by the day after you will have dropped back into your old ways of criminal eating and foolish drinking and sagged standing and congested sitting and narrow thinking and deadly fearing—until the next progress paper of New Thought or Mental Science or Dietetics or Physical Culture prods you into momentary activity.

Between now and December we shall tell you just how to preserve the right attitude, physical and mental, without a single external aid; and how, every moment of every day, to tingle and pulsate and leap with the boundless ecstasy of manhood consciously nearing perfection.



A BRIEF HISTORY OF EARLY AMERICAN MEDICINE WITH AN EMPHASIS ON NATURAL HEALING

To understand the evolutionary history of naturopathic medicine in this country, it is necessary to view the internal development of the profession against the historical, social, and cultural backdrop of American social history.

Medicine in America: 1800–1875

In the America of 1800, although a professional medical class existed, medicine was primarily domestically oriented. An individual who fell ill was commonly nursed by a friend or family member who relied upon William Buchan's *Domestic Medicine* (1769), John Wesley's *Primitive Physic* (1747), or John Gunn's *Domestic Medicine* (1830).[1]

Professional Medicine

Professional medicine transferred from England and Scotland to America in pre-revolutionary days. However, eighteenth and early nineteenth century America considered the concept of creating a small, elite, learned profession to run counter to the political and institutional concepts of early American democracy.[1]

The first medical school in the American colonies opened in 1765 at what was then the College of Philadelphia (later the University of Pennsylvania), and the school was dominated by revolutionary leader and physician Benjamin Rush, a signatory to the Declaration of Independence. The proliferation of medical schools to train the new professional medical class began seriously after the war of 1812. Between 1810 and 1820, new schools were established in Baltimore, Lexington, Cincinnati, and even in rural communities in Vermont and Western New York. Between 1820 and 1850 a substantial number of schools were established in the western rural states. By 1850, there were 42 medical schools recognized in the United States, although there were only three in all of France.

Generally, these schools were started by a group of five to seven local physicians approaching a local college with the idea of establishing a medical school in conjunction with the college's educational facilities. The schools were largely apprenticeship based, and the professors received their remuneration directly from fees paid by the students.

The requirements for a Doctor of Medicine (MD) degree in late eighteenth and early nineteenth century America were roughly as follows:

- Knowledge of Latin and natural and experimental philosophy
- Three years of serving an apprenticeship under practicing physicians

- Attending two terms of lectures and passing of attendant examinations
- A thesis

Graduating students had to be at least 21 years of age.[1]

The rise of any professional class is gradual and marked by difficulties, and varying concepts existed as to the demarcation of a "professional" physician. Contrasts included graduates of medical school versus nongraduates, medical society members versus nonmembers, and licensed physicians versus unlicensed "doctors." Licensing statutes came into existence between 1830 and 1850, but were soon repealed, as they were considered "undemocratic" during the apex of Jacksonian democracy.[1]

Thomsonianism

In 1822 the rise in popularity of Samuel Thomson and his publication of *New Guide to Health* helped to frustrate the creation of a professional medical class. Thomson's work was a compilation of his personal view of medical theory and American Indian herbal and medical botanical lore. Thomson espoused the belief that disease had one general cause—"cold" influences on the human body—and that disease had therefore one general remedy—"heat." Unlike the followers of Benjamin Rush and the American "heroic" medical tradition who advocated blood-letting, leeching, and the substantial use of mineral-based purgatives such as antimony and mercury, Thomson believed that minerals were sources of "cold" because they came from the ground and that vegetation, which grew toward the sun, represented "heat."[1]

As noted in Griggs' *Green Pharmacy* (the best history of herbal medicine to date), Thomson's theory developed as follows[2]:

> *Instead, he elaborated a theory of his own, of the utmost simplicity: "All diseases … are brought about by a decrease or derangement of the vital fluids by taking cold or the loss of animal warmth … the name of the complaint depends upon what part of the body has become so weak as to be affected. If the lungs, it is consumption, or the pleura, pleurisy; if the limbs, it is rheumatism, or the bowels, colic or cholera morbus … all these different diseases may be removed by a restoration of the vital energy, and removing the obstructions which the disease has generated …"*
>
> *Thus the great object of his treatment was always to raise and restore the body's vital heat: "All … that medicine can do in the expulsion of disorder, is to kindle up the decaying spark, and restore its energy till it glows in all its wonted vigor."*

Thomson's view was that individuals could be self-treating if they had a sincere "guide to health" philosophy and a copy of his book, *New Guide to Health*. The right to sell "family franchises" for use of the Thomsonian method of healing was the basis of a profound lay movement between 1822 and Thomson's death in 1843. Thomson adamantly believed that no professional medical class should exist and that democratic medicine was best practiced by laypersons within a Thomsonian "family" unit.

By 1839, Thomson claimed to have sold some 100,000 of these family franchises called "friendly botanic societies." Although he professed to have solely the interests of the individual at heart, his system was sold at a profit under the protection of a patent he obtained in 1813.

The Eclectic School of Medicine

Some of the "botanics" (professional Thomsonian doctors) wanted to separate themselves from the lay movement by creating requirements and standards for the practice of Thomsonian medicine. Thomson, however, was adamantly against a medical school founded on his views. Thus, it was not until the decade after Thomson's death that independent Thomsonians founded a medical college (in Cincinnati) and began to dominate the Thomsonian movement. These Thomsonian botanics were later absorbed into the medical sectarian movement known as the "eclectic school," which originated with the New Yorker Wooster Beach.

Beach was another of medical history's fascinating characters. From a well-established New England family, he started his medical studies at an early age, apprenticing under an old German herbal doctor, Jacob Tidd. After Tidd died, Beach enrolled in the Barclay Street Medical University in New York. Griggs[2] described the following:

> *Beach's burning ambition was to reform medical practice generally—not to alienate the entire profession by savage attacks from without—and he was convinced that he would be in a stronger position to do so if he were himself a diplomatized doctor. The faculty occasionally listened to criticism from within their own number: against onslaughts of "illiterate quacks" like Samuel Thomson, they simply closed ranks in complacent hostility.*

After opening his own practice in New York, Beach set out to win over fellow members of the New York Medical Society (into which he had been warmly introduced by the screening committee) to his point of view that heroic medicine was inherently dangerous to mankind and should be reduced to the gentler theories of herbal medicine. He was summarily ostracized from the medical society.

To Beach this was a bitter blow, but he soon founded his own school in New York, calling the clinic and educational facility "The United States Infirmary." However, due to continued pressure from the medical society, he was unable to obtain charter authority to issue legitimate diplomas. He then located a financially ailing but legally chartered school, Worthington College, in Ohio. He opened a full-scale medical college; out of its classrooms he launched what became known as the *Eclectic School of Medical Theory.* Griggs related the following[2]:

> *Beach had a new name for his practice: While explaining to a friend his notions of combining what was useful in the old practice with what was best in the new, the friend exclaimed, "You are an eclectic!" to which, according to legend, Beach replied, "You have given me the term which I have wanted: I am an eclectic!"*

Cincinnati subsequently became the focal point of the eclectic movement, and the E. M. Institute medical school remained until 1938 (the last eclectic school to exist in America).[3] The concepts of this sect helped to form some of the theoretical underpinnings of Lust's naturopathy. Lust himself graduated from the Eclectic Medical College of the City of New York in the first decade of the 1900s.

Despite his criticism of the early allopathic movement (although the followers of Rush were not as yet known by the term "allopath," reputed to have been coined by Samuel Hahnemann) for their "heroic" tendencies, Thomson's medical theories were "heroic" in their own fashion. Although he did not advocate blood-letting, heavy metal poisoning, and leeching, botanic purgatives—particularly *Lobelia inflata* (Indian tobacco)—were a substantial part of the therapy.

The Hygienic School of Thought

One other forerunner of American naturopathy, also originating as a lay movement, grew into existence at this time. This was the "hygienic" school, which had its genesis in the popular teachings of Sylvester Graham and William Alcott.

Graham began preaching the doctrines of temperance and hygiene in 1830. In 1839, he published *Lectures on the Science of Human Life*, two hefty volumes that prescribed healthy dietary habits. He emphasized a moderate lifestyle, recommending an anti-flesh diet and bran bread as an alternative to bolted or white bread.

Alcott dominated the scene in Boston during this same period and, together with Graham, saw that the American hygienic movement—at least as a lay doctrine—was well established.[4]

Homeopathy

By 1840, the profession of homeopathy had also been transplanted to America from Germany. Homeopathy, the creation of an early German physician, Samuel Hahnemann (1755–1843), had three central doctrines:

- The "law of similars" (that like cures like)
- That the effect of a medication could be heightened by its administration in minute doses (the more diluted the dose, the greater the "dynamic" effect)
- That nearly all diseases were the result of a suppressed itch, or "psora"

The view was that a patient's natural symptom-producing disease would be displaced after homeopathic medication by a similar, but much weaker, artificial disease that the body's immune system could easily overcome.

Originally, most homeopaths in this country were converted orthodox medical men, or "allopaths." The high rate of conversion made this particular medical sect the archenemy of the rising orthodox medical profession. (For a more detailed discussion of homeopathy, see Chapter 39.)

The first homeopathic medical school was founded in 1850 in Cleveland; the last purely homeopathic medical school, based in Philadelphia, survived into the early 1930s.[1]

The Rise and Fall of the Sects

Although these two nonallopathic sects were popular, they never comprised more than one fifth of the professional medical class in America. Homeopathy at its highest point reached roughly 15%, and the eclectic school roughly 5%. However, their very existence for many years kept the exclusive recognition desired by the orthodox profession from coming within its grasp. Homeopathy was distasteful to the more conventional medical men not only because it resulted in the conversion of a substantial number of their peers, but also because homeopaths generally also made a better income. The rejection of the eclectic school was more fundamental: it had its roots in a lay movement that challenged the validity of a privileged professional medical class.

The existence of three professional medical groups—the orthodox school, the homeopaths, and the eclectics—combined with the Jacksonian view of democracy that prevailed in mid-nineteenth century America, resulted in the repeal of virtually all medical licensing statutes existing before 1850. However, by the 1870s and 1880s, all three medical groups began to voice support for the restoration of medical licensing.

Views differ as to what caused the homeopathic and eclectic schools to disappear from the medical scene in the 50 years after 1875. One view defined a sect as follows[5]:

> *A sect consists of a number of physicians, together with their professional institutions, who utilize a distinctive set of medically invalid therapies which are rejected by other sects …*

By this definition, the orthodox or allopathic school was just as sectarian as the homeopathic and eclectic schools. Rothstein's view was that these two nineteenth century sects disappeared because, beginning in the 1870s, the orthodox school grasped the European idea of "scientific medicine." Based on the research of such men as Pasteur and Koch and the "germ theory," this approach supposedly proved to be the medically proper view of valid therapy and gained public recognition because of its truth.

Another view was that the convergence of the needs of the three sects for professional medical recognition (which began in the 1870s and continued into the early 1900s) and the "progressive era" led to a political alliance in which the majority orthodox school was ultimately dominant by sheer weight of numbers and internal political authority. Starr[1] noted the following:

> *Both the homeopaths and eclectics wanted to share in the legal privileges of the profession. Only afterward did they lose their popularity. When homeopathic and eclectic doctors were shunned and denounced by the regular profession, they thrived, but the more they gained an access to the privileges of regular physicians, the more their numbers declined. The turn of the century was both the point of acceptance and the moment of incipient disintegration …*

In any event, this development was an integral part of the drive toward professional authority and autonomy established during the progressive era (1900–1917). It was acceptable to the homeopaths and the eclectics because they controlled medical schools that continued to teach and maintain their own professional authority and autonomy. However, it was after these professional goals were attained that the lesser schools of medical thought went into rapid decline.[1]

The American Influence

From 1850 to 1900, the medical counterculture continued to establish itself in America. From its lay roots in the teachings of the hygienic movement grew professional medical recognition, albeit a small minority and "irregular" view, that hygiene and hydropathy were the basis of sound medical thought (much like the Thomsonian transition to botanic and eclectic medicine).

Trall

The earliest physician who had a significant impact on the later growth of naturopathy as a philosophical movement was Russell Trall, MD. As noted in James Whorton's *Crusaders for Fitness*,[4] he "passed like a meteor through the American hydropathic and hygienic movement":

> *The exemplar of the physical educator-hydropath was Russell Thatcher Trall. Still another physician who had lost his faith in regular therapy, Trall opened the second water cure establishment in America, in New York City in 1844. Immediately he combined the full Preissnitzian armamentarium of baths with regulation of diet, air, exercise and sleep. He would eventually open and or direct any number of other hydropathic institutions around the country, as well as edit the Water-Cure Journal, the Hydropathic Review, and a temperance journal. He authored several books, including popular sex manuals which perpetuated Graham-like concepts into the 1890's, sold Graham crackers and physiology texts at his New York office, was a charter member (and officer) of the American Vegetarian Society, presided over a short-lived World Health Association, and so on. His crowning accomplishment was the Hygeian Home, a "model Health Institution [which] is beautifully situated on the Delaware River between Trenton and Philadelphia." A drawing presents it as a palatial establishment with expansive grounds for walking and riding, facilities for rowing,*

sailing, and swimming, and even a grove for open-air "dancing gymnastics." It was the grandest of water cures, and lived beyond the Civil War period, which saw the demise of most hydropathic hospitals. True, Trall had to struggle to keep his head above water during the 1860's, but by the 1870's he had a firm financial footing (being stabilized by tuition fees from the attached Hygeio-therapeutic College). With Trall's death in 1877, however, the hydropathic phase of health reform passed.

As evident later in this chapter, this plethora of activity was similar to that engaged in by Benedict Lust between 1896 and his death in 1945, when he worked to establish naturopathy. The Hygeian Home and later "Yungborn" establishments at Butler, New Jersey, and Tangerine, Florida, were similar to European nature cure sanitariums, such as the original Yungborn founded by Adolph Just and the spa/sanitarium facilities of Preissnitz, Kneipp, and Just.

Trall gave a famous address to the Smithsonian Institution in Washington, DC, in 1862, under the sponsorship of the Washington Lecture Association. "The true healing art: or hygienic vs drug medication," a 2.5-hour lecture purported to have received rapt attention, was devoted to Trall's belief in the hygienic system and in hydropathy as the true healing art. The address was reprinted by Fowler and Wells (New York, 1880) with an introduction written by Trall, before his death in 1877.

Trall also founded the first school of natural healing arts in this country to have a 4-year curriculum and the authorization to confer the degree of MD. It was founded in 1852 as a "hydropathic and physiological school" and was chartered by the New York State Legislature in 1857 under the name "New York Hygio-Therapeutic College," with the legislature's authorization to confer the MD degree.

In 1862, Trall went to Europe to attend the International Temperance Convention. He took a prominent part at this meeting of reformers, specifically related to the use of alcohol as a beverage and as a medicine. He eventually published more than 25 books on the subjects of physiology, hydropathy, hygiene, vegetarianism, and temperance, among many others.

The most valuable and enduring of these was his *Hydropathic Encyclopedia*, a volume of nearly 1000 pages that covered the theory and practice of hydropathy and the philosophy and treatment of diseases advanced by older schools of medicine. At the time of his death, according to the December 1877 *Phrenological Journal* cover article featuring a lengthy obituary of Trall, this encyclopedia had sold more than 40,000 copies since its original publication in 1851.

For more than 15 years, Trall was editor of the *Water-Cure Journal* (also published by Fowler and Wells). During this period, the journal went through several name changes, including the *Hygienic Teacher* and *The Herald of Health*. When Lust originally opened the American School of Naturopathy, an English-language version of *Kneipp's Water-cure* (or in German *Meine Wasser-kurr*) being unavailable, he used only the works and writings of Trall as his texts.

By 1871, Trall moved from New York to the Hygeian Home on the Delaware River. His water-cure establishment in New York became The New Hygienic Institute. One of its co-proprietors was Martin Luther Holbrook, who later replaced Trall as the editor of *The Herald of Health*. Professor Whorton noted the following[4]:

But Holbrook's greatest service to the cause was as an editor. In 1866 he replaced Trall at the head of The Herald of Health, which had descended from the Water-Cure Journal and Herald of Reforms (1845-1861) by the way of the Hygienic Teacher and Water-Cure Journal (1862). Under Holbrook's direction the periodical would pass through two more name changes (Journal of Hygiene Herald of Health, 1893-1897, and Omega, 1898-1900) before merging with Physical Culture.

Trall and Holbrook both advanced the idea that physicians should teach the maintenance of health rather than simply provide a last resort in times of health crisis. Besides providing a strong editorial voice espousing vegetarianism, the evils of tobacco and drugs, and the value of bathing and exercise, dietetics and nutrition, along with personal hygiene, were strongly advanced by Holbrook and others of the hygienic movement during this era. Whorton described the idea as follows[4]:

The orthodox hygienists of the progressive years were equally enthused by the recent progress of nutrition, of course, and exploited it for their own ends, but their utilization of science hardly stopped with dietetics. Medical bacteriology was another area of remarkable discovery, bacteriologists having provided, in the short space of the last quarter of the 19th century, an understanding, at long last, of the nature of infection. This new science's implications for hygienic ideology were profound—when Holbrook locked horns with female fashion, for example, he did not attack the bulky, ground-length skirts still in style with the crude Grahamite objection that the skirt was too heavy. Rather he forced a gasp from his readers with an account of watching a smartly dressed lady unwittingly drag her skirt "over some virulent, revolting looking sputum, which some unfortunate consumptive had expectorated."

Holbrook expanded on the work of Graham, Alcott, and Trall and, working with an awareness of the European concepts developed by Preissnitz and Kneipp, laid further groundwork for the concepts later advanced by Lust, Lindlahr, and others[4]:

For disease to result, the latter had to provide a suitable culture medium, had to be susceptible. As yet, most physicians were still so excited at having discovered the causative agents of infection that they were paying less than adequate notice to the host. Radical hygienists, however, were bent just as far in the other direction. They were inclined to see bacteria as merely impotent organisms that throve only in individuals whose hygienic carelessness had made their body compost heaps. Tuberculosis is contagious, Holbrook acknowledged, but "the degree of vital resistance is the real element of protection. When there is no preparation of the soil by heredity, predisposition or lowered health standard, the individual is amply guarded against the attack." A theory favored by many others was that germs were the effect of disease rather than its cause; tissues corrupted by poor hygiene offered microbes, all harmless, an environment in which they could thrive.

In addition to introducing the works of Kneipp and his teachings to the American hygienic health care movement, Holbrook was a leader of the fight against vivisection and vaccination[4]:

Vivisection and vaccination were but two of the practices of medicine criticized in the late 19th century. Therapy also continued to be an object of protest. Although the heroism of standard treatment had declined markedly since mid-century, a prescription was still the reward of any visit to the doctor, and drugless alternatives to healing were appearing in protest. Holbrook published frequent favorable commentaries on the revised water cure system of Germany's Kneipp. A combination of baths, herbal teas, and hardening exercises, the system had some vogue in the 1890's before flowering into naturopathy. Holbrook's journal also gave

positive notices to osteopathy and "chiropathy" [chiropractic], commending them for not going to the "drugstore or ransack[ing] creation for remedies nor load[ing] the blood with poison." But though bathing and musculoskeletal manipulation were natural and nonpoisonous, Holbrook preferred to give the body complete responsibility for healing itself. Rest and proper diet were the medicines of this doctor who billed himself as a "hygienic physician" and censured ordinary physicians for being engrossed with disease rather than health.

The Beginnings of "Scientific Medicine"

While the hygienic movement was making its impact, the orthodox medical profession, in alliance with the homeopaths and eclectics, was making significant advances. The orthodox profession, through the political efforts of the American Medical Association (AMA), first tried to remove sectarian and irregular practitioners by segregating them from the medical profession altogether. It did so by formulating and publishing its first national medical code of ethics in 1847. (In 1846 the orthodox profession formed the AMA to represent their professional views.) The code condemned proprietary patents (even carrying over into a physician's development of surgical or other medical implements, which led to its greatest criticism); encouraged the adoption of uniform rules for payment in geographic areas; condemned the practice of contract work; prohibited advertising and fee-sharing even among specialists and general practitioners; eliminated blacks and women; and, most significantly, prohibited any consultation or contact with irregulars or sectarian practitioners. The code stated the following[6]:

No one can be considered as a regular practitioner, or a fit associate in consultation, whose practice is based on an exclusive dogma, to the rejection of the accumulated experience of the profession, and of the aids actually furnished by anatomy, physiology, pathology, and organic chemistry.

In the late 1870s and into the 1880s, the major sects—the orthodox or allopathic school, the homeopaths, and the eclectics—began to find more reason to cooperate to obtain common professional goals. These included the enactment of new licensing laws and the creation of a "respectable" medical educational system. Also at this time, the concept of "scientific medicine" was brought to America. (Although Starr differed from Rothstein regarding the causes of the decline of the homeopathic and eclectic sectarian schools, he noted that Rothstein clearly documented the nineteenth century transition of medicine into a recognized professional class composed of both the minority sects and the orthodox school.)

This transition from conflict between the major sects resulted in the erosion of the implementation of the code of ethics, the cooperation among the sects to revive medical licensing standards, the admission of sectarian physicians to regular medical societies, and, ultimately, a structural reorganization of the AMA, which occurred between 1875 and 1903.[1,5]

Once the cooperation among the three medical views began, the medical class dominated by the regular school came fully into power. The homeopathic and eclectic schools of thought met their demise finally due to two significant events: (1) the rapid creation of new medical educational standards between 1900 and 1910, culminating in the publication of the famous "Flexner Report" (1910), and (2) the effective infusion of millions of dollars into selected allopathic medical schools by the newly created capitalistic philanthropic foundations, principally the Carnegie and Rockefeller foundations.

The Foundations

The impact of the monies from the Carnegie and Rockefeller foundations was clearly documented[7] and described in detail in Brown's *Rockefeller Medicine Men*.[8] The impact of the monies from these foundations, contributed to medical schools that met the AMA's views on medical education and philosophy, cannot be underestimated.

This process has been well documented.[1,7,9,10] As discussed by Burrows,[10] these educational reforms allowed the AMA to forge a new alliance with state legislators and push quickly for medical licensing designed to reward the educational and medical expertise of the newly orthodox "scientific medicine" and to the exclusion of all others.

Medical Education in Transition

Based on the rising example of scientific medicine and its necessary connection to research, the educational laboratory, and a more thorough scientific education as a preamble to medical practice, Harvard University (under the presidency of Charles Elliott) created a 4-year medical educational program in 1871. The primal modern medical educational curriculum was devised and set in motion more than 20 years later at Johns Hopkins University under the leadership of William Osler and William Welch, using the resources from the original endowment of the hospital and university from the estate of Johns Hopkins.[1]

Other schools followed suit. By the time the AMA set up its Council on Medical Education in 1904, it was made up of five members from the faculties of schools modeled on the Johns Hopkins prototype. This committee set out to visit and rate each of the 160 medical schools then in operation in the country. The ratings used were class "A" (acceptable), class "B" (doubtful), and class "C" (unacceptable).

Eighty-two schools received a class "A" rating, led by Harvard, Rush (Chicago), Western Reserve, the University of California and, notably, Johns Hopkins. Forty-six schools received a class "B" rating, and thirty-two a class "C" rating. The class "C" schools were mostly in rural areas, and many of them were proprietary in nature.

Flexner Report

Subsequent to the AMA ratings, the Council on Medical Education applied to the Carnegie Foundation to commission an independent report to verify its work. Abraham Flexner, a young, energetic, and noted educator, was chosen for this task by the Carnegie Foundation and accompanied by the secretary (Nathan Colwell, MD) of the Council on Medical Education, who participated in all of the committee site visits.

Flexner visited each of the 162 operating U.S. medical schools. The widely publicized *Flexner Report* put the nails in the coffins of all schools with class "C" ratings and many with class "B" ratings. Significantly, the educational programs of all but one eclectic school (in Cincinnati) and one homeopathic school (in Philadelphia) were eliminated by 1918.

The eclectic medical schools, in particular, were severely affected by the report. Griggs explained this effect as follows[2]:

Of the eight Eclectic schools, the Report declared that none had "anything remotely resembling the laboratory equipment which is claimed in their catalogs." Three of them were under-equipped;

the rest "are without exception filthy and almost bare. They have at best grimy little laboratories … a few microscopes, some bottles containing discolored and unlabeled pathological material, in an incubator out of commission, and a horrid dissecting room." The Report found them more culpable than a regular school for these inadequacies: "… the Eclectics are drug-mad; yet, with the exception of the Cincinnati and New York schools, they are not equipped to teach the drugs or drug therapy which constitutes their sole reason for existence."

The other regular schools that conducted homeopathic or eclectic programs had by that time phased them out in the name of "scientific medicine" (see also Haller[3]).

Pharmaceutical Industry

During this same time, the AMA, through several of its efforts, began a significant alliance with the organized pharmaceutical industry of the United States, shaping it in a manner acceptable to the allopathic profession.[1,9,11]

The New "Sects"

The period from 1890 to 1905 saw the rise of three new medical sects and several other smaller "irregular" schools that replaced those soon to pass from the scene. In Missouri, Andrew Taylor Still, originally trained as an orthodox practitioner, founded the school of medical thought known as "osteopathy" and in 1892 opened the American School of Osteopathy in Kirksville, Missouri. In 1895, Daniel David Palmer, originally a magnetic healer from Davenport, Iowa, performed the first spinal manipulation, which gave rise to the school he termed "chiropractic." He formally published his findings in 1910, after having founded a chiropractic school in Davenport, Iowa. In 1902, Lust founded the American School of Naturopathy in New York.

Although some of the following discussions are devoted to the schools of healing called osteopathy and chiropractic, only that portion of their histories related to the history of naturopathy is mentioned.[12] (A full study of osteopathic medicine in America may be found in *The D.O.'s* by Gevitz,[13] and a reasonable sketch of chiropractic medicine may be found in Kapling's chapter in *Alternative Medicine.*[12])

As noted by Starr,[1] these new sects, including Christian Science, formulated by Mary Baker Eddy,[14] either rose or fell on their own without ever completely allying with orthodox medicine. Starr theorized that these sects arose late enough that the orthodox profession and its political action arm, the AMA, had no need to ally with them and would rather battle with them publicly. This made these sectarian views separate and distinct from the homeopathic and eclectic schools.

THE FOUNDING OF NATUROPATHIC MEDICINE

Benedict Lust

Lust came to the United States in 1892 at the age of 23. He suffered from a debilitating condition in his late teens while growing up in Michelbach, Baden, Germany, and was sent by his father to undergo the Kneipp cure at Woerishofen. He stayed there from mid-1890 to early 1892; not only was he "cured" of his condition, but he also became a protégé of Kneipp. Dispatched by Kneipp to bring the principles of the Kneipp water cure to America, he emigrated to New York City.

By making contact in New York with other German Americans who were also becoming aware of the Kneipp principles, Lust participated in the founding of the first "Kneipp Society," which was organized in Jersey City, New Jersey, in October 1896.

Lust also attended the first organizational meeting (in mid-October 1896) of the Kneipp Society of Brooklyn. Subsequently, through Lust's organization and contacts, Kneipp Societies were founded in Boston; Chicago; Cleveland; Denver; Cincinnati; Philadelphia; Columbus; Buffalo and Rochester, New York; New Haven, Connecticut; San Francisco; New Mexico; and Mineola on Long Island, New York.

The members of these organizations were provided with copies of the *Kneipp Blatter* and a companion English publication Lust began to put out called *The Kneipp Water Cure Monthly*.

The first "sanatorium" using Kneipp's principles was organized in this country shortly before Lust's arrival. Charles Lauterwasser, an earlier student of Kneipp's who called himself a hydrothic physician and natural scientist, opened the Kneipp and Nature Cure Sanatorium in Newark, New Jersey, in 1891.

In 1895, the Brooklyn Light and Water-Cure Institute was established in Brooklyn, New York, by L. Staden and his wife Carola, both graduates of Lindlahr's Hygienic College in Dresden, Germany. According to their advertising, they specialized in natural healing, Kneipp water treatment, and Kuhne's and Preissnitz's principles (including diet cure, electric light baths [both white and blue], electric vibration massage, Swedish massage and movements, and Thure-brandt massage).

In 1895, Lust opened the Kneipp Water-Cure Institute in New York City, listing himself as the owner and Dr. William Steffens as the residing physician. At the same address (on 59th Street) in October of that year, Lust opened the first "Kneipp store." In the originating November 1896 edition of *The Kneipp Water Cure Monthly* and *Kneipp Blatter*, he advertised his store and sanitarium as personally authorized by Kneipp. In the first part of 1896, just before his organizing of various Kneipp Societies around the New York area, Lust returned to Woerishofen to study further with Kneipp.

Kneipp died in Germany, at Woerishofen, in June 1897. With his passing, Lust was no longer bound strictly to the principles of the Kneipp water cure. He had begun to associate earlier with other German-American physicians, principally Dr. Hugo R. Wendel (a German-trained *Naturarzt*), who began, in 1897, to practice in New York and New Jersey as a licensed osteopathic physician. In 1896, Lust entered the Universal Osteopathic College of New York, graduated in 1898, and became licensed as an osteopathic physician. In 1897, Lust became an American citizen.

Once he was licensed to practice as a health care physician in his own right, Lust began the transition toward the concept of "naturopathy." Between 1898 and 1902, when he adopted the term "naturopath," Lust acquired a chiropractic education and changed the name of his Kneipp store to Health Food Store (the original facility to use that name and concept in this country), specializing in providing organic foods and the materials necessary for drugless cures. He also began the New York School of Massage (listed as established in 1896) and the American School of Chiropractic, all within the same facility—Lust's Kneipp Institute.

Photographs of this facility taken between 1902 and 1907, when the facility moved to another location, show a five-story building listing "Benedict Lust—Naturopath, Publisher, Importer."

He returned to Germany in 1907 to visit with Dr. Baumgarten, Kneipp's medical successor at the Woerishofen facility, which was then run, in cooperation with Baumgarten, by the Reverend Prior Reily, the former secretary to Kneipp and his lay

successor at Woerishofen. As directed by Kneipp, Reily had completed, after Kneipp's death, Kneipp's master work *Das grosse Kneipp—Buch*. Lust maintained contact with the partnership of Reily and Baumgarten throughout the early part of the twentieth century.

In 1902, when he purchased and began using the term naturopathy and calling himself a "naturopath," Lust, in addition to his New York School of Massage and American School of Chiropractic, his various publications, and his operation of the Health Food Store, began to operate the American School of Naturopathy, all at the same 59th Street New York address.

By 1907, Lust's enterprises had grown sufficiently large that he moved them to a 55-room building. It housed the Naturopathic Institute, Clinic and Hospital; the American Schools of Naturopathy and Chiropractic; the now entitled Original Health Food Store; Lust's publishing enterprises; and New York School of Massage. The operation remained in this four-story building, roughly twice the size of the original facility, from 1907 to 1915.

From 1912 to 1914, Lust took a "sabbatical" from his operations to further his medical education. By this time he had founded his large estate-like sanitarium in Butler, New Jersey, known as "Yungborn" after the German sanitarium operation of Adolph Just.

In 1912 he attended the Homeopathic Medical College in New York, which, in 1913, granted him a degree in homeopathic medicine and, in 1914, he received his degree in eclectic medicine. In early 1914, Lust traveled to Florida and obtained an MD's license on the basis of his graduation from the Homeopathic Medical College and the Eclectic Medical College of New York City.

He founded another "Yungborn" sanitarium facility in Tangerine, Florida, and for the rest of his life, while continuing his publications, he engaged in active public lecturing. He also continued to maintain a practice in New York City and operated the sanitariums in Florida and New Jersey. His schools were operated primarily by Hugo R. Wendel.

From 1902, when he began to use the term naturopathy, until 1918, Lust replaced the Kneipp Societies with the Naturopathic Society of America. Then, in December 1919, the Naturopathic Society of America was formally dissolved due to its insolvency and Lust founded the American Naturopathic Association (ANA). Thereafter, 18 states incorporated the association.

In 1918, as part of his effort to replace the Naturopathic Society of America (an operation into which he invested a great deal of his funds and resources in an attempt to organize a naturopathic profession) and replace it with the ANA, Lust published the first *Universal Naturopathic Directory and Buyer's Guide* (a "yearbook of drugless therapy").

Although a completely new version was never actually published, despite Lust's announced intention to make this volume an annual publication, annual supplements were published in either *The Naturopath and Herald of Health* or its companion publication *Nature's Path* (which commenced publication in 1925). The *Naturopath and Herald of Health*, sometimes printed with the two phrases reversed, was published from 1902 to 1927, and from 1934 until after Lust's death in 1945.

This volume documented the merging of the German and American influences that influenced Lust in his development of the practice of naturopathy. The voluminous tome, which ran to 1416 pages, was dedicated to:

> *The memory of all those noble pioneers and discoverers who have died in the faith of Naturopathy, and to their courageous successors in the art of drugless healing, all of whom have suffered persecution for saving human lives that medical autocracy could not save, this work is respectfully dedicated by its editor Benedict Lust, N.D., M.D., "The Yungborn," Butler, New Jersey, U.S.A., April 1, 1918.*

Lust's introduction is reprinted here in its entirety to show the purpose of the directory and the status of the profession in the early 1900s:

> **Introduction**
> *To the Naturopathic Profession, the Professors of Natural Healing in all its branches, the Professors of Scientific Diet, Hydrotherapy, Heliotherapy, Electrotherapy, Neuropathy, Osteopathy, Chiropractic, Naprapathy, Magnetopathy, Phytotherapy, Exercise, Swedish Movements, Curative Gymnastics, Physical and Mental Culture, Balneopathy, and all forms of Drugless Healing, the Faculties of all Drugless Colleges, Institutions, Schools, and all Professors of Hygiene and Sanitation; Manufacturers of Naturopathic Supplies; Publishers of Health Literature, and Natural Healing Societies, GREETINGS:*
>
> *I have the honor to present to your consideration and goodwill, this Volume, No. 1, Year 1918-1919, of the Universal Naturopathic Directory, Year Book of Drugless Healing, and Buyers' Guide.*
>
> *For twenty-two years past, the need of a directory for Drugless Therapy has been felt. The medical world is in a condition of intense evolution at the present time. It is evolving from the Drugging School of Therapy to the Drugless School. People by the million have lost confidence in the virtues of Allopathy and are turning with joyful confidence to the Professions of Natural Healing until it has been estimated that there are at least forty thousand practitioners of Naturopathic healing in the United States.*
>
> *The motto that IN UNITY THERE IS STRENGTH is the foundation of the present enterprise.*
>
> *Hitherto, the drugless profession has lacked that prestige in the eyes of the public, which comes from the continuous existence of a big institution, duly organized and wielding the immense authority which is derived no less from organization and history than from the virtues of the principles that are held and practiced by such institutions. The public at large instantaneously respects an institution that is thoroughly organized and has its root earthed in history.*
>
> *The time has fully arrived when the drugless profession should no longer exist in the form of isolated units, not knowing one another and caring but little for such knowledge. Our profession has been, as it were, as sheep without a shepherd, but the various individuals that constitute this movement so pregnant with benefits to humanity, are now collected for the first time into a Directory and Year-Book of Drugless Healing, which alone will give immense weight and dignity to the standing of the individuals mentioned therein.*
>
> *Not only will the book add to the prestige of the practitioner in the eyes of his patients, but when the scattered members of our profession in every State desire to obtain legislative action on behalf of their profession and themselves, the appeal of such a work as our directory will, in the eyes of legislators, gain for them a much more respectful hearing than could otherwise be obtained.*

Now, for the first time, the drugless practitioner finds himself one of a vast army of professional men and women who are employing the most healthful forces of nature to rejuvenate and regenerate the world. But the book itself throws a powerful light upon every phase of drugless healing and annihilates time and distance in investigating WHO IS WHO in the realm of Drugless Therapy.

A most sincere effort has been made to obtain the name and address of every adherent of the Rational School of Medicine who practices his profession within the United States, Canada and the British Isles. It is impossible at this stage of Naturopathic history, which is still largely in the making, to obtain the name and address of every such practitioner. There were some who, even when appealed to, refused to respond to our invitation, not understanding the object of our work. Many of even the most intelligent members have refused to advertise their professional cards in our pages. But we can only attribute these drawbacks to the fact that every new institution that has suddenly dawned upon human intelligence will find that a certain proportion of people who do not understand the nature of the enterprise because the brain cells that would appreciate the benefits that are sought to be conferred upon them, are undeveloped, but a goodly proportion of our Naturopaths have gladly responded to the invitation to advertise their specialty in our columns. These, of course, constitute the brightest and most successful of our practitioners and their examples in this respect should be followed by every practitioner whose card does not appear in this book.

We take it for granted that every one of the forty thousand practitioners of Naturopathy is in favor of the enterprise represented by this Directory. This work is a tool of his trade and not to possess this book is a serious handicap in the race for success.

Here will be found an Index of by far the larger number of Naturopaths in the country arranged in Alphabetic, Geographic and Naturopathic sections. Besides this, there is a classified Buyers' Guide that gives immediate information regarding where you can find special supplies, or a certain apparatus, or a certain book or magazine, its name, and where it is published. The list of Institutions with the curriculum of each will be found exceedingly useful.

Natural healing, that has drifted so long, and, by reason of a lack of organization, has been made for so many years the football of official medicine, to be kicked by any one who thought fit to do so, has now arrived at such a pitch of power that it has shaken the old system of bureaucratic medicine to its foundations. The professors of the irrational theories of life, health and disease, that are looking for victims to be inoculated with dangerous drugs and animalized vaccines and serums, have begun to fear the growth of this young giant of medical healing that demands medical freedom, social justice and equal rights for the new healing system that exists alone for the betterment and uplifting of humanity.

I want every Professor of Drugless Therapy to become my friend and co-worker in the great cause to which we are committed, and those whose names are not recorded in this book should send them to me without delay. It will be of far greater interest and value to themselves to have their professional card included amongst those who advertise with us than the few dollars that such advertisement costs.

It will be noted that there are quite a number of Drugless Healers belonging to foreign countries (particularly those of the Western Hemisphere) represented in this Directory. The profession of medicine is not confined to any race, country, clime or religion. It is a universal profession and demands universal recognition. It will be a great honor to the Directory, as well as to the Naturopathic profession at large to have every Naturopathic practitioner, from the Arctic Circle to the furthest limits of Patagonia, represented in the pages of this immense and most helpful work.

I expect that the Directory for the year 1920 will be larger and even more important than the present Directory and that it will contain the names of thousands of practitioners that are not included in the present work.

The publication of this Directory will aid in abolishing whatever evils of sectarianism, narrow-mindedness and lack of loyalty to the cause to which we are devoted, that may exist. That it will promote a fraternal spirit among all exponents of natural healing, and create an increase of their prestige and power to resist the encroachments of official medicine on their constitutional rights of liberty and the pursuit of happiness, by favorably influencing Legislators, Law courts, City Councils and Boards of Health everywhere, is the sincere belief of the editor and publisher.

Having introduced the volume, Lust leads off with his article entitled "The principles, aim and program of the nature cure system."

Again, this relatively brief article is reproduced here in its entirety, so that one can see the merging of influences:

The principles, aim and program of the nature cure system

Since the earliest ages, Medical Science has been of all sciences the most unscientific. Its professors, with few exceptions, have sought to cure disease by the magic of pills and potions and poisons that attacked the ailment with the idea of suppressing the symptoms instead of attacking the real cause of the ailment.

Medical science has always believed in the superstition that the use of chemical substances which are harmful and destructive to human life will prove an efficient substitute for the violation of laws, and in this way encourages the belief that a man may go the limit in self indulgences that weaken and destroy his physical system, and then hope to be absolved from his physical ailments by swallowing a few pills, or submitting to an injection of a serum or vaccine, that are supposed to act as vicarious redeemers of the physical organism and counteract life-long practices that are poisonous and wholly destructive to the patient's well-being.

From the earliest ages to the present time, the priests of medicine have discovered that it is ten times easier to obtain ten dollars from a man by acting upon his superstition, than it is to extract one dollar from him, by appealing to reason and common sense. Having this key to a gold mine within their grasp, we find official medicine indulging at all times in the most blatant, outrageous, freakish and unscientific methods of curing disease, because the methods were in harmony with the medical prestige of the physician.

Away back in pre-historic times, disease was regarded as a demon to be exorcized from its victim, and the medicine man of his tribe belabored the body of his patient with a bag in which rattled bones and feathers, and no doubt in extreme cases the tremendous faith in this process of cure that was engendered in the mind of the patient really cured some ailments for which

mental science and not the bag of bones and feathers should be given credit.

Coming down to the middle ages, the Witches' Broth—one ingredient of which was the blood of a child murderer drawn in the dark of the moon—was sworn to, by official medicine, as a remedy for every disease.

In a later period, the "docteur a la mode," between his taking pinches of snuff from a gold snuff box, would order the patient bled as a remedy for what he denominated spirits, vapors, megrims, or miasms.

Following this pseudo-scientific diagnosis and method of cure, came the drugging phase in which symptoms of disease were unmercifully attacked by all kinds of drugs, alkalis, acids and poisons which were supposed, that by suffocating the symptoms of disease, by smothering their destructive energy, to thus enhance the vitality of the individual. All these cures have had their inception, their period of extensive application, and their certain desuetude. The contemporary fashion of healing disease is that of serums, inoculations and vaccines, which, instead of being an improvement on the fake medicines of former ages are of no value in the cure of disease, but on the contrary introduce lesions into the human body of the most distressing and deadly import.

The policy of expediency is at the basis of medical drug healing. It is along the lines of self-indulgence, indifference, ignorance and lack of self-control that drug medicine lives, moves and has its being. The sleeping swineries of mankind are wholly exploited by a system of medical treatment, founded on poisonous and revolting products, whose chemical composition and whose mode of attacking disease, are equally unknown to their originators, and this is called "Scientific medicine."

Like the alchemist of old who circulated the false belief that he could transmute the baser metals into gold, in like manner the vivisector claims that he can coin the agony of animals into cures for human disease. He insists on cursing animals that he may bless mankind with such curses.

To understand how revolting these products are, let us just refer to the vaccine matter which is supposed to be an efficient preventive of smallpox. Who would be fool enough to swallow the putrid pus and corruption scraped from the foulest sores of smallpox that has been implanted in the body of a calf? Even if any one would be fool enough to drink so atrocious a substance, its danger might be neutralized by the digestive juices of the intestinal tract. But it is a far greater danger to the organism when inoculated into the blood and tissues direct, where no digestive substances can possibly neutralize its poison.

The natural system for curing disease is based on a return to nature in regulating the diet, breathing, exercising, bathing and the employment of various forces to eliminate the poisonous products in the system, and so raise the vitality of the patient to a proper standard of health.

Official medicine has in all ages simply attacked the symptoms of disease without paying any attention to the causes thereof, but natural healing is concerned far more with removing the causes of disease, than merely curing its symptoms. This is the glory of this new school of medicine that it cures by removing the causes of the ailment, and is the only rational method of practicing medicine. It begins its cures by avoiding the uses of drugs and hence is styled the system of drugless healing. It came first into vogue in Germany and its most famous exponents in that country were Priessnitz, Schroth, Kuhne, Kneipp, Rickli, Lahmann, Just, Ehret, Engelhardt, and others.

In Sweden, Ling and others developed various systems of mechano-therapy and curative gymnastics.

In America, Palmer invented Chiropractic; McCormick, Ophthalmology. Still originated Osteopathy; Weltmer, suggestive Therapeutics. Lindlahr combined the essentials of various natural methods, while Kellogg, Tilden, Schultz, Trall, Lust, Lahn, Arnold, Struch, Havard, Davis, Jackson, Walters, Deininger, Tyrell, Collins and others, have each of them spent a lifetime in studying and putting into practice the best ideas of drugless healing and have greatly enlarged and enriched the new school of medicine.

Life maltreated by allopathy

The prime object of natural healing is to give the principle of life the line of least resistance, that it may enable man to possess the most abundant health.

What is life?

The finite mind of man fails to comprehend the nature of this mysterious principle. The philosopher says "Life is the sum of the forces that resist death," but that definition only increases its obscurity. Life is a most precious endowment of protoplasm, of the various combinations of oxygen, hydrogen, carbon and nitrogen, and other purely mineral substances in forming organic tissues. As Othello says, referring to Desdemona's life, which he compares to the light of a candle—

"If I quench thee thou flaming minister,

I can thy former light restore

Should I repent me; but once put out THY light,

I know not whence is that Promethean heat

That can thy light relume."

The spark of life flickers in the sockets of millions and is about to go out. What system of medicine will most surely restore that flickering spark to a steady, burning flame?

Will [it be] the system that employs poisonous vaccines, serums and inoculations, whose medical value has to be supported by the most mendacious statements, and whose practitioners are far more intent on their emoluments and fame, than they are in the practice of humanity?

The Allopathic system, which includes nine tenths of all medical practitioners, is known by its fruits, but it is an appalling fact that infant mortality, insanity, heart disease, arteriosclerosis, cancer, debility, impoverished constitutions, degeneracy, idiocy and inefficiency have enormously increased, particularly during the last twenty-five years, that is, during the regime of inoculations, serums and vaccines.

Naturopathy, on the other hand, so far as it has been developed, and so far as official medicine will allow it to act, leaves no such trail of disease, disaster and death behind it. Natural healing is emancipation from medical superstition, ignorance and tyranny. It is the true Elixir of Life.

The Allopaths have endeavored to cure sick humanity on the basis of the highly erroneous idea that man can change the laws of nature that govern our being, and cure the cause of disease by simply ignoring it. To cure disease by poisoning its symptoms is medical manslaughter.

Dr. Schwenninger of Germany says: "We are suffering under the curse of the past mistakes of our profession. For thousands of years medical doctors have been educating the public into the false belief that poisonous drugs can give health. This belief has become in the public mind such a deep-seated superstition, that those of us who know better and who would like to adopt more sensible, natural methods of cure, can do so only at the peril of losing practice and reputation.

"The average medical man is at his best but a devoted bigot to this vain school-craft, which we call the Medical Art and which alone in this age of science has made no perceptible progress since the days of its earliest teachers. They call it recognized science! Recognized ignorance! The science of to-day is the ignorance of to-morrow. Every year some bold guess lights up as truth to which but the year before the schoolmen of science were as blind as moles."

And Dr. O.W. Holmes, Professor of Anatomy in Harvard University, states: "The disgrace of medicine has been that colossal system of self-deception, in obedience to which mines have been emptied of their cankering minerals, entrails of animals taxed for their impurities, the poison bags of reptiles drained of their venom, and all the inconceivable abominations thus obtained thrust down the throats of human beings, suffering from some fault of organization, nourishment, or vital stimulation."

And these misguided drug doctors are not only not ashamed of their work, but they have induced subservient legislators to pass laws that perpetuate the age-long scandal of allopathic importance, and the degenerative influence of the poisons, and to actually make it a crime on the part of nature doctors to cure a man of his ailment. The brazen effrontery of these medical despots has no limits. They boast of making the State legislators their catspaw in arresting, fining and imprisoning the professors of natural healing for saving human life.

Legislators have no right to sit in judgment over the claims of rival schools of healing. They see tens of thousands of sick people go down to their graves by being denied the cures that the employers of nature's forces alone can give them. It is their business to provide for the various schools of medicine a fair field and no favor.

A citizen has an inalienable right to liberty in the pursuit of happiness. Yet the real saviors of mankind are persecuted by the medical oligarchy which is responsible for compulsory vaccination, compulsory medical inspection of public school children, and the demands for State and Federal departments of health, all for the ostensible good of the people, but in reality for the gain of the Medical Trust.

The naturopaths

The Naturopaths are desirous of freedom for all schools of medicine. They are responsible practitioners who are willing to be examined by an impartial council, appointed by and acting for the State, who will testify to the life and character of every drugless physician before he is entitled to practice medicine. Not one invidious discrimination should be made between the different schools of medicine. The state should see to it that each school should have a full opportunity to do its best for the up-lifting of its citizens.

The program of naturopathic cure

1. ELIMINATION OF EVIL HABITS, or the weeds of life, such as over-eating, alcoholic drinks, drugs, the use of tea, coffee and cocoa that contain poisons, meat eating, improper hours of living, waste of vital forces, lowered vitality, sexual and social aberrations, worry, etc.
2. CORRECTIVE HABITS. Correct breathing, correct exercise, right mental attitude. Moderation in the pursuit of health and wealth.
3. NEW PRINCIPLES OF LIVING. Proper fasting, selection of food, hydropathy, light and air baths, mud baths, osteopathy, chiropractic and other forms of mechano-therapy, mineral salts obtained in organic form, electropathy, heliopathy, steam or Turkish baths, sitz baths, etc.

Natural healing is the most desirable factor in the regeneration of the race. It is a return to nature in methods of living and treatment. It makes use of the elementary forces of nature, of chemical selection of foods that will constitute a correct medical dietary. The diet of civilized man is devitalized, is poor in essential organic salts. The fact that foods are cooked in so many ways and are salted, spiced, sweetened and otherwise made attractive to the palate, induces people to over-eat, and over eating does more harm than under feeding. High protein food and lazy habits are the cause of cancer, Bright's disease, rheumatism and the poisons of auto-intoxication.

There is really but one healing force in existence and that is Nature herself, which means the inherent restorative power of the organism to overcome disease. Now the question is, can this power be appropriated and guided more readily by extrinsic or intrinsic methods? That is to say, is it more amenable to combat disease by irritating drugs, vaccines and serums employed by superstitious moderns, or by the bland intrinsic congenial forces of Natural Therapeutics, that are employed by this new school of medicine, that is Naturopathy, which is the only orthodox school of medicine? Are not these natural forces much more orthodox than the artificial resources of the druggist? The practical application of these natural agencies, duly suited to the individual case, are true signs that the art of healing has been elaborated by the aid of absolutely harmless, congenial treatments, under whose ministration the death rate is but five per cent of persons treated as compared with fifty per cent under the present allopathic methods.

The Germanic Influence

The philosophical origins of naturopathy were Germanic. The most significant influences, except those of Russell Trall, the osteopathic concepts of A.T. Still (at this time strictly the correction of spinal lesions by adjustment), and the chiropractic principles of D.D. Palmer, were originally Germanic. (This was well established in the January 1902 editorial in *Water Cure Monthly*.)

The specific influences on which Lust drew for his work, in order of their chronological contributions to the system of naturopathy, are the following:

1. Vincent Preissnitz (1799–1851)
2. Johann Schroth (1798–1856)
3. Father Sebastian Kneipp (1821–1897)
4. Arnold Rickli (1823–1926)

5. Louis Kuhne (c. 1823–1907)
6. Henry Lahman (no dates known)
7. F.E. Bilz (1823–1903)
8. Adolph Just (1859–1939).

Also of note were Theodor Hahn and T. Meltzer, who, in the 1860s, were well known for their work in the movement called, in German, *Naturatz* or "naturism."

In photographs accompanying his article "The principles, aim and program of the nature cure system," Lust described each of these thinkers as follows:

1. *VINCENT PREISSNITZ, of Graefenberg, Silesia. Founder of Hydropathy. Born October 4, 1799. A pioneer Naturopath, prosecuted by the medical authorities of his day, and convicted of using witchcraft, because he cured his patients by the use of water, air, diet and exercise. He took his patients back to Nature—to the woods, the streams, the open fields—treated them with Nature's own forces and fed them on natural foods. His fame spread over the whole of Europe, and even to America. His cured patients were numbered by the thousands. The Preissnitz compress or bandage is in the medical literature. Preissnitz is no more, but his spirit lives in every true Naturopath.*
2. *JOHANN SCHROTH, a layperson, not described in Lust's directory but often talked of in later works and prominently mentioned for his curative theories in Bilz's master work, The Natural Method of Healing. Schroth smashed his right knee in an accident with a horse and it remained stiff in spite of repeated medical treatment. At last, a priest told Schroth that Preissnitz's methods might help, and Schroth decided to give them a try. In order to avoid frequent changing of the packs that were directed by Preissnitz, he placed several packs on top of one another, wrapping the whole portion with a woolen cloth. He left this pack on the injured knee for several hours and produced a moist heat which he theorized to cause the poisonous toxins to dissolve and be swept away. These packs are still used as part of the "Schroth cure" and have reportedly become famous for their blood-cleansing effect. (From an article in the March 1937 Naturopath and Herald of Health by Dr. T.M. Schippel.) As noted by Bilz, the Schroth cure, called by Bilz "the regenerative treatment," was developed for treatment of chronic diseases through the use of an extreme diet following total fasting by withdrawing of all food and drink and then the use of totally dry grain products and the eventual reintroduction of fluids.*
3. *FATHER SEBASTIAN KNEIPP, of course, is much described and the photos include one of Kneipp lecturing to the multitudes at Wandelhale at Woerishofen, attending Pope Leo XIII in 1893, noting this is the only consultation on health care matters that Kneipp ever consented to outside of Woerishofen, though many famous and aristocratic individuals desired his counsel, and a picture of Kneipp with the Archdukes Joseph and Francis Ferdinand of Austria walking barefoot in new-fallen snow for purposes of hardening the constitution. It was noted that the older Archduke was cured by Kneipp of Bright's disease in 1892, and it noted that the Archduke Joseph, in appreciation of this cure, donated a public park in the town of Woerishofenat a cost of $150,000 florens. The Archduke Francis Ferdinand, the son of Archduke Joseph, was the individual whose murder precipitated World War I. There is a further picture of Kneipp surrounded by "Doctors" from different parts of the world while he gave consultation to numerous patients.*
4. *ARNOLD RICKLI, founder of the light and light and air cures (atmospheric cure). Dr. Rickli was one of the foremost exponents of natural living and healing. In 1848, he established at Veldes, Krain, Austria, the first institution of light and air cure or as it was called in Europe the "atmospheric cure." In a limited way (rather very late) his ideas have been adopted by the medical profession in America for the cure of consumption. He was an ardent disciple of the vegetarian diet and exemplified the principles of natural living in his own life. The enclosed photo shows him at the age of 97, when he was still active and healthy. He has since passed on, but his work still lives as a testimonial of his untiring efforts. He was the founder and for over 50 years the President of the National Austrian Vegetarian Association.*
5. *LOUIS KUHNE wrote, in 1891, The New Science of Healing, the greatest work of basic principles in natural healing. In the tradition of Natural Healing and prevention, Kuhne has been described as one who "… advocated sun, steam baths, a vegetarian diet, and whole-wheat bread … in these relatively early days." His renowned work constitutes the only true scientific philosophy for the application of all Drugless Methods. He was the first to give to the world the comprehensible idea of pathology and the first to proclaim the doctrine of the "unity of cure." His book Facial Expression gives the means of diagnosing a patient's pathological condition and determining the amount and location of the systemic encumbrance. He is the founder and first Master of Naturopathy.*
6. *DR. H. LAHMAN. When the University of Leipzig expelled H. Lahman for his spreading medical sedition among the students, it added a staunch advocate to natural healing. Dr. Lahman finished his medical education in Switzerland and returned to Germany to refute in practice the false ideas of medical science. He later founded the largest Nature Cure institution in the world at Weisser Hirsch, near Dresden, Saxony. He was a strong believer in the "Light and Air" cure and constructed the first appliances for the administration of electric light treatment and baths. He was the author of several books on Diet, Nature Cure and Heliotherapy. As noted in Other Healers, Other Cures: "Heinrich Lahmann came along to stress no salt on foods and no water with meals … "[15] His works on diet are authoritative and his "nutritive salts theory" forms the basis of rational dietetic treatment. This work has but recently come to light in America, and progressive dietitians are forsaking their old, worn-out, high protein, chemical and caloric theories for the "organic salts theory." Carque, Lindlahr, McCann, and other wide awake food scientists have adopted it as a basis for their work. Dr. Lahman was a medical nihilist. He denounced medicine as unscientific and entirely experimental in its practice and lived to prove the saneness of his ideas as evidenced by his thousands of cured patients.*
7. *PROFESSOR F.E. BILZ. That real physicians are born, not made, is well illustrated in the case of Dr. Bilz, who achieved his first success in healing as a lay practitioner. As a mark of gratitude, a wealthy patient presented him with land and a castle in which to found a Nature Cure sanitarium.… The Bilz institution at Dresden-Rdebeul, Germany, became world renowned and was long considered*

the center of the Nature Cure movement. Professor Bilz is the author of the first Naturopathic encyclopedia, The Natural Method of Healing, which has been translated into a dozen languages, and in German alone has run into 150 editions. He has written many works on Nature Cure and Natural Life, among them being The Future State, in which he predicted the present World War, and advocated a federation of nations as the only logical solution of international problems.

8. *ADOLPH JUST, famous author of Return to Nature and founder of original "Yungborn" in Germany.*

Both Adolph Just's *Return to Nature* and Louis Kuhne's *The Natural Science of Healing* were translated into English by Lust and released through his publication house.

The Convergence with American Influences

The Universal Naturopathic Directory was truly eclectic in its compilation and composition. Besides the Lust articles the volume included: "How I became acquainted with nature cure" by Henry Lindlahr, MD, ND (which was reproduced in large part in the introduction to volume 1 of Lindlahr[16]); "The nature cure" by Carl Strueh, MD, ND; "Naturopathy" by Harry E. Brook, ND; "The present position of naturopathy and allied therapeutic measures in the British Isles" by Allen Pattreiouex, ND; "Why all drugless methods?" by Per Nelson; and "Efficiency in drugless healing" by Edward Earle Purinton (a reprint of the 1917 publication, referred to earlier, which was composed of a series of articles published in *The Herald of Health and Naturopath* between August 1914 and February 1916).

The volume also contained Louis Kuhne's "Neo-naturopathy (the new science of healing)" in the first publication of the translation by Lust, and articles on electrotherapy, neuropathy, dietology, chiropractic, mechanotherapy, osteopathy, phytotherapy, apyrtropher, physical culture, optometry, hydrotherapy, orthopedics, pathology, natural healing and living, astroscopy, phrenology, and physiology—all of which were specially commissioned for the directory from practitioners and authors considered expert in these subjects.

Also included was a national directory of drugless physicians in alphabetical order, geographically arranged and itemized by profession; biographical notes on American contributors of note; the naturopathic book catalog; a guide to natural healing and natural life books and periodicals; a classified list of medical works; a series of book reviews; a buyer's guide for naturopathic supplies; and, in addition to extensive indexes, a "parting word" by Lust.

The volume contained numerous advertisements for naturopathic schools, sanitariums, and individual practices, and it closed with the following note:

This, then, completes Volume 1 of the Naturopathic Directory, Drugless Yearbook and Buyer's Guide for the years 1918 and 1919.

Into it, has been placed the conscientious labor of many willing hearts, hands and minds. It is their contribution to the noble cause of natural healing. It will stand as a monument to their endeavors, as well as a memorial to the great souls, the fathers of natural healing, who have passed on.

Let this, then, herald a new era—the era wherein man shall recognize the omniscience of Nature, and shall profit through conforming to her laws.

In the biographical sections, it is apparent that Lust owed a great deal of the feeling of camaraderie in the nature cure movement to some varied American practitioners. The most prominent of these had their biographical sections contained in the 1918 directory. Two of them deserve specific note and attention: Palmer and Still.

Lust met A.T. Still in 1915 in Kirksville, MO, shortly before Still's death. From their meetings, Lust noted later in the *Naturopath and Herald of Health* (June 1937) that Still believed that osteopathy by "compromising with medicine is doomed as the school that could have incorporated all the natural and biological healing arts." Lust wanted naturopathy to fill this void.

Lust also had lengthy acquaintance with B.J. Palmer (the son of D.D. Palmer, the founder of chiropractic), who, following in his father's footsteps, put Davenport, Iowa, and the Palmer Chiropractic College on the map.

Lust also became connected with Henry Lindlahr, MD, ND, of Chicago (as noted in the autobiographical sketch contained in the directory[17] and reprinted in volume 1 of Lindlahr[16]). Lindlahr was a rising businessman in Chicago with all the bad habits of the "gay nineties" era. In his 30s, he became chronically ill. He had gone to the orthodox practitioners of his day and received no relief.

Then, he was exposed to Schroth's works, and in following them began to feel somewhat better. Subsequently, he liquidated all his assets and went to a German sanitarium to be cured and to learn nature cure. He returned to Chicago and enrolled in the Homeopathic/Eclectic College of Illinois. In 1903, he opened a sanitarium, which included a residential sanitarium, located in Elmhurst, Illinois, a "transient" clinic (office) on State Street in Chicago, and "Lindlahr's Health Food Store."

Shortly thereafter. he founded the Lindlahr College of Natural Therapeutics, which included hospital internships at the sanitarium. The institution became one of the leading naturopathic colleges of the day. In 1908, he began to publish *Nature Cure Magazine* and began publishing his series of *Philosophy of Natural Therapeutics*, with volume 1 ("Philosophy") in 1918. This was followed by volume 2 ("Practice") in 1919, volume 3 ("Dietetics"; republished with revisions as originally published in 1914), and, in 1923, volume 6 ("Iridiagnosis"). The intended volumes 4 and 5 were in production at the time of Lindlahr's death in 1927. As described in *Other Healers, Other Cures*[15]:

Henry Lindlahr, another American, is remembered for his conviction that disease did not represent an invasion of molecules, but the body's way of healing something. In other words, he viewed symptoms as a positive physiological response—proof that the body is fighting whatever's wrong. Accordingly, a fever is a "healthy" sign and one should be let alone, unless it is dangerously high, of course.

The impact of all these gentlemen on the development of naturopathy in America, under Lust's guidance, was profound.

From these beginnings, the naturopathic movement gathered strength and continued to grow through the 1920s and 1930s, having a major impact on natural healing and natural lifestyle in the United States.

Along the way, Lust was greatly influenced by the writings of John H. Tilden, MD (largely published between 1915 and 1925). Tilden was originally a practicing physician in Denver who became disenchanted with orthodox medicine and began to rely heavily on dietetics and nutrition, formulating his theories of "auto-intoxication" (the effect of fecal matter remaining too long in the digestive process) and "toxemia."

Lust was also greatly influenced by Elmer Lee, MD, who became a practicing naturopath about 1910 and whose movement was called the "hygienic system," following the earlier works of Russell Trall. Lee published *Health Culture* for many years.

In addition to John Tilden, MD, and Elmer Lee, MD, another medical doctor, John Harvey Kellogg, MD, who turned to more nutritionally based natural healing concepts, was greatly respected by Lust. Kellogg was renowned through his connection with the Battle Creek Sanitarium. The sanitarium itself was originally founded in the 1860s as a Seventh Day Adventist institution designed to perpetuate the Grahamite philosophies of Sylvester Graham and William Alcott. The sanitarium was on the verge of being closed, however, due to economic failure, when in 1876, Kellogg, a new and more dynamic physician-in-chief, was appointed.

Kellogg, born in 1852, was a "sickly child" who, at the age of 14, ran across the works of Graham and converted to vegetarianism. At the age of 20, he studied for a term at Trall's Hygio-Therapeutic College and then earned a medical degree at New York's Bellevue Medical School. He maintained an affiliation with the regular schools of medicine during his lifetime, due more to his practice of surgery than his beliefs in the area of health care.[4]

Kellogg designated his concepts, which were basically the hygienic system of healthful living, "biologic living." Principally, Kellogg defended vegetarianism, attacked sexual misconduct and the evils of alcohol, and was a prolific writer through the late nineteenth century and early twentieth century. He produced a popular periodical, *Good Health*, which continued in existence until 1955. When Kellogg died in 1943 at the age of 91, he had had more than 300,000 patients through the Battle Creek Sanitarium (which he had had renamed from Western Health Reform Institute shortly after his appointment in 1876), including many celebrities, and the "San" became nationally well known.

Kellogg, along with Tilden and Elie Metchnikoff (director of the prestigious Pasteur Institute and winner of the 1908 Nobel Prize for a contribution to immunology), wrote prolifically on the theory of auto-intoxication. Kellogg, in particular, felt that humans in the process of digesting meat, produced various intestinal self-poisons that contributed to auto-intoxication.

As a result, Kellogg became a near fanatic on the subject of helping humans return to a more healthy, natural state by returning to the naturally designed usage of the colon. He felt that the average modern colon was devitalized by the combination of sedentary living, the custom of sitting rather than squatting to defecate, and the modern civilized habit of ignoring "nature's call" out of an undue concern for politeness. Further, Kellogg concentrated on the fact that the modern diet had insufficient bulk and roughage to stimulate the bowels to proper action.

Kellogg was also extremely interested in hydrotherapy. In the 1890s, he established a laboratory at the San to study the clinical applications of hydrotherapy. This led, in 1902, to his writing *Rational Hydrotherapy*. The preface espoused a philosophy of drugless healing that came to be one of the bases of the hydrotherapy school of medical thought in America.

Tilden, as mentioned, was of a similar mind. He must have been to have provided natural health care literature with his 200-plus page dissertation entitled "constipation," with a chapter devoted to the evils of not responding when nature called.

This belief in the "evils" drawing away from the natural condition of the colon was extremely important to Kellogg's work.[4] Because of Lust's interest, Kellogg's *The New Dietetics* (1921) became one of the bibles of naturopathic literature.[18]

Lust was also influenced by the works of Sidney Weltmer, the father of "suggestive therapeutics." The theory behind Professor Weltmer's work was that whether it was the mind or the body that first lost its grip on health, the two were inseparably related. When the problem originated in the body, the mind nonetheless lost its ability and desire to overcome the disease because the patient "felt sick" and consequently slid further into the diseased state. Alternatively, if the mind first lost its ability and desire to "be healthy" and some physical infirmity followed, the patient was susceptible to being overcome by disease.

Weltmer's work dealt specifically with the psychological process of desiring to be healthy. Lust enthusiastically backed Weltmer's work and had him appear on the programs at various annual conventions of the American Naturopathic Association (which commenced after its founding in 1919).

Lust was also personal friends with and a deep admirer of Bernarr MacFadden.[19] MacFadden was the founder of the "physical culture" school of health and healing, also known as "physcultopathy." This school of healing gave birth across the country to gymnasiums at which exercise programs, designed to allow the individual man or woman to maintain the most perfect state of health and human condition possible, were developed and taught.[4] *Other Healers, Other Cures* described it as follows[15]:

> *The next Naturopathic star, after Kellogg, was Bernarr MacFadden, the physical culturist who built a magazine-publishing empire (his first magazine was Physical Culture founded in 1898). MacFadden proselytizes for exercise and fresh vegetables, hardly eccentric notions. But his flamboyant efforts to publicize them and his occasional crack-pot ideas (like freezing the unemployed, then thawing them out when the Depression was over) alienated many people. Still, he was his own best advertisement. He fathered nine children by four wives and was parachuting from planes in his 80s. One of MacFadden's admirers was that arch-foe of the medical profession, George Bernard Shaw, the longevous eccentric in his own right …*

Lust was also interested in, and helped to publicize, "zone therapy," originated by Joe Shelby Riley, DC, a chiropractor based in Washington, D.C., and one of the early practitioners of "broad chiropractic." Zone therapy was an early forerunner of acupressure as it related "… pressures and manipulations of the fingers and tongue, and percussion on the spinal column, according to the relation of the fingers to certain zones of the body. …"[17]

Several other American drugless healers contributed to a broad range of "-opathies" that Lust merged into his growing view of naturopathy as the eclectic compilation of methods of natural healing. The *Universal Directory* also contained a complete list of osteopaths and chiropractors as drugless healers within the realm of Lust's view of naturopathic theory. His other significant compatriots at the time of the publication of the directory were Carl Stueh, described by Lust as "one of the first medical men in this country who gave up medicine and operation for natural healing"; F.W. Collins, MD, DO, DC, an early graduate of the American School of Naturopathy (1907) who went on to graduate from the New Jersey College of Osteopathy (1909) and the Palmer School of Chiropractic (1912); another "broad chiropractor," Anthony Matijaca, MD, ND, DO, the naturopathic resident expert in electrotherapy and an associate editor of the *Herald and Health Naturopath* (the inverted name of the Lust journal at the time of the directory); and Carl Schultz, ND, DO, MD, president and general manager of the Naturopathic Institute and Sanatorium of California, essentially the second school in the country to pursue the education of physicians under the name of "naturopathy."

In *Inner Hygiene: Constipation and the Pursuit of Health in Modern Society*, Whorton[20] offered his first assessments of the work of Lust as it related to the emergence of naturopathy in the early twentieth century:

> *Most of the drugless clan also identified themselves as practitioners of naturopathy, a system of practice that grew out of hydropathy, as well as German water-cure and nature-cure traditions. Organized in the late 1890s under the leadership of German immigrant Benedict Lust, naturopathy sought to cure the full scope of human ills with natural agents (herbs, water, air, sunlight, electricity, massage, and others), agents that supported and stimulated the body's own healing mechanisms.*

In his extensive assessments of Lust's work and writings in *Nature Cures: the History of Alternative Medicine in America*, Whorton[21] attempted to put the philosophical development of naturopathy in a reasonable historical context:

> *However much a dreamer Lust was in some respects, he was an insightful realist in others. He was correct in believing that simply giving nature support as it ran its course was the best one could do with many diseases in his day. He was correct in seeing self-abuse as the source of much physical, and emotional, suffering and attacked it with an ardor that MDs could not bring to the task until nearly a century later. Recent medical lamentations over the evils of smoking, sexual promiscuity, and other risky behaviors adopted in the thoughtless chase after pleasure have nothing on Lust's jeremiads …*
>
> *Lust was right in reprimanding allopaths for focusing so strongly on disease as to lose sight of the importance of promoting health. He was right in appreciating the need to "individualize" the treatment of each patient—and in seeing patient self-responsibility as part of that individualization.*



EARLY TWENTIETH-CENTURY MEDICINE

The Metamorphosis of Orthodox Medicine

Naturopathy's formative years, and in some respects its halcyon days, were from 1900 to 1917. In many jurisdictions modern licensing laws were not yet in effect, so varied schools of healing were openly practiced. By 1920, however, the American world of medicine had undergone a sharp transition, culminating in four decades of change.

A look at the structure of early medical care in the United States is instructive, even as practiced and dominated by the orthodox school, when noting the changes that occurred between 1875 and 1920.

In 1875, the following was descriptive of American medical practice:

- The practice, even in urban areas, sent the doctor to the patient; the "house call" was the norm.
- There was little modern licensing regulation.
- Hospitals were charitable institutions where persons too poor to otherwise receive health care were usually sent when ill.
- The AMA, although formed in 1846, and generally representative of the professional goals of the regular or orthodox school of medicine, had scarcely begun to make any political inroads at all.
- Medical schools required little or no college education for entrance and were largely apprenticeship based and proprietary in nature, having changed little throughout the century.
- Although some doctors had begun to specialize, to do so was far from the norm. The major recognized specialties were surgery, obstetrics, and gynecology.
- Many different types of doctors existed, and society's reaction to of the profession neither recognized specific expertise nor necessarily rewarded professionals in medical practice well.
- Although the orthodox school made up roughly 80% of professional medical practitioners, the homeopaths and the eclectics were visible and respected in their own communities for their abilities and expertise, and much of the public relied on other "irregular" practitioners.

By comparison, in 1920, a total metamorphosis of the medical profession had occurred:

- By 1920, practices had become office oriented and clinic oriented.
- Modern licensing principles had become fully developed, and physicians and surgeons were licensed in all jurisdictions. Most other health care providers had some licensing restrictions placed on them, if they were recognized at all.
- Due largely to the introduction into surgery of the practice of antiseptic techniques and aseptic procedures and a correspondent decline in operative mortality, institutional care in the hospital became increasingly accepted. Also, clinical pathology and diagnostic laboratory procedures had become well developed, and the hospital had become a major training and clinical research facility that was generally more acceptable to the patient.
- The AMA was approaching the peak of its political power, having exercised, through its Council on Medical Education and its Council of Pharmacy and Chemistry, major effects on medical schools and the pharmaceutical industry.
- The transition to research- and education-based medical schools, instead of practitioner apprenticeships and proprietary education, had become complete. All recognized medical schools had a 4-year curriculum, with an undergraduate degree or substantial undergraduate study required as a prerequisite. In addition, most schools, in conjunction with most licensing statutes, required a year's internship.
- Specialization was becoming well developed, and the number of specialty groups had increased considerably. This would continue through the 1930s and into the early 1940s.
- Professional authority and autonomy had undergone a substantial transition, and the allopathic physician was now recognized as the medical expert.
- By 1922, the last eclectic school was on the verge of closure, and in the early 1930s, the last of the homeopathic schools in the United States was also on the verge of closure. The influence of these sects on orthodox medicine had dwindled to almost nothing. Naturopaths and other alternative health care practitioners had adopted the areas of expertise previously considered the territory of homeopaths and eclectics.

The Halcyon Years of Naturopathy

In 1924 Morris Fishbein succeeded George Simmons as editor of the *Journal of the American Medical Association (JAMA)*. Fishbein had joined the editorial staff of *JAMA* under Simmons immediately after his graduation from Chicago's Rush Medical School in 1913. Campion pointed out the following[9]:

> *Over the years, Fishbein not only established himself as the gifted editor of the most widely read medical journal in the United States; he also learned how to extend his editorial position, how to project his opinions nationwide. He became, as the saying*

went in those years, a "personality." TIME referred to him as "the nation's most ubiquitous, the most widely maligned, and perhaps most influential medico."

In addition to his development of *JAMA* as an editorial and personal voice, Fishbein also continually railed against "quackery." Lust, among others, including MacFadden, became Fishbein's epitome of quackery. When MacFadden became a wealthy man, after his publishing company included popular magazines like *True Confessions* and *True Detective*, he began campaigning for the 1936 Republican presidential nomination. In response, a physician submitted, under the initials "K.G.," a tongue-in-cheek listing of the cabinet that would exist under MacFadden, including the newly created "Secretary of Aviation" for Lust. Lust was a popular figure by this time who conducted such a busy lecture schedule and practice, alternating between the "Yungborns" in Butler, New Jersey, and Tangerine, Florida, that he had become almost as well known as an airline traveler. Lust devoted a complete editorial in *Nature's Path* to a response.

Although Fishbein had *JAMA* as a personal editorial outlet, Lust had his own publications. Commencing with the *Naturopath and Herald of Health* in 1902 (which changed its name to *Herald of Health and Naturopath* in 1918), Lust continually published this and other monthly journals. In 1919 it became the official journal of the ANA, mailed to all members. Each edition contained the editorial column "Dr. Lust Speaking."

In the early 1920s, the "health fad" movement was reaching its peak in terms of public awareness and interest. As described, somewhat wistfully, in his June 1937 column, Lust announced the approach of the 41st Congress of Natural Healing under his guidance:

The progress of our movement could be observed in our wonderful congresses, in 1914 Butler, N.J., 1915 Atlantic City, 1916 in Chicago, 1917 Cleveland, 1918 New York, 1919 Philadelphia, 1920 and 1921 again New York, and 1922 in Washington, D.C., where we had the full support and backing of the Congress of the United States. President Harding received the president and the delegates of our convention and we were the guests of the City of Washington. Through the strenuous efforts of Dr. T.M. Schippel, Hon. Congresswoman Catherine Langley of Kentucky, and eight years of hard work financed and sustained by Dr. Schippel and her powerful friends in Congress, Naturopathy was fully legalized as a healing art in the District of Columbia and the definition was placed on record and the law affirmed and amended by another act which has been fully published over and over again in the official journal of the A.N.A., Naturopath.

In 1923 in Chicago, with the help and financing of the great and never-to-be forgotten Dr. Henry Lindlahr, we had a great convention. Not only were all the Naturopaths there but even to an extent our congress was recognized and acknowledged as official and of great importance by the medical people, particularly by the Health Commissioner of Chicago. We held a banquet, and there were discussions covering all platforms of the healing art. It was the first congress in the United States where medicine and Naturopathy in all its branches such as the general old-time Nature Cure, Hydrotherapy and Diet, Osteopathy, Naprapathy, Chiropractic, Neuropathy and Physiotherapy were represented on the same platform. The speakers represented every modern school of healing and the movement at that time was in the direction of an entirely recognized and independent school of healing. There were two camps, official medicine and official Naturopathy, the medical camp having all that is good and bad in medicine and surgery and all the other schools of healing that had sold their birthright and trusted to the allurement of organized medicine, such as Homeopaths, Eclectics, Physio-medics, and the Osteopaths to a large extent. The Osteopaths were always in the wrong camp when they went on mixed boards and Dr. Andrew Taylor Still, the father of Osteopathy, told me in 1915 that by compromising with medicine Osteopathy is doomed as the school that could have incorporated all of the natural and biological healing arts.

The year following we had the great congress in Los Angeles which has never been duplicated. We had to meet in two hotels because the crowds ran over 10,000. The glorious banquet will never be forgotten and the congress celebrated and demonstrated that the initial and first intent of the A.N.A. to teach the public Natural Living and Nature Cure was realized. We will never forget the glorious week in Los Angeles where the authorities and the whole city joined us. The success of that congress was largely due to the talent of Dr. Fred Hirsch, the successor to Prof. Arnold Ehret and the noble and generous Naturopaths of the A.N.A. of Cal. There was never a second congress like that.

Then we had the great congresses of New York in 1925, Indianapolis 1926, Philadelphia 1927, Minneapolis 1928, Portland, Oregon 1929, New York 1930, Milwaukee 1931, Washington, D.C., 1932, Chicago 1933, Denver 1934, San Diego 1935, and Omaha 1936.

In 1925 Lust began to try to reach more of the general populace through the lay publication *Nature's Path*. *The Naturopath* and *Nature's Path* were later merged because the self-supporting advertising and subscription monies were more available by publication to the general populace than to the members of the association (*The Naturopath*, 1902–1927; *Nature's Path*, 1925–1927; merged 1927–1933; separated 1934–1938; *Nature's Path*, 1939–1945).

How large a professional movement Lust inspired during this period of naturopathy's emergence was difficult to gauge. An extensive government survey was not undertaken until 1965. However, as Whorton described in *Nature Cures*,[21] naturopathy had an impact:

Those were messages that had enough appeal, evidently, to allow naturopathy to expand steadily through the first decades of the century until by 1923 Lust could estimate that there were nine thousand naturopaths, a "vast army of professional men and women" working on all continents to "rejuvenate and regenerate the world." His figures were undoubtedly inflated. An independent study [the work of the CCMC discussed later] put the number of naturopaths at "possibly 1500," allowing that if the "allied groups" that advocated drugless healing under other names [physiotherapy, sanipractic] were added on the total may reach 2500. Yet whatever their numbers, naturopaths had grown into a force not to be ignored.

Although Lust's claim of 9000 naturopaths worldwide is impossible to assess, 5000 practitioners may be a reasonable estimate of the reach of his naturopathy in the United States by the late 1920s and into the 1930s. As Whorton[21] reported, the mixer orientation within chiropractic was also becoming a growing presence. This orientation was a philosophy that tended to merge chiropractic and naturopathy in education and practice.[22] Although homeopathy has undergone a small revival in recent years, very few MDs now practice it. It is currently mainly of interest to naturopaths, who earn doctor of naturopathy (ND) degrees and to a few

chiropractors. Naturopaths closely resemble chiropractors in that they use spinal manipulative therapy and because so-called mixer chiropractors also use naturopathic methods such as heat, cold, hydrotherapy, physiotherapy, dietary supplements, and even some herbal and homeopathic remedies, which is why the traditional, or "straight," chiropractors disparagingly call them "medipractors." Until the middle of the twentieth century, a few mixer schools offered both DC and ND degrees, either as alternatives or together after an additional semester of study. Whorton noted a "1930 survey in which some 1,800 chiropractors participated, found, for example, that 1,124 employed hydrotherapy, 1,173 used light therapy, 1,257 provided electrotherapy, and a full 1,352 trusted vibration therapy."[21]

In January 1934, Lust commenced republication of the title *Naturopath and Herald of Health* in addition to *Nature's Path*. Each volume opened with his personal column, different for each publication. Both publications were issued through 1938, when the *Nature's Path* again became the sole publication until Lust's death in 1945.

After the *Universal Directory*, Lust continued to write volumes on naturopathic principles, although he was more of a synthesizer, organizer, lecturer, and essayist than a scientific documenter of naturopathic principles. His most enduring contributions may remain his early translations of Kuhne's and Just's works.

During the 1920s and up until 1937, Lust's brand of "quackery," so labeled by Fishbein, was in its most popular phase. Although the institutional markings of the orthodox school had gained ascendancy, before 1937 it had no real therapeutic success in the treatment of disease outside of the broad advancements in public health.

Lust's naturopathy, together with chiropractic and osteopathy, continued to be on the outside looking in, this lack of therapeutic advancement notwithstanding. Practitioners of all three movements were continually prosecuted for practicing medicine without a license, although they often won their cases by establishing to juries that their practices were (even according to the testimony of medical men) not the same as medicine at all. At the time orthodox practitioners could offer little or no expectation of cure for many diseases, and the "health food and natural health" movement was generally popular.

During the 1920s, Gaylord Hauser, later to become the health food guru of the Hollywood set, came to Lust as a seriously ill young man. Lust, through application of the nature cure, removed Hauser's afflictions and was rewarded by Hauser's lifelong devotion. His regular columns in *Nature's Path* became widely read among the Hollywood set.

As noted in *Other Healers, Other Cures*[15]:

> *The last big name in Naturopathy was Gaylord Hauser, a Viennese-Born food scientist (as one of his early books identified him) turned to Naturopathy in his later years. He is best remembered for advising the eating of living foods, not dead foods, and for escorting Greta Garbo around. In addition to fresh fruits and vegetables, Hauser's "Wonder Foods" were skinned milk, brewers yeast, wheat germ, yogurt, and black strap molasses.*

The naturopathic journals of the 1920s and 1930s are instructive. Much of the dietary advice focused on poor eating habits, including the lack of fiber in the diet and an overreliance upon red meat as a protein source. More than half a century later in the 1980s, the pronouncements of the orthodox profession, the National Institute of Health, and the National Cancer Institute finally accepted the validity of these early assertions by naturopaths that poor dietary and living habits (particularly smoking) would lead to degenerative diseases, including cancers associated with the lungs, the digestive tract, and the colon.

The December 1928 volume of *Nature's Path* was the first American publication of the works of Herman J. DeWolff, a Dutch epidemiologist who was one of the first individuals to assert, based on studies of the incidence of cancer in the Netherlands, that there was a correlation between exposure to petrochemicals and various types of cancers. He saw a connection between chemical fertilizers and their usage in some soils (principally clay) that led to poisons remaining in vegetables after they had arrived at the market and were purchased for consumption. Again, it was 50 years before orthodox medicine began to accept the wisdom of such concerns.

As Whorton noted in *Nature Cures*, naturopaths were less successful than osteopaths and chiropractors in accomplishing professionalization by the elevation of professional standards, including professional education. This occurred despite the formation of a National Board of Naturopathic Examiners of the ANA in 1940. There was constant internal bickering, which "by the 1940s had taken on a more ominous tone." Although "standards at naturopathic schools were steadily raised from the 1940s on, thanks to both professional idealism and the requirements of state licensing laws," based on "a perusal of the statutes of the dozen states in which naturopaths were licensed in the late 1940s," the divisive trends within naturopathy "would not begin to be reversed until the 1970s."

Whorton[21] observed that there was no misunderstanding where Lust himself stood on the need for professional standards:

> *Obtaining their own licensing statutes was perceived by alternative practitioners as a critical measure for purging incompetence and quackery from their own rank. "Where there is no official recognition and regulation," the founder of naturopathy, Benedict Lust maintained, "you will find the plotters, the thieves, the charlatans … (The) riff-raff opportunists bring the whole art into disrepute." By the time Lust said this, shortly before his death in 1945, frustrating experience had demonstrated that "that is the fate of any science—any profession—which the unjust laws have placed beyond the pale." In following the evolution of alternative medicine over the first third of the twentieth century, it is essential to keep in mind that constant battle of each system to bring itself within the pale.*

The Emerging Dominance of American Medical Association Medicine

In 1937, the status of conventional (allopathic) medicine began to change. The change came with the beginning of the era of "miracle medicine." Lewis Thomas in his interesting work *The Youngest Science*[23] compared his education and internship as a physician to his father's life as a physician. His father believed that bedside manner was more important than any actual medication offered by the physician. His father went into general surgery so that he could offer some service to his patients that actually made some change in their condition. Thomas pointed out that the major growth of "scientific medicine" until 1937 advanced diagnosis rather than offering any hope of cure.

This introduction of "miracle medicine," the social impact of World War II on health care, and the death of Lust in 1945 all combined to contribute a precipitous decline for naturopathy and natural healing in the United States. (During the war, the necessity for crisis surgical intervention techniques for battlefront conditions encouraged use of morphine, sulfa drugs, and penicillin for diseases not previously encountered in civilian life by American

combat soldiers. This resulted in rapid development of higher-technology approaches to medicine and highly visible successes.)

Lust recognized this and his editorializing became, if anything, even more strident. From the introduction of sulfa drugs in 1937 to the Salk vaccine's release in 1955, the American public became used to annual developments of miracle vaccines and antibiotics.

Lust died in September 1945 at the Yungborn facility in Butler, New Jersey, preparing to attend the 49th Annual Congress of his American ANA. In August 1945, for the official program of that congress held in October 1945 just after his death, he dictated the following remarks:

> *What is the present condition of Naturopathy? What is its future? I can give my opinion in a very few words. For fifty years I have been in the thick of the fight to bring to the American people the Nature Cure. During that period I have had an opportunity to judge what Naturopathy has done, and can accomplish and the type of men and women, past and present, who make up the Naturopathic ranks.*
>
> *Let us take the present situation first. What is Naturopathy accomplishing? The answer to that is: "Everything." Naturopathy holds the key for the prevention, alleviation and cure of every ailment, to man and beast alike. It has never failed in the hands of a competent Naturopath. Whatever the body can "catch"—that same body, with proper handling, can eliminate. And that takes in cancer, tumors, arthritis, cataract and the whole gamut of "incurable medical" disease and ailments. During my years of practice I, personally, have seen every type of human ailment and so-called serious "disease" give way to the simple, proven Naturopathic methods. I make no exception to that statement.*
>
> *Now let us see the type of men and women who are the Naturopaths of today. Many of them are fine, upstanding individuals, believing fully in the effectiveness of their chosen profession—willing to give their all for the sake of alleviating human suffering and ready to fight for their rights to the last ditch. More power to them! But there are others who claim to be Naturopaths who are woeful misfits. Yes, and there are outright fakers and cheats masking as Naturopaths. That is the fate of any science—any profession—which the unjust laws have placed beyond the pale. Where there is no official recognition and regulation, you will find the plotters, the thieves, the charlatans operating on the same basis as the conscientious practitioners. And these riff-raff opportunists bring the whole art into disrepute. Frankly such conditions cannot be remedied until suitable safeguards are erected by law, or by the profession itself, around the practice of Naturopathy. That will come in time.*
>
> *Now let us look at the future. What do we see? The gradual recognition of this true healing art—not only because of the efforts of the present conscientious practitioners but because of the bungling, asinine mistakes of orthodox medicine—Naturopathy's greatest enemy. The fiasco of the sulpha drugs as emphasized disastrously in our armed forces is just one straw in the wind. The murderous Schick test—that deadly "prevention" of diphtheria—is another. All these medical crimes are steadily piling up. They are slowly, but inevitably, creating a public distrust in all things medical. This increasing lack of confidence in the infallibility of Modern Medicine will eventually make itself felt to such an extent that the man on the street will turn upon these self-constituted oppressors and not only demand but force a change. I may not be here to witness this revolution but I believe with all my soul that it is coming. Yes, the future of Naturopathy is indeed bright. It merely requires that each and every true Naturopath carry on—carry on—to the best of his and her abilities. May God bless you all.*

The effects of postwar events on osteopathy and chiropractic were completely different from the effect on naturopathy. In the early days of osteopathy, there was a significant split between the strict drugless system advocated by A.T. Still (osteopathy's originator) and the beliefs of many MDs who converted to osteopathy because of its therapeutic value. The latter group did not want to abandon all of the techniques they had previously learned and all of the drugs they had previously used when those therapy techniques were sometimes effective. Ultimately, most schools of osteopathy, commencing with the school based in Los Angeles, converted to more of an imitation of modern orthodox medicine. These developments led to more of an accommodation between the California osteopaths and the members of the California Medical Association. (This developing cooperation between the California Osteopathic and Medical Association was one of the major issues leading to the downfall, in 1949, of Fishbein's editorial voice in *JAMA*.) Thus, osteopathy found a place in professional medicine, at the cost of its drugless healing roots and therapies.[9]

Naturopathy had become an element of chiropractic education and practice at least as early as 1910 with the founding of the Peerless College of Chiropractic and Naturopathy in Portland, Oregon.[22] From this point on, naturopathic education developed in two tracks: schools of naturopathy owned and operated by naturopaths and chiropractic schools that had naturopathic curricula in addition to the core chiropractic programs. These latter schools were a central part of the mixer orientation within chiropractic.[22,24]

Initial assessments of schools of naturopathy occurred in the 1920s and 1930s. These assessments came from those within, or allied with, allopathy and were therefore hardly unbiased, but much of the information in these assessments seemed credible. The progression of education in naturopathy would be expected to have been similar to that of chiropractic, if somewhat smaller in scale. In this regard, Wardwell noted[22]:

> *Wiese and Ferguson[25] identified 392 different chiropractic schools as having existed in the United States. When those for which there is no evidence of more than a year of operation are eliminated, the number is reduced to 188. Most of them probably produced few graduates—the number of schools increased rapidly to their largest between 1910 and 1926, and then contracted, particularly during the depression of the 1930s and World War II.*

The history of schools of naturopathy followed much the same pattern. Whorton[21] noted in *Nature Cures* that this was the case. The operators of these schools seemed, at least on the surface, aware of the kind of criticisms to which proprietary trade and professional schools were subjected: limited facilities, limited resources, and an emphasis on collecting revenue versus providing a full professional education.[22,24] The leading operators of schools of naturopathy sought, at least on paper, to respond to these criticisms. By letter agreement dated October 7, 1922, four of the most identifiable leaders of naturopathy—Benedict Lust, Joe Shelby Riley, F.W. Collins, and Henry Lindlahr—committed to the formation of the Associated Naturopathic Schools and Colleges of America and committed themselves as "the Presidents of Naturopathic Schools in the United States of America" to specific educational minimums "on and after January 2, 1923": "all

matriculants must have a primary school education* and all naturopath courses must be composed of four years of six months each." Additionally, the letter provided that "time allowance or credits may be given to practitioners in the field who desire to take up the naturopathic courses, and to licensed physicians of other methods of healing," the amount of such credit being left to each school's discretion.

In the summer and fall of 1927, representatives of the AMA's Council on Medical Education and Hospitals conducted inspections—unannounced and incognito—of schools of "chiropody, chiropractic, naturopathy, optometry, osteopathy, physical therapy, as well as a large number of institutions." From these inspections, several reports were generated, including the Council's report on "Schools of Chiropractic and Naturopathy in the United States," which appeared first as part of the Council's *Annual Report, 1928*, and later as reprinted in *JAMA.* The report identified 40 schools of chiropractic and 10 schools of naturopathy and detailed the inspections of "some schools of Chiropractic and of Naturopathy": Palmer School of Chiropractic (a straight school), National College of Chiropractic (a mixer school that was reported as having recently purchased and assimilated Lindlahr College of Natural Therapeutics), Los Angeles College of Chiropractic (another leading mixer school), the combined American School of Naturopathy, Inc. and American School of Chiropractic, Inc. (Lust's own New York City schools, although Lust was observed to have been "in Florida" at the time of the inspections), and the Naturopathic College and Hospital of Philadelphia. The reports were predictably negative with regard to facilities, resources, and the clearly proprietary nature of the establishments.

Louis Reed of the Committee on the Costs of Medical Care, in discussing "Naturopathic Schools"[24] relied heavily on this report from the AMA's Council and observed that "in 1927, according to the American Medical Association, there existed twelve naturopathic colleges with not over 200 students. These figures would probably hold good for the present time." Reed also concluded that there were "a considerable number of miscellaneous drugless healers of a type similar to chiropractors practice in this country" as of 1932 and that "the naturopaths form the largest group of these practitioners.… Of these various cults, only the naturopaths and the sanipractors have any considerable membership. Many of the (other) cults are really part of the naturopathic group."[24]

As to numbers of drugless practitioners, Reed observed that "only the roughest estimate can be made—probably there are about 2500," of which naturopaths "number possibly 1500," and sanipractors—"only the name distinguishes sanipractors from the naturopaths"—numbered some 500 in their Washington state "stronghold." Reed also observed that as of 1932: "A few states—Connecticut, Florida, Oregon, South Carolina, Utah, Washington and the District of Columbia—provide for licensing of naturopaths as limited practitioners.… In addition to those mentioned, certain states (Alabama, Colorado, Illinois, Indiana, Michigan, Ohio, Pennsylvania, New Jersey, and Wyoming) make (other) provision for the licensing of drugless or limited practitioners."[24]

Reed's work for the CCMC, although clearly biased against all of the healing philosophies he identified as "medical cults" (a la Fishbein), principally osteopathy, chiropractic, and naturopathy, was the only work that attempted to survey the presence and impact of these schools of healing in the United States in the 1920s and 1930s.* A decade later, in April 1945, another work of this kind appeared in the *Rhode Island Medical Journal*. The article, "Naturopathic Legislation and Education," was written by the Rhode Island Medical Society's Executive Secretary, John E. Farrell, to set out some of the society's reasons for opposing legislation that would license naturopathy in Rhode Island. The article noted that according to the 1942–1943 Report of the Committee on Education of the ANA, 13 schools of naturopathy in the United States met the criteria of the ANA; the article went on to make a lengthy "Report on Schools" through visits to most of the identified schools.† The predictable criticisms of these schools as underfinanced, underresourced, and proprietary in nature appeared once again, although by actual detail of description, National College (Chicago) and Western States (Portland) seemed to be well-established, functioning mixer schools of chiropractic and naturopathy.

The effect on chiropractic of the post World War II years was somewhat different. Because of educational recognition under the G.I. Bill, the number of chiropractors in the country grew substantially, and their impact on the populace grew accordingly. The sect eventually grew powerful enough in terms of numbers and economic clout that it could pose a legal challenge to the orthodox monopoly of the AMA. However, in the immediate postwar years, the AMA gained tremendous political clout. Combined with the American Legion and the National Board of Realtors,[26] these three groups posed a powerful political triumvirate before the U.S. Congress.

These years, called the years of the "great fear" in Caute's book by that name,[27] were the years during which to be unorthodox was to be "un-American."

Across the country, courts began to take the view that naturopaths were not truly doctors, since they espoused doctrines from "the dark ages of medicine" (something American medicine had apparently come out of in 1937) and that drugless healers were intended by law to operate without "drugs" (which became defined as anything a person would ingest or apply externally for any remedial medical purpose). In this regard, the Washington State Supreme Court case of *Kelly v. Carroll*‡ and the Arizona State Supreme Court case of *Kuts-Cheraux v. Wilson* document how significant limitations were placed on naturopaths under the guise of calling them "drugless healers."

In the state of Tennessee, as a reaction to the 1939 publication of the book *Back to Eden* by herbalist Jethro Kloss, court action initiated by the Tennessee State Medical Association led first to the publishers being forbidden to advertise the book for any therapeutic purpose. They were allowed only to acknowledge that it was in stock. Then, following a serious licensing scandal during

*"Primary education"—circa 1922—was an eighth-grade education, and this educational base would have been the same as that required by chiropractic.

*The results of Reed's work are also summarized in the CCMC's Publication No. 27, The Costs of Medical Care, Falk, Rorem and Ring (1933), p. 292, as 'Naturopaths and Other Drugless Healers.'

†With lengthy discussion of Central States College of Physiatrics (Eaton, Ohio), The Colorado Mineral Health School (Denver), Columbia College of Naturopathy (Kansas City), First National University of Naturopathy (Newark, New Jersey, earlier the United States School), The Metropolitan College (Cleveland), The Nashville College of Drugless Therapy (Tennessee), The National College of Drugless Physicians (part of the National College of Chiropractic, Chicago), The Polytechnic College and Clinic of Natural Therapeutics (Fort Wayne, Indiana), The Southern University of Naturopathy and Physio-Medicine (Miami), The University of Natural Healing Arts (Denver), and The Western States College (Portland, Oregon).

‡The defendant was Otis G. Carroll of Spokane, Washington. He and his brother, Robert V. Carroll, Sr., of Seattle were longtime associates of Benedict Lust. As members of Lust's American Naturopathic Association, they had advanced naturopathy's presence in Washington state through the Washington State Naturopathic Association.

the war years, the Tennessee State Legislature declared the practice of naturopathy in the state of Tennessee to be a gross misdemeanor, punishable by up to one year in jail.

Although it was under considerable public pressure in those years, the ANA undertook some of its most scholarly work, coordinating all the systems of naturopathy under commission. This resulted in the publication of a basic textbook on naturopathy (*Basic Naturopathy* published in 1948 by the ANA[28]) and a significant work compiling all the known theories of botanical medicine (as commissioned by the ANA's successor after its 1950 name change to the American Naturopathic Physicians and Surgeons Association), the *Naturae Medicina* published in 1953.[29] Naturopathic medicine began splintering when Lust's ANA was succeeded by six different organizations in the mid-1950s.

The primary organizations among these were the successor to the ANA, which underwent a name change in 1950 to the American Naturopathic Physician and Surgeon's Association, and subsequently changed to the American Association of Naturopathic Physicians (AANP) in 1956, and the International Society of Naturopathic Physicians formed under the leadership of M.T. Campenella of Florida shortly after Lust's death, with its American offshoot, the National Association of Naturopathic Physicians.

In the face of the AMA's determination to eliminate chiropractic, and with it naturopathy—healing philosophies that were linked through the mixer orientation within chiropractic (during the 1930s and through the 1960s the majority camp within a divided chiropractic)—naturopathy went through a period of decline described by Hans Baer (see Bibliography).

Walter Wardwell was a sociology professor who became an early leader in what developed as a subspecialty in the 1950s: medical sociology. His earliest work, starting with his doctoral dissertation (1951) at Harvard, focused on chiropractic as an example of a marginalized health profession (see Bibliography). As early as his doctoral dissertation, Wardwell discussed naturopathy as an adjunct discipline to chiropractic in the context of the continuing division of chiropractic into mixers and straights. As he later noted[30]:

> *Comparison of the survival of chiropractic with that of osteopathy and naturopathy is a quite different matter which does not involve metaphysical or epistemological differences between them. Furthermore, the overlap in theory between chiropractic, osteopathy and naturopathy is very great. Differences between osteopathic and chiropractic manipulative treatment appear to be more a matter of who applies the technique rather than differences in technique itself. The distinction between chiropractors and naturopaths is even more blurred because they often trained at the same schools and sometimes they studied both fields simultaneously. As recently as 1948, three of the currently accredited chiropractic colleges offered N.D. (Doctor of Naturopathy) and D.C. (Doctor of Chiropractic) degrees.*

In this context he described naturopathy as a school of healing that became extinct as two historical factors converged: the death of Lust in 1945, leaving naturopathy without its "founder," and the mandate in the early 1950s by the major mixers' professional group, the National Chiropractic Association (NCA), that it would no longer accredit chiropractic schools that granted degrees in naturopathy:

> *In the case of naturopathy, chiropractic's victory is nearly complete. Although there may still be up to 2000 naturopaths in practice* with naturopaths licensed in a few states, and one small school in Portland, Oregon, still offers naturopathic degrees, none of the schools that formerly offered both chiropractic and naturopathic degrees currently does so. With practically no new recruits entering the profession, naturopathy must disappear.*

By the late 1970s, Wardwell had learned of efforts in the Pacific Northwest to keep naturopathy alive. In his chapter in the *Handbook of Medical Sociology*, Wardwell noted this presence in the Northwest (which had received no mention in the first two editions in 1963 and 1972)[31]:

> *The accrediting of chiropractic colleges is encouraging uniformity, not only in curricula but in scope of practice. Those colleges that formerly offered the Doctor of Naturopathy (N.D.) as well as the D.C. degree have ceased doing so, leaving naturopathy with only one remaining small college in Portland, Oregon.*

By publication of his masterwork, *Chiropractic: History and Evolution of a New Profession* (1992),[22] Wardwell devoted substantial attention to the impact of naturopathy on the mixer orientation within chiropractic and traced naturopathy's final educational decline to the untimely death in 1954 of William A. Budden, DC, ND, the president of Western States Chiropractic College (WSCC; Portland, Oregon). After Budden's death, WSCC continued to teach naturopathy until 1958, but dropped its ND degree program in 1956. This was the last resistance to the position of the accrediting committee of the NCA, and no chiropractic ND programs remained. Wardwell observed, though, that the seeds of a naturopathic reemergence had been planted in the Northwest after Budden's death and that naturopathy might survive.

The last ND diplomas were granted at WSCC in 1958 to students who were enrolled in the ND program at the time of Budden's death. Brinker[32] noted the following:

> *Political pressure from the chiropractic profession had begun in the late 1940s to force chiropractic schools to relinquish programs granting naturopathic degrees. After threatening loss of accreditation, the National Chiropractic Association finally forced Western States College to drop its School of Naturopathy in 1956, and it became exclusively Western States Chiropractic College.*

Efforts to keep naturopathy alive through education and licensure were examined by two reports prepared in 1958, a time when the Utah legislature was reexamining naturopathy's licensure in the aftermath of a case from the Utah Supreme Court that had dealt its practicing NDs a crippling blow. The first was *A Study of the Healing Arts with a Particular Emphasis Upon Naturopathy* (November 1958), prepared as "A Report to the Utah Legislative Council" by legislative council staff. As part of its work, the staff conducted inquiries of and site visits to seven schools accredited by the Utah Naturopathy Examining Board as of August 1957.

Separately, the Bureau of Economic and Business Research* of the University of Utah (BEBR) undertook a study focusing on schools that had granted naturopathy degrees and produced *Survey of Naturopathic Schools* ("Prepared for the Utah State Medical Society," December 1958). Preparation of the study was, as noted in the title, undertaken by the university research program at the request of the state medical society, but the preparation of the study was independent, and "no attempt was made by that group to influence the results of the study" (Foreword and Acknowledgements).

*As to those calling themselves naturopaths, this number was considerably too high, as will become apparent.

*Now the National Bureau of Economic Research.

The BEBR study, done with the requested cooperation of investigators from five other universities located in various sections of the United States, surveyed all of the schools listed by Utah licensees as schools of graduation or schools attended, using records maintained by the Utah Department of Business Registration.[10] Because the state of naturopathic education in the 1950s is relevant, some observations from this study are worth noting[33]:

> *One of the most important results to emerge from this study is that there are virtually no schools now teaching naturopathy.*

Of the twenty-six schools investigated during this study, only nine were still in existence in the fall of 1958. Of these nine, only three are now granting naturopathic degrees and two others are teaching naturopathy.

Of the three schools granting ND degrees, the study found that one school, Sierra States University in California, began offering a "postgraduate" ND degree after the most highly respected chiropractic program in the country, Los Angeles College of Chiropractic, had discontinued its ND degree program in 1948. National College of Naturopathic Medicine (NCNM), the Oregon school, had—in 1957, its first year of operation—four ND students who were starting at NCNM and 60 enrolled "postgraduate" DCs pursuing ND degrees. The school had been recognized by the Utah examining board but had not yet granted degrees. The third school granting ND degrees as of 1957-1958 was the Central States College of Physiatrics in Eaton, OH, essentially the one-man operation of H. Riley Spitler, author of *Basic Naturopathy* (published by the ANA in 1948). This school granted a Doctor of Mechanotherapy (DM) degree, recognized in only Ohio and Alabama by law, or an ND degree to anyone who sought licensure in a state where an ND degree would qualify a graduate for licensure. The course of study for both degrees was the same, and the school had graduated 10 students in the previous 2 years. Its ND degrees were recognized in Utah.

By 1955, the AANP, as it ultimately became known, had recognized only two schools of naturopathic medicine, the Central States College of Physiatrics in Eaton, Ohio, under the leadership of H. Riley Spitler, and Western States College of Chiropractic and Naturopathy located outside Portland, Oregon, under the leadership of R.A. Budden. Budden was a Lindlahr graduate and among the group that took over control of the Lindlahr College after Lindlahr's death in the 1920s. He moved west after World War II when the northwestern states, including Oregon, became the last bastion of naturopathic medicine in this country.

This state of affairs was accurately described by Homola[34] in his book on the history and evolution of chiropractic:

> *As of 1958, only five states (Arizona, Connecticut, Oregon, Virginia and Utah) separately classified and provided licensing provisions for the naturopath. A few states, however, did permit licensing of drugless healers following examination by (a) board. (A good number of states have repealed their laws licensing naturopaths in recent years.) Chiropractic schools that employ the use of physiotherapy teach a course that is very similar to the practice of naturopathy. Likewise, the three or four naturopathic schools still operating today have a curriculum similar to that of many chiropractic colleges. In fact, at least four chiropractic colleges awarded naturopathic degrees along with the chiropractic degree before they came under the jurisdiction of the national Chiropractic Association. With the approval of this organization, the schools were prohibited from issuing naturopathic degrees. This practically amounted to a death-dealing blow to the profession of naturopathy.*[34]

In 1967, the U.S. Department of Health, Education, and Welfare; the Public Health Service; and the National Center for Health Statistics (NCHS) published Public Health Service Publication number 1758, *State Licensing of Health Occupations*. With the assistance of The Council of State Governments, the NCHS collected data regarding licensure of health professionals at the state level. "Chapter 8: Naturopaths" recorded the available data for the naturopathic profession as of the mid-1960s. In summary, the NCHS identified five states and the District of Columbia as licensing naturopaths as of 1967: Arizona, Connecticut, Hawaii, Oregon, and Utah. California and Florida were identified as renewing existing licenses but granting no new licenses. The publication reported that by 1965, California had renewed 66 licenses and Florida, 136. Licenses in effect by state were: Arizona (100), Connecticut (47), Hawaii (14), Oregon (148), and Utah (42). No numbers were provided for the District of Columbia. The report stated the following[35]:

> *In addition to Doctors of Naturopathy (ND) there are other limited branches of medicine; these have not been included in the study. In the State of Washington the Drugless Therapeutics Examining Committee functions (for such licensure). The Ohio law states which branches are to be specified on certificates issued by the State Medical Board to limited practitioners. No attempt has been made to collect information on these drugless healers who are few in number.*

Active state practitioners were also numbered (although the reason for the differentiation is not clear) as: Arizona (53), Connecticut (29), Hawaii (13), and Oregon (121). Given the existence of approximately 50 practitioners at the time in Washington, and some practicing in Idaho under a decision of the Idaho Supreme Court, there appear to have been perhaps as many as 600 to 700 remaining naturopaths practicing at the end of the 1960s.*

According to documentation provided to the federal Department of Health Education and Welfare in 1968 by the again-remaining professional association—the National Association of Naturopathic Physicians—only 17 degrees were granted from 1960 to 1968. By 1968, this association had 168 members and estimated that there were perhaps 500 "active" naturopaths in the United States. Congress adopted Medicare in 1965. The legislation covered payment for the services of physicians (essentially MDs and DOs), hospital services, and "other therapeutic services" that would commonly be provided through these conventional means. As Wardwell reported,[22] in 1967, Congress directed the Secretary of the Department of Health, Education, and Welfare (HEW), Wilbur Cohen, to study the inclusion services of "additional types of licensed practitioners." The surgeon general and other HEW staff prepared the resulting *Independent Practitioners under Medicare* using advisory committees only (Wardwell served on the Expert Review Committee for Chiropractic and Naturopathy), which actually had little input. This report documented the ebb tide of naturopathy's "period of decline"

*The State Licensing of Health Occupations; U.S. Department of Health, Education, and Welfare; and the National Center for Health Statistics Public Health Service Publication No. 1758 (1967) reported: "Naturopaths are specifically licensed in at least five States and the District of Columbia. The absence of a State from this list does not imply that there are no licensed naturopaths. Illinois, for example, could be covered by the medical practice act. Texas and Virginia provide for naturopaths on examining boards but no information is available on licensing practices. Elsewhere licensing powers have been abolished and no new licenses have been issued; for example, in 1965 naturopathic licenses renewed in California numbered 66 and in Florida, 136."

as Baer later labeled it.[36] The section of the report *Naturopathy* concluded that as of 1968:

> *Naturopathic theory and practice are not based on the body of basic knowledge related to health, disease, and health care which has been widely accepted by the scientific community. Moreover, irrespective of its theory, the scope and quality of naturopathic education do not prepare the practitioner to make an adequate diagnosis and provide adequate treatment.*

Considering the state of the profession in 1968, these negative assessments were hardly unexpected.

THE MODERN REJUVENATION

After the counter culture years of the late 1960s and feeding of an American disenchantment with organized medicine which began after the miracle drug era faded, exposing some of orthodox medicine's limitations, alternative medicine began to gain new respect. Naturopathic medicine underwent an era of rejuvenation as a late 1970s consumer interest in more "holistic" medicine began to emerge.

As succinctly described in Cassedy's[37] *Medicine in America: A Short History*, this phenomenon, which was not limited to naturopathic medicine, was consistent with the modern and continuing, "search for health beyond orthodox medicine":

> *It should not have been surprising to anyone that certain organized therapeutic sects continue to exist in mid–twentieth century America as successful and conspicuous alternatives to regular medicine. This is not to say that they offer the same threats to the medical establishment or play the same roles as their nineteenth-century counterparts had, as complete therapeutic systems. But they do continue to hold a strong collective appeal for individuals who mistrust or are somehow disenchanted with mainline medicine. They have appealed also to antiauthoritarian sentiments that flourish throughout society. Moreover, as earlier, they satisfy various needs that regular medicine continues to neglect or ignore.*

The same author, in describing the post-World War II decades and the changing fortunes of such healing theories as naturopathic medicine, observed as follows:

> *The period also brought about the renewal or updating of certain previously widely used therapies and considerable experimentation with others, some of them exotic. To an extent this trend represented the rediscovery by trained physicians, nurses, and other regular health professionals of certain values and older styles of therapy. The participation of such professionals proved to be an essential ingredient in the rebirth of several such therapies. However, the major reason for the new successes was the wide-spread active interest and involvement of America's literate lay people in the search for more personal or humane forms of treatment.*

As another author, John Duffy,[38] observed in *From Humors to Medical Science*:

> *Since health is too closely related to cultural, social, and economic factors to be left exclusively to doctors, American lay people have always engaged in do-it-yourself medicine, resorted to "irregulars and quacks," and supported health movements. As a result of the current fad for physical fitness, our streets are beset by sweat-suited individuals of all ages doggedly jogging their way to health and long life. In addition, stores selling "natural" foods are flourishing, physical fitness salons have become a major business, and anti-smoking and weight-loss clinics and workshops are attracting thousands of individuals bent on leading cleaner and leaner lives. And those for whom physical activity in itself is not enough are seeking physical and mental well-being through faith healing, yoga, and a host of major and minor gurus.*

When neither mental effort nor physical exercise can solve medical problems, the sceptics of modern medicine can always turn to the irregulars. A recent estimate places a number of Americans who have relied on an irregular practitioner at some time in their lives at 60 million, and, aided by the high cost of orthodox medicine, irregular medical practice appears to be on the rise…

At the beginning of this period of rejuvenation, the profession's educational institutions had dwindled to one, the National College of Naturopathic Medicine (which had branches in Seattle, Washington and Portland, Oregon), which was founded after the death of R.A. Budden and the conversion of Western States College to a straight school of chiropractic. Kruger's[15] book *Other Healers, Other Cures* described it as follows in 1974:

> *Today, Naturopaths in seventeen states are licensed to diagnose, treat, and prescribe for any human disease through the use of air, light, heat, herbs, nutrition, electrotherapy, physiotherapy, manipulations, and minor surgery. At present, one can earn an D.N. [a misnomer, actually—N.D.] degree at the National College of Naturopathic Medicine in Seattle and Emporia, Kansas, [where, by contract, the first two years of the four-year medical education were then taught], or the new North American Naturopathic Institute in North Arlington, New Jersey [there is also a school in Montreal]. The four-year curriculum covers many standard medical courses—anatomy, bacteriology, urology, pathology, physiology, X-ray reading etc.—but also includes botanical medicine, hydrotherapy, electrotherapy, and manipulative technique…*

The public, by the late 1970s, was particularly ripe for another rejuvenation of naturopathy's brand of "alternative" health care. As described in Murphy's *Enter the Physician: The Transformation of Domestic Medicine*, 1760–1860, when discussing this cyclical rejuvenation in the mid-twentieth century[39]:

> *Contemporary crusaders still stress prevention as the layperson's primary duty, but a growing chorus is calling for every person to assume the newly proactive role in his or her own health care.*

What would this entail? There are probably as many answers to this question as there are respondents, but it is striking to note how many of the solutions would have been familiar to our ancestors who lived between 1760 and 1860. One recurring idea, for instance, is that each person knows his or her own constitution history the best, and therefore has a duty to communicate that knowledge to medical personnel. Another is a refurbished concept of *vis medicatrix naturae*, the belief that many diseases are self-limiting and therefore do not require much medical intervention—and certainly not the amount or the sort to which contemporary Americans are accustomed. Most significantly, today's analysts are calling on professionals and non-professionals to build and nurture a health care partnership very much like that envisioned by nineteenth-century health publicists: a partnership based on mutual respect, clear understanding and faithful execution. In that scenario, both as it originally evolved and in its updated version, it is the doctor who directs treatment, but crucial to a successful outcome are the informed and responsible actions of the patients, other care givers, and the patient's family and friends.

In 1978, the John Bastyr College of Naturopathic Medicine was formed in Seattle, Washington, by Joseph E. Pizzorno, Jr., ND (founding president), Lester E. Griffith, ND, and William Mitchell, ND (all graduates of the National College of Naturopathic Medicine), and Sheila Quinn, who felt that it was necessary to have more institutions devoted to naturopathic care and the teaching of naturopathic therapeutics. To differentiate Bastyr from the other "irregular"[38] schools, Pizzorno coined the term "science-based natural medicine" and developed the curriculum to implement it. Bastyr's co-founder and first president, Joseph Pizzorno, recognized that "anecdotal and unverified 'cures', particularly when associated with unusual therapies do our cause little good." Consequently, instruction at the school "has concentrated more on the scientifically verifiable aspects of natural medicine and less on the relatively anecdotal nature cure aspects."[21]

In *Other Healers, Unorthodox Medicine in America*,[40] a volume written to provide "a scholarly perspective on unorthodox movements and practices that have arisen in the United States" (from the editor's preface), author Martin Kauffman, a modern expert in homeopathy from the Department of History at Westfield State College, detailed Bastyr's homeopathic requirements to graduate:

> *In 1978, three naturopathic practitioners in Seattle founded the John Bastyr College of Naturopathic Medicine. During the sixth quarter all students at that school are required to take 44 hours of course work in homeopathy, after which they may elect another 66 hours and up to 238 hours of clinical homeopathic instruction. The significance of the naturopathic schools to the resurgence of homeopathy is demonstrated by the fact that "about one third of the graduating class specialized in homeopathic practice, a total of about 50 each year in all."*[40]

During the late 1970s, other naturopathic doctors also recognized the need to establish educational institutions for students of naturopathic medicine; subsequent efforts included colleges in Arizona (the Arizona College of Naturopathic Medicine), Oregon (the American College of Naturopathic Medicine), and California (the Pacific College of Naturopathic Medicine). Unfortunately, none of these three survived.

As public demand for natural healing grew in the 1980s and 1990s, the emerging profession continued to grow a breadth and quality of educational opportunity for those seeking accredited doctorate-level programs in naturopathic medicine.

With thriving enrollments at Bastyr and National College, the Council on Naturopathic Medicine was founded in 1978 to establish and oversee educational standards, and today is recognized by the U.S. Secretary of Education as the national accrediting agency for programs leading to the Doctor of Naturopathic Medicine (ND or NMD) or Doctor of Naturopathy (ND) degree. To further build on the cornerstone of accredited education and ensure educational quality, in 1986 the Naturopathic Physician Licensing Examination became the first national board exam for graduates; today, graduates must pass a two-part medical exam in biomedical and clinical sciences before they are eligible to use the title "ND." This exam is modeled after the conventional medical board exam for allopathic graduates, the U.S. Medical Licensing Exam, which assigns the "MD" license. This training was described in detail in a report from 2001 by the University of California San Francisco Center for Health Professions: "Naturopathic physicians are typically trained in a wide array of alternative therapies including herbology, homeopathy, massage, hydrotherapy, physical medicine, behavioral medicine, Traditional Chinese medicine, Ayurvedic medicine, acupuncture, and nutrition therapy, as well as clinical practices such as minor surgery, pharmacology and obstetrics."[41]

With educational standards set, throughout the 1990s and 2000s, a select group of new programs and institutions attained accreditation status with the Council on Naturopathic Medicine: Southwest College of Naturopathic Medicine and Health Sciences, Tempe, Arizona; the College of Naturopathic Medicine at the University of Bridgeport, Connecticut; the Canadian College of Naturopathic Medicine, Toronto, Ontario; and, in 2011, the Boucher Institute of Naturopathic Medicine, British Columbia, Canada. The establishment of multiple geographic locations for this type of education paves a solid future for the profession, providing hundreds of newly graduated naturopathic doctors every year in the United States and Canada.

There are favorable commentaries on the current state of naturopathic medicine. *Other Healers, Unorthodox Medicine in America*,[40] is a volume written to provide "a scholarly perspective on unorthodox movements and practices that have arisen in the United States." As described in the Encyclopedia of Alternative Health Care by Olsen[42]:

> *While naturopathic medicine is now legal (in several states), many naturopaths practicing in other states are old-timers, practicing under their original "drugless therapy" licenses, issued before laws prohibiting new naturopathic practices went into effect.*

In cooperation with regional associations, the AANP has won licensure and scope of practice protection at a steady rate on par with the growth of schools accredited by the Association of Accredited Naturopathic Medical Colleges. As of 2011, 15 U.S. states, the District of Columbia, five Canadian provinces, and the U.S. territories of Puerto Rico and the U.S. Virgin Islands regulate the naturopathic profession (Box 4-1).

Baer's interest in the evolution of chiropractic as a philosophy of healing led him to Wardwell's work and to Wardwell's earlier scholarship, which had been tied to the mixer orientation within chiropractic. Baer took note of his descriptions of naturopathy as a near-extinct philosophy. Predictions of extinction were consistent among the assessments of social scientists in the 1970s

BOX 4-1 States/Provinces that Regulate the Naturopathic Profession

United States
Alaska
Arizona
California
Connecticut
District of Columbia
Hawaii
Idaho
Kansas
Maine
Minnesota
Montana
New Hampshire
North Dakota
Oregon
Utah
Vermont
Washington
U.S. Virgin Islands
Puerto Rico

Canada
Alberta
British Columbia
Manitoba
Nova Scotia
Ontario
Saskatchewan

As of 2011, the following states have ND legislation pending:
Colorado
Illinois
Iowa
Massachusetts
New York
North Carolina
Pennsylvania
Wisconsin

and continued into the mid-1980s. Twaddle and Hessler, Rosengren, Whorton, and most notably Wardwell, all discussed naturopathy as a once-observable but marginalized philosophy of health and healing at odds with the conventional medical claims of a scientific medicine (see Bibliography). These social scientists placed naturopathy's demise sometime in the 1950s when chiropractic severed its open naturopathic link by terminating ND programs.

Baer, before Wardwell, took special note of Bastyr and the professionalization represented by its scientific medicine–based curriculum and the publication of a John Bastyr College of Naturopathic Medicine project, *The Textbook of Natural Medicine*.

In his 1992 *Medical Anthropology* article[36] "The Potential Rejuvenation of American Naturopathy as a Consequence of the Holistic Health Movement," Baer detailed his own view of Naturopathy's "three stages of development" noted at the outset of this chapter. Besides relying on material covered in the original chapter of "The History of Naturopathic Medicine," which first appeared in 1985, Baer covered much of the new material regarding the emerging (1900–1930s) and declining (1940–1970s) stages of naturopathy.

Baer particularly broke new ground with his recognition of a "potential rejuvenation" of naturopathy as naturopathic medicine and his recognition that the profession had knowingly or unknowingly adopted a recognized survival strategy as a matter of organizational policy: professionalization. Baer also advanced a theory regarding the "potential rejuvenation" as tied to the emergence in the 1970s of holistic medicine. Holistic medicine, as a philosophy of healing, had a cultural affinity with the eclecticism inherent in naturopathic philosophy. In his 2001 book,[43] *Biomedicine and Alternative Healing Systems in America*, Baer updated this view of the status of naturopathic medicine in a chapter entitled "Naturopathy and Acupuncture as Secondary Professionalized Heterodox Medical Systems." With the passage of the additional 10 years, Baer observed[43]:

> *Unlike chiropractic, which no longer poses a serious threat to biomedicine because of its status as a specialty emphasizing spinal manipulation, a rejuvenated naturopathy finds itself in direct competition with biomedicine because both systems claim to provide a comprehensive approach to health care.*
>
> *As osteopathy and chiropractic did earlier, naturopathy … (is) increasingly incorporating the theory and social organization of biomedicine.*
>
> *(N)aturopathy with (its) reductionist philosophy and (its) focus on individual responsibility for healthy living may well undergo further growth in an era of growing health costs.*

THE TWENTY-FIRST CENTURY AWAITS

Baer carried his examination of the sociopolitical aspects forward in his 2001 article,[44] "The Sociopolitical Status of U.S. Naturopathy at the Dawn of the 21st Century" which examined the state of naturopathic medicine as it prepared to enter the twenty-first century. Although "professionalized naturopathy has undergone tremendous growth and legitimization since the late 1970s, nevertheless, it finds itself in a tenuous situation at the dawn of the twenty-first century in that its strength is confined primarily to the Far West and New England; it faces increasing competition from the partially professionalized and lay naturopaths; and it faces the danger of being overshadowed by a powerful biomedical system that is increasingly incorporating aspects of holistic health into its own practice."

He offered no definitive answers to these questions of naturopathic medicine's future, but he also highlighted areas needing further attention by social scientists: continued exploration of the reasons for naturopathy's decline and rejuvenation and continued study of the naturopathic profession in recognition of its state of professionalization.

In closing, Baer observed: "In sum, while changes in the popular ideas about health and healing unleashed the social forces that enabled professional naturopathy to get back on its feet, those same social forces may overwhelm its core claim to being a unique, natural approach to healing."

Whorton expressed the view that in many respects the transition from the marginalized naturopathy to the professionalized naturopathic medicine has now been accomplished.[45] He traced his view of this transformation as part of the larger transformation "from alternative medicine to complementary medicine" on the part of osteopathy, chiropractic, and naturopathy. Whorton described the factors that allowed this transformation even after the death of Lust in 1945: the issue of the "field's lack of a scientific basis" was determined internally when the "died-in-the-wool believers in 'nature cure'" were outlasted by the "liberal practitioners belonging to the so-called western group, naturopaths concentrated in the western states who recognized the validity of mainstream medicine's scientific foundation and sought to incorporate biomedical science into their own system and apply it under the guidelines of naturopathic philosophy."

As Whorton noted, "a key figure among the pseudo-medicals was John Bastyr—a practitioner in Seattle since the 1930s, and particularly well-known for his advocacy of natural childbirth." Bastyr, Whorton noted, "recognized the necessity of naturopathy staying abreast of advances in biomedical science and applying those advances 'in ways consistent with naturopathic principles'."[21] Bastyr was directly involved with the formation and maintenance of the NCNM during the years of naturopathy's decline and lived to see much of "the short history of John Bastyr College (of Naturopathic Medicine) (which) is the most compelling illustration of the triumphant rebirth of naturopathy as naturopathic medicine."[21]

Bastyr has been called "The Father of Modern Naturopathic Medicine" by Pizzorno, ND,[45] the moving spirit behind the professionalization of naturopathic medicine and the founding president of Bastyr University. No individual has carried the practice of NDs in the United States in the way that Lust did, but Bastyr and the others profiled by Kirchfeld and Boyle in *Nature Doctors* kept naturopathy alive during its decline in the 1950s and 1960s so that it could, in time, reemerge.

The movement continues to grow, and so, the impact of natural healing has come full circle. In an era where the statistical number of persons born who are expected to contract cancer, now recognized as a degenerative disease, has increased rather than declined, and the incidence of other degenerative diseases (arthritis, arteriosclerosis, atherosclerosis, etc.) has increased in direct relation to the lengthening of life expectancies produced by improved sanitation and nutrition (although speciously claimed by AMA medicine to be the result of their therapies), the early teachings of Lust, Lindlahr, and others appear to have more validity than ever.

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CHAPTER 5

Philosophy of Naturopathic Medicine

Rachelle S. Bradley, ND

CHAPTER CONTENTS

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INTRODUCTION

This chapter examines the philosophical foundation of naturopathic medicine and its modern applications. Unlike most other health care systems, naturopathy is not identified by any particular therapy or modalities (e.g., conventional medicine, drugs and surgery; chiropractic, spinal manipulation). A wide variety of therapeutic styles and modalities are found within the naturopathic community (Box 5-1). For example, there are still practitioners who adhere to the strict "nature cure" tradition and focus only on diet, "detoxification," lifestyle modification, and hydrotherapy. There are also those who specialize in homeopathy, acupuncture, or natural childbirth. At the other end of the spectrum are naturopathic physicians who use botanical medicines, nutraceuticals, and pharmacology extensively to manipulate the body's biochemistry and physiology. Finally, there is the majority, who practice an eclectic naturopathic practice that includes a little of everything.

Since its inception 120 years ago, naturopathic medicine has been an eclectic system of health care. This characteristic has allowed it to adopt many of this century's more effective elements of natural and alternative medicine as well as to adopt conventional medicine's basic and clinical sciences, diagnostics, and pharmacology. Through all of this eclecticism, naturopathic medicine has always identified the Latin expression *vis medicatrix naturae* (the healing power of nature) as its philosophical linchpin.

However, the expression *vis medicatrix naturae*, by itself, does not provide a clear picture of naturopathic medical philosophy or an understanding of the practice of naturopathic medicine in all of its varied forms. With the profession's history of eclecticism, no two practitioners treat any individual patient exactly alike. This situation has its advantages (e.g., individualization of each patient's care, more therapeutic options) but also makes it difficult to perceive the profession's philosophic cohesiveness. Another major disadvantage of this eclecticism is the difficulty in developing consistent practice standards.

To attempt to solve this problem, the modern profession has articulated a general statement of naturopathic principles that expand on *vis medicatrix naturae* (Box 5-2). However, to gain a more in-depth understanding of naturopathic medicine, one must discuss medical philosophy in general.

MEDICAL PHILOSOPHY

The issues fundamental to a discussion of medical philosophy have changed little since naturopathy first appeared as a distinct profession at the end of the nineteenth century. What has changed is the level of understanding of the biological process and the language of science. Most people who study the early writers on naturopathic medical philosophy quickly get lost in the archaic language and arguments used to justify the theories. This chapter translates these concepts and issues into modern terms.

Vitalism Versus Mechanism

Historically, there have been two main medical philosophies, those of vitalism and mechanism. Their origins can be traced to the Hippocratic writings of ancient Greece. Throughout history, the line separating these two schools of thought has not always been clear, but their philosophical perspectives have

generally been in opposition. The conflicting goals and philosophical foundations of these two concepts remain relevant as the modern practices of conventional and alternative physicians come into conflict. As will be seen, the foundations of naturopathic medical philosophy are found in vitalism. However, naturopathy also recognizes the practical value of the mechanistic approach to health care.

Mechanism

Up to the early part of the twentieth century, there was considerable debate over the issue of vitalism versus mechanism in the field of biology. The mechanists, or materialists, maintained that the phenomenon of life could be explained exclusively as the product of a complex series of chemical and physical reactions. They denied the possibility that the animate had any special quality that distinguished it from the inanimate. It was their contention that the only difference between life and non-life was the degree of complexity of the system.

Mechanism has several other distinctive characteristics. Its most obvious is that it is reductionistic. *Reductionism* is often used as a synonym for *mechanism*. Mechanistic science is also characterized by an emphasis on linear causality. Without this emphasis on reductionism and linear causality, Western science and medicine would probably have not been so successful. As the twentieth century advanced, each new discovery in biological and medical science reinforced the arguments for mechanism, until, by the middle of the century, the biology community had almost exclusively embraced the philosophy of mechanism.

Mechanism is the philosophical foundation of biomedical science and conventional medicine. It is especially visible in the treatment modalities of surgery and most pharmaceuticals. Mechanistic medicine identifies disease and its accompanying signs and symptoms as simply the result of a disruption of normal chemical reactions and physical activities. Such disruptions are caused by the direct interference in these reactions and activities of a "pathogenic agent." (For the purposes of this discussion, the expression pathogenic agent refers to any known or unknown etiologic agent, influence, or condition; examples are microbial agents, autotoxins, genetic defects, environmental toxins, non–end-product metabolites, and physical and emotional stress and trauma.) A living organism, then, is simply a very complex machine that, due to external agents and influences and "wear and tear," breaks down. Because the signs and symptoms of disease are thought to be due only to these mechanical disruptions and interference with reactions, they are considered to be completely destructive phenomena and are therefore to be eliminated. Disappearance of the signs and symptoms indicates that the pathogenic agent and its resulting disease have been eradicated or, more likely, controlled. The goals of mechanistic medicine tend to be the quick removal of the signs, symptoms, and pathogenic agent.

Mechanistic medicine is being practiced in cases in which the intention of the therapy is to intervene in the perceived mechanism of the disease and/or to relieve the symptoms. Examples would be the use of antihistamines to relieve rhinitis, vitamin B_6 to help carpal tunnel syndrome, emergency care for traumatic injuries, coronary bypass surgery for blocked arteries, and insulin in juvenile-onset diabetes. Mechanism is also being used when an identified pathogenic agent is directly attacked or eliminated, for example, the use of antibiotics or the isolation of a patient from a particular allergen. Clearly, mechanistic medicine can be very effective in achieving its goals. In the presence of modern medical technology, it is easy to see how this philosophy came to dominate biology, medicine, and the attention of the public.

However, the unsolved problems of mechanistic medicine—particularly those of chronic degenerative disease; authoritarianism, which alienates patients from responsibility for their own health; and the rising cost of health care—suggest that there are limits to the mechanistic perspective and explain why vitalism has not disappeared and is in resurgence.

BOX 5-1 Naturopathic Modalities

Naturopathic physicians are trained to use a number of diagnostic and treatment techniques. These modalities include the following:

- *Diagnosis.* All of the conventional clinical laboratory, physical diagnosis, and imaging (e.g., radiography) techniques, as well as holistic evaluation techniques
- *Counseling.* Lifestyle, nutritional, and psychological
- *Natural medicines.* Nutraceuticals (i.e., all food constituents, constituents of biochemical pathways, etc.), botanical medicine, and homeopathy
- *Physical medicine.* Hydrotherapy, naturopathic manipulative therapy, physiotherapy modalities, exercise therapy, and acupuncture
- *Family practice.* Natural childbirth, minor surgery, natural hormones, biologicals, and pharmaceuticals

BOX 5-2 The Principles of Naturopathic Medicine

The Healing Power of Nature: *Vis Medicatrix Naturae*
Nature acts powerfully through healing mechanisms in the body and mind to maintain and restore health. Naturopathic physicians work to restore and support these inherent healing systems when they have broken down by using methods, medicines, and techniques that are in harmony with natural processes.

First Do No Harm: *Primum Non Nocere*
Naturopathic physicians prefer noninvasive treatments that minimize the risks of harmful side effects. They are trained to know which patients they can treat safely and which ones they must refer to other health care practitioners.

Find the Cause: *Tolle Causam*
Every illness has an underlying cause, often in aspects of the lifestyle, diet, or habits of the individual. A naturopathic physician is trained to find and remove the underlying cause of a disease.

Doctor as Teacher: *Docere*
A principal objective of naturopathic medicine is to educate the patient and emphasize self-responsibility for health. Naturopathic physicians also recognize and employ the therapeutic potential of the doctor–patient relationship.

Treat the Whole Person
Health or disease comes from a complex interaction of physical, emotional, dietary, genetic, environmental, lifestyle, and other factors. Naturopathic physicians treat the whole person, taking all of these factors into account.

Preventive Medicine
The naturopathic approach to health care can prevent minor illnesses from developing into more serious or chronic degenerative diseases. Patients are taught the principles with which to live a healthy life; by following these principles they can prevent major illnesses.

Vitalism

The philosophy of vitalism is based on the concept that life is too well organized to be explained simply as a complex assemblage of chemical and physical reactions (i.e., a living system is more than just the sum of its parts). This is in contrast to the mechanist's contention that "the only difference between life and non-life is the degree of complexity."

Throughout the nineteenth century, the debate between vitalism and mechanism was carried out mostly by biologists and, in medicine, between the "regular" doctors and those doctors who would now be called alternative. In the medicine of the nineteenth and early twentieth century these would have been homeopathic, hydrotherapy, nature cure, and eclectic doctors—all medical doctors with equivalent credentials under the laws of the time. Although the specific terms of "vitalism" and "mechanism" were not necessarily the nomenclature of their debate, the perspectives were the same.

Interestingly, through most of the nineteenth century this debate within the medical community was distinctively not based on science as we currently think of it. The "regular" doctors of the era, as represented by the American Medical Association, were still strongly influenced by Galen's theory of disease of the four humors with its imaginary anatomy and physiology, bleeding, leeches, mercury, and other horrific treatments. Both the homeopaths and eclectic doctors argued based on empirical evidence; on the other side, the regular doctors argued based on a dogmatic theory that was more than 1500 years old and unsupported by any evidence. Harris Coulter produced the seminal work on this debate in his three-volume book *The Divided Legacy*.

The debate between vitalism and mechanism within the field of biology is well documented within the biology journals of the time. This was an era of amazing discoveries about how life functioned. Naturally, this is where the focus of this debate took place for biologists. As the secrets of cellular metabolism were revealed, this debate lurched from one specific argument to the next. The issue was where in the living organism did "God" have direct control. For example, at one point it was argued that the "seat of the soul" was the cell. As the cell was better understood, the place that was the point of God's intervention was postulated to be the nucleus. As research further revealed how the organelles functioned, the vitalistic biologists gave up ground until vitalism as a distinct philosophy in biology was finally abandoned.

The error that doomed the vitalistic oriented biologists was that they were all reductionistic in the same way as the mechanistic biologists. Reductionistic science seems completely able to learn how life functions from a biochemical and biophysical perspective. Eventually, all of the individual chemical and physical reactions that are found in the processes of life will probably be identified. However, the vitalistic biologists missed the most essential aspect of vitalism: *holism*.

In naturopathy's early years there were few interactions between it and the academic and research worlds. The great authors and practitioners came to naturopathy through "conversion," in other words, most had been cured of some health problem by a natural cure and felt naturopathy and curing the sick was now their calling. There is no evidence that these naturopaths even knew that this debate between vitalism and mechanism was going on in the biology literature. Research in this early era of naturopathy consisted of observing nature and applying these observations to treating patients. This led to a deep appreciation of "nature's" desire for balance and order (what a physiologist would call homeostasis). This holistic perspective, combined with the results of the naturopathic treatments, was the empirical evidence that drove their understanding of health and disease. It was only in the later half of the twentieth century that the field of naturopathic medicine began to converge with the academic and research worlds. Since the 1970s this convergence has moved at breakneck speed, until today there is no longer any real distinction (although this is not evident in some of the politically motivated diatribes against the field of natural medicine). However, by this time the academic and research worlds had long since forgotten about vitalism.

An organism's unique complexity—as demonstrated by its ability to grow and develop, respond to stimuli, reproduce, and repair itself—requires a level of organization and coordination that suggests a distinct quality that is not readily explained by mechanism. This is studied extensively by all medical students in physiology class as the "normal" homeostatic process common to all living organisms. However, the tendency in conventional medical school is to put the concept aside when the student moves on to study pathology and the clinical sciences. Yet, up to the point of death, maintaining homeostasis is a prime, if not the primary, driving force in all living organisms. To think that homeostasis is only an important factor in "normal" physiologic processes and has no relevance in pathology is to ignore all of the basic sciences. All life is attempting to return to this ideal state whenever injured or ill. The only point in the life cycle that an organism is no longer "trying" to maintain homeostasis is death.

Reductionistic science has done a wonderful job elucidating the functions of the various components of life, but it tends to focus the researcher and the physician on the disease process as an isolated phenomenon rather than the result of a complex reaction of the whole organism to a pathologic agent. Fortunately, the debate between the vitalistic and mechanistic perspectives in the modern era focuses on the more relevant and holistic general concepts. Although modern vitalism is inherently holistic in its view, there is no conflict with the findings of biomedical science. What is significant is not the individual biochemical or biophysical reactions, but the fact that they are all coordinated to such a degree as to produce the special activities of a living organism. Because there is no inanimate counterpart to this level of complexity and organization, homeostasis is the most dramatic general argument in favor of vitalism.

A less dramatic argument supporting the vitalistic perspective is the "problem of entropy." Entropy is the tendency of any closed system to find equilibrium, that is, the state of least organization. In other words, systems tend to run down and become less complex over time. In defiance of this universal rule, life, up until the point of death, consistently creates more complex systems out of simple ones. To do this, life actively pursues external matter and energy to incorporate into itself while also selectively eliminating by-products from its utilization of this matter and energy.

When the problem of entropy is examined on the molecular level, the same individual chemical processes and elements may be found in both animate and inanimate systems. In the inanimate system, however, there is a constant move toward a state of chemical equilibrium. This type of system cannot maintain an unstable chemical state and always seeks stabilization. Even after the addition of external exciting energy, the system returns to the simplest, least reactive state possible. The animate system is virtually the opposite. It is continuously in a state of dynamic chemical instability, actively seeking energy to maintain this instability and consistently moving to more complex and more organized states (and back again). It is only at the onset of death that an animate system begins to move toward equilibrium, and, of course, then it is no longer animate.

The third general argument in favor of a vitalistic view of life is evolution. For evolution to exist as a force in nature, generations

of living organisms have to survive long enough to grow, reproduce, and then evolve. For this survival to take place, the organisms' homeostatic and repair processes must be consistently directed toward maintaining a state of balance with the external environment (i.e., health). Any organism that does not behave biochemically and physiologically in this manner dies and cannot evolve. Thus the phenomenon of evolution, as the action of countless living organisms over eons, multiplies life's antientropic quality and is incompatible with a mechanistic view of living systems.

These easily observable examples of life's "special quality" suggest an "organizing force" that goes beyond what is possible from mere chemistry. This quality that makes life unique should not be mistaken as a metaphysical concept, although an argument for or against such concepts is not intended here. The point is only that vitalism is a medical philosophy based on observable scientific phenomena. Unfortunately, a definitive definition of this quality (in the old literature called the "vital force," defense mechanism, or simply "Nature") will have to wait for vitalistically or holistically oriented researchers. Reductionistic research has not provided much clarification of these special qualities of life—just ask a modern reductionistic biologist to explain how homeostasis works. They can describe what happens on a biochemical and biophysical level but they cannot describe why it happens.

At this point in the discussion, not many mechanistic practitioners would have reason to be uncomfortable. However, the conflict becomes evident with examination of the premises upon which the practice of vitalistic medicine is based. What truly separates vitalism from mechanism and makes it useful as a medical philosophy is its perspective on disease and its associated symptoms.

Meaning of Disease

Vitalism maintains that the pathogenic agent does not directly cause most symptoms accompanying disease; rather, they are the result of the organism's intrinsic response or reaction to the agent and the organism's attempt to defend and heal itself. Symptoms, then, are part of a constructive phenomenon that is the best "choice" the organism can make, given the circumstances at any particular time.

These symptoms can be further described as arising from two situations. The first and most common situation is when the symptoms are from what could be called a "healing reaction"—the organism's concerted and organized attempt to defend and heal itself (i.e., the organism's homeostatic process). These healing reactions produce what can be called "benign symptoms." Examples are fever and inflammation in infections, almost any reaction of the immune system, and many of the symptoms of chronic disease.

This interpretation of symptoms is generally ignored by mechanism. Instead, it views a symptom as the result of a destructive process and focuses on intervening by relieving the symptom or manipulating the pathologic mechanism. Mechanistic medicine is therefore most often working contrary to homeostasis and the organism's attempt at healing (this is usually its intent). When this therapeutic approach is effective, vitalists call the result a "suppression" (Box 5-3). This approach to health care is so pervasive that

BOX 5-3 Cure, Suppression, Palliation, and Healing

Cure: A cure occurs when:
(a) a treatment is given to the person;
(b) the signs and symptoms of the disease go away;
(c) the treatment is removed and the signs and symptoms stay away; and
(d) the whole person is healthier and less likely to get sick than before the illness.

This is almost always going to occur only when the whole person was treated, and not just the disease or its symptoms. Palliation and suppression never lead to cure in and of themselves.

Palliation: Palliation occurs when:
(a) a treatment is given for the disease;
(b) the signs and symptoms of the disease go away; but
(c) when the treatment is removed the signs and symptoms return.

The symptoms of the disease are simply being controlled (not cured) as long as the treatment is continued.

It is a classic error of many practitioners and patients to equate palliation with moving towards cure. Palliation is on the opposite end of the spectrum as cure and is closer to suppression. Palliation can be useful, but in and of itself, never leads to cure—other more vitalistic and holistic interventions are necessary and may be as simple as changing to a healthier diet, removing some obstacle to recovery, or reducing stress, or as complex as classical homeopathy or traditional Chinese medicine. When palliation is used over a long enough time, suppression is the natural consequence.

Palliation is the most common result of almost all health care interventions. This is especially true of conventional medicine but also true for much of alternative medicine as well. Unfortunately, both the practitioner and the patient's expectations are frequently satisfied with palliation. This is the most frustrating aspect of modern health care, whether conventional or alternative. Too few people are striving for a cure.

Suppression: Suppression is when:
(a) a treatment is given for a disease;
(b) the signs and symptoms of the disease go away;
(c) the treatment is removed and the signs and symptoms stay away; but
(d) the whole person is less healthy.

Although the symptoms of concern are better, the whole person is worse, which leads to more and worse disease in the future. In conventional medicine suppression is often a goal. Alternative medicine tries for a higher standard, but because palliation is often what happens, suppression can occur here, too.

Suppression frequently occurs because a treatment is given for a symptom or disease rather than the whole person being treated. Suppression leads later to another more invasive illness. An example is when steroids are given to suppress eczema and later asthma develops. If at this later point the person is given a treatment that is curative, there will be a return of the eczema as the asthma gets better.

Healing: Healing is what a living organism (body–mind) does, or attempts to do, for itself. A treatment can only:
(a) control signs and symptoms (palliate or suppress);
(b) support life in a crisis (palliate or suppress);
(c) attack an invading organism such as bacteria or remove a pathologic agent such as a toxin or allergen (palliate);
(d) mechanically repair tissues that have been damaged or are malformed (palliate); or
(e) support and/or stimulate the organism's innate healing processes while the body–mind does the work of healing itself (cure).

Curative treatment involves stimulating the whole organism to heal itself. The palliation and suppression of symptoms does not help to stimulate self-healing. Palliation tends to create the opposite effect and suppression actually gets in the way of the whole body–mind's efforts to self-heal.

most people, lay and professional alike, still think nothing of suppressing mild fevers with antipyretics.

In contrast, vitalism considers these symptoms to be the product of a constructive phenomenon and therapeutically stimulates and encourages this directed healing process. Rather than simply trying to eliminate a pathogenic agent, as mechanistic therapy might, vitalism focuses more on augmenting the organism's resistance to that agent. That is not to say that vitalists object to removing the agent, only that it should be done in the context of simultaneously increasing resistance (in other words, decreasing susceptibility). The importance of this approach becomes evident when one recognizes that disease is only possible when both a pathogenic agent and a susceptibility to that agent are present.

Healing reactions can take several forms. In the first type, an organism's response to a pathogenic agent does not produce symptoms. When the organism is capable of easily defending itself from the agent, no symptoms are perceivable. This is a common homeostatic process and is demonstrated when a potential pathogen, such as β-hemolytic streptococcus, is cultured from a healthy person's throat. However, when the organism is more susceptible or the relative strength of the pathogenic agent is greater, a threshold is reached and symptoms become perceivable. Successful healing reactions of this type include vigorous acute diseases that quickly resolve. The early naturopaths would have called these acute reactions "healing crises." As the susceptibility of the organism increases relative to the strength of the pathogenic agent, there is a greater likelihood that the healing attempt will not be successful. When such a reaction is unsuccessful but vigorous, death may result, unless there is timely application of vitalistic or mechanistic therapy. Examples of this situation are acute bacterial meningitis and cholera.

When the healing attempt is feeble and therefore ineffective, the reaction usually goes into the "chronic disease" stage. Vitalists observe that suppression seems to increase the likelihood that the reaction will be forced to go into such a chronic stage. In this situation the reaction is "smoldering," and most often the organism cannot overcome the pathogenic agent unassisted. It just "holds its own," and as the organism's general health decreases over the years, the reaction gradually degenerates, producing symptoms that become less benign as it moves to an end-stage pathology. Palliating the symptoms during this phase of the disease contributes to the declining health over time because palliation means that the underlying susceptibility or problem is not being addressed in a curative manner. If the organism can be therapeutically stimulated to produce a more vigorous healing reaction, it can often successfully complete the original healing attempt. This augmented reaction is another example of a naturopathic healing crisis and would also be called an "aggravation" by the vitalists who practice homeopathic medicine.

Intervening mechanistically by relieving symptoms does little to stimulate or encourage the healing response; it usually actually inhibits the healing response. In contrast, vitalistic therapies can be very effective in helping these healing reactions, because the goals of such therapies are precisely the same as those of the organism. Thus, it is thought that vitalistic medicine works because, by honoring this process and thereby strengthening the whole organism, it encourages a more effective healing effort. Ideally, the organism is then able to accelerate and complete its reaction against the pathogenic agent, leading to the permanent disappearance of the symptoms as it returns to a state of health.

It would be naive to say that every stage of the healing reaction is positive and in the best interest of the organism or that no symptoms should be palliated. The modern vitalist acknowledges that palliative intervention is sometimes necessary. In contrast, it is important to note that routine mechanistic intervention can encourage its own worst case scenarios. When mechanistic therapies successfully suppress an organism's chosen healing reaction, a less effective and less desirable response is often produced. Therefore, when suppression occurs, it can lead to a more complicated medical situation. Consequently, the very practice of mechanistic medicine tends to reinforce its practitioner's conviction that such intervention is usually necessary. It should be noted, however, that not all mechanistic intervention leads to suppression. It happens less often when the pathogenic agent can be readily eliminated, such as the use of an antibiotic in nonrecurring acute bacterial infections, or when relatively noninvasive therapies are used, such as natural medicines.

The second type of symptom-producing situation occurs when the organism produces symptoms in response to an organic lesion that arises from the direct pathologic influence of a pathogenic agent. These could be called "morbid symptoms," examples of which are symptoms from the mass of an invasive tumor, shortness of breath from emphysema, and pain of an injury or myocardial infarction. It should be mentioned that even these symptoms are the result of the organism's overall effort to maintain homeostasis, and benign symptoms are also often present. In addition, a morbid symptom is not necessarily produced for a negative reason. For instance, pain is valuable as an indication of tissue damage. As can be seen, many, if not most, of these situations involve end-stage disease. Here mechanistic therapies can be very positive when the goals of the therapy do not conflict with those of the organism.

There are instances when invasive mechanistic intervention will probably be required to save "life and limb." These include such conditions as birth and genetic defects, serious traumatic injuries, crisis situations, overwhelming infections, and many malignancies. Unfortunately, mechanistic intervention does not guarantee a successful outcome either. Even in these situations, however, the effectiveness of vitalistic and natural therapy should not be underestimated, and their concurrent use will certainly augment any mechanistic intervention.

The concept of benign and morbid symptoms can be a useful tool to help the understanding of the healing and disease processes, but in many situations, it may not be possible to categorize the type of symptoms produced. A rough rule of thumb, however, would be that virtually all symptoms accompanying reversible or functional diseases are benign. In contrast, many of the symptoms associated with traumatic injury and end-stage pathology would be morbid symptoms.

Scientific Medicine

Although mechanism and vitalism represent opposing perspectives, the systems of medicine that represent these philosophies can be successfully tested and examined with the scientific method.* That is not to say that the philosophy of vitalism has been unquestionably proven—only that the validity of vitalistic

*A thorough review of all health care modalities in use today reveals a category that could be called "esotericia." Although the category is not historically relevant to this discussion of medical philosophy, and its brief mention is not intended as an argument for or against "legitimacy," esotericia would include such things as prayer, faith healing, psychic healing, healing touch, touch for health, and medical dowsing. Generally speaking, the actual operator of the therapy must call on God or have some special endogenous skill or "power" that goes beyond intellectual knowledge. These modalities are all "operator-dependent" and cannot be examined separately from the practitioner—thus greatly increasing the difficulty of their scientific verification.

interventions can be scientifically demonstrated. If a therapy can be proven effective, the effectiveness implies the accuracy of the philosophy upon which it is based. Unfortunately, very few of the vast resources of the biomedical community have been directed toward investigating vitalistic medicine.

Conventional medicine, as the dominant health care system and a representative of mechanism, has claimed for itself the title "scientific medicine." However, it is inherently no more or less scientific than vitalistic medicine. A system is scientific only when it has met the criteria of the scientific method. This method requires the collection of data through observation and experimentation and the formulation and testing of hypotheses. Nonprejudicial science can effectively study any system, but the researcher must understand the system's particular paradigm. Experiments on a vitalistic therapy based on a reductionistic and mechanistic model are not going to be constructed to show success, or if they do show success, it will be entirely fortuitous.

The criteria of the scientific method can be met by vitalistic medicine, but only when the researchers recognize that it cannot be studied as though it is reductionistic or based on a simplistic model of linear causality. When the experimental model acknowledges the complexity of a living system in a social context (i.e., holism and circular causality/feedback loops), vitalistic medicine proves to be both verifiable and reproducible and, thus, scientific. Unfortunately, because of its current political and economic dominance, conventional medicine is in the position to dictate (through economic and publication control) that research and, therefore, the scientific method will be applied primarily to itself. The result is that most conventional practitioners dismiss vitalistic medicine, along with all alternatives, as unscientific. Ironically, most vitalistic physicians also have extensive training in mechanistic and/or conventional medicine. Generally, they are capable of practicing mechanistically and do so to greater or lesser degrees.

NATUROPATHIC PHILOSOPHY

Vis Medicatrix Naturae

Naturopathic physicians assert that all true healing is a result of *vis medicatrix naturae* (the healing power of nature). Unfortunately, some people in the field of alternative medicine (including some naturopathic physicians and students) have mistakenly translocated this concept to the therapy. These practitioners tend to operate as though this "healing power" is an intrinsic property of the natural therapy or medicinal substance itself. In contrast, proponents of vitalism and naturopathic medicine have always understood that the "healing power of nature" is an inherent property of the living organism. *Vis medicatrix naturae* is the living organism's "desire" and ability to heal itself. As mentioned, the homeostatic process best exemplifies this.

Historically, naturopathy is a vitalistic system of medicine. However, over the last 120 years its eclecticism has allowed it to incorporate a number of therapies that can function mechanistically. What makes these mechanistic therapies acceptable, given naturopathic medicine's vitalistic foundation, is the emphasis on meeting each patient's pragmatic health care needs. So the application of *vis medicatrix naturae* in practice is constantly adjusted depending on the situation at hand.

Ideally, naturopathic practice involves only the use of therapies that support the organism and encourage its intrinsic healing process to work more effectively while avoiding the use of medicines and procedures that interfere with natural functions or have harmful side effects. Natural medicines and therapies are therefore preferred, because when they are used properly and in appropriate circumstances, they are the least harmful, least invasive, and best able to work in harmony with the intrinsic natural healing process. In addition, their constituents have been encountered in nature for millions of years. This long period of exposure has enabled the body to develop metabolic pathways capable of effectively utilizing, processing, and detoxifying these medicines.

The total organism is involved in the healing attempt, so the most effective approach to diagnosis and treatment is to consider the whole person. In addition to physical and laboratory findings, important consideration is given to the patient's attitude, psychological and spiritual state, social circumstances, lifestyle, diet, heredity, and environment. Careful attention to each person's unique individuality and susceptibility to disease is critical to the proper evaluation and treatment of any health problem.

Naturopathic physicians contend that most disease is the direct result of the ignorance and violation of what would be traditionally called "natural living laws." These general lifestyle rules (including diet) are based on the concept that there is an environment (both internal and external) that optimizes the health of an organism. Analysis of the lifestyles of Paleolithic and healthy primitive and modern cultures gives naturopathic physicians and their progenitors many clues as to what a healthy lifestyle should involve.

Throughout most of modern history, biomedical science has focused primarily on researching the sick. Recently it has finally begun to evaluate what constitutes a healthy lifestyle. To no one's surprise, this lifestyle looks like the same one advocated by naturopaths for the last 120 years. A healthy lifestyle could be generalized to include the following:

- Consuming natural unrefined foods
- Getting adequate amounts of exercise and rest
- Living a moderately paced lifestyle
- Having constructive and creative attitudes
- Connecting to other people socially
- Being present to the spiritual aspects of life
- Avoiding toxins and polluted environments
- Maintaining proper elimination

It is also important to control these areas during illness to remove as many unnecessary stresses as possible and to optimize the chances that the organism's healing attempt will be successful. Therefore, patient education and responsibility, lifestyle modification, and preventive medicine are fundamental to naturopathic practice.

Although the practice of naturopathic medicine is grounded in *vis medicatrix naturae*, it also recognizes that mechanistic intervention in the disease process is sometimes efficacious and, at times, absolutely necessary. Therefore, naturopathic physicians treat patients with a wide variety of vitalistic and mechanistic therapeutic modalities. It is the circumstances and the goal of the therapy that ultimately determines which approaches are utilized. Naturopathic physicians have a long-standing tradition of integrating the best aspects of traditional, alternative, and conventional medicine in the interest of the patient. As appropriate, patients are referred to other health care practitioners. Whenever possible, every effort is made to use all treatment techniques in a manner that is harmonious with the naturopathic philosophy.

Natural Medicines and Therapies

Traditionally, medicines administered and prescribed by naturopathic physicians have been primarily natural and relatively unprocessed. Four categories of natural medicines can be defined.

The first consists of substances found in nature that have been only minimally processed. Examples include, but are not limited to, foods, clean air and water, and whole herbs. The early "nature cure" practitioners used this category primarily. The second category involves agents extracted or made from naturally occurring products. Although these medicines have undergone processing, their constituents are still in the form found in the original natural substance. These first two types of natural medicinal substances have synergistic constituents that allow their use at lower doses with a resultant broader and safer therapeutic index. Examples of this category are tinctures and other botanical extracts, homeopathic medicines, glandular extracts, and other substances of animal origin.

The third category of natural medicines comprises those highly processed medicinal substances that are derived from a natural source. Often everything has been removed from such substances but the identified active ingredient, and they no longer have any synergistic constituents. Examples of these are the many new nutraceuticals made from plant substances, constituents of biochemical pathways, enzymes, amino acids, minerals, vitamins, and other food extracts.

The fourth category that may be considered natural are those manufactured medicines that are presumed to be identical to naturally occurring substances. They have the advantage of being less expensive and are typically available in higher concentrations. Examples of these manufactured natural medicines include bioidentical hormones, synthetic vitamins, and analogues of plant and animal constituents. However, their use is a compromise because:

- It is difficult to determine whether they are the equivalent of the natural product.
- They lack natural synergistic components.
- They include contaminates from the manufacturing process; these contaminates are often chemically and structurally similar to the desired medicine but generally interfere with the normal pathways rather than enhance them.

Naturopathic physicians also use many natural therapies. What makes a therapy natural is that it is derived from a phenomenon of nature and is used to stimulate the body to heal itself. Examples of these phenomena are air, light, heat, electricity, sound, and mechanical force. Some of these natural therapies are mechanical and manual manipulation of the bony and soft tissues (naturopathic manipulative therapy), physiotherapy modalities (e.g., electrotherapy and ultrasound), hydrotherapy, and exercise therapy. Naturopathic physicians also use lifestyle modification, counseling, and suggestive therapeutics. These therapies are all discussed in more detail in other chapters.

Family and Specialty Practice

Naturopathic physicians, like other types of primary care providers, develop practices that meet their personal interests and skills. Although most are engaged in general and family practice, many have also specialized in particular therapeutic modalities and/or types of health problems. In all situations, however, the emphasis is still on treating the whole person. The practice of family medicine requires the use of some medicines, techniques, and devices that are not natural but belong among the comprehensive family practice services offered by the naturopathic profession.

In the modern era of naturopathic medicine many states have expanded the scope of practice so that naturopathic physicians now practice much like other primary care practitioners with pharmaceutical prescribing rights. However, naturopathic physicians generally approach the use of pharmaceuticals differently than conventional physicians. They are seen as temporary interventions to be used to support the patient while other, more vitalistic natural therapies are used to help the patient recover his or her health with the ultimate goal of no longer needing the pharmaceutical.

Many naturopaths have also developed advanced expertise in different natural therapeutic modalities. These practitioners have usually invested in postgraduate training, such as that available through residencies. Three therapeutic specialties that merit mention are natural childbirth, acupuncture, and homeopathy. There is also a growing trend of specializing in organ systems (e.g., gastroenterology) or diseases (e.g., cardiology).

THE PHILOSOPHICAL CONTINUUM

When the various healing systems are examined and placed on a philosophical continuum, mechanism and vitalism are on different ends of the same health care spectrum. Both ends of this health care continuum have their strengths and weaknesses. Mechanistic medicine is effective for trauma, crisis care, end-stage disease, and many acute disorders. However, it is essentially a failure for chronic disease. Conventional medicine considers most chronic diseases incurable. Vitalistic medicine, in contrast, has its most dramatic successes with chronic disease and is effective with many kinds of acute disease. It is not very effective with trauma and crisis care or with end-stage disease, although it can be a very useful complement to conventional medicine. As can be seen, both ends of the health care spectrum are necessary if every patient's health care needs are to be met.

Although aspects of naturopathic medicine (e.g., constitutional hydrotherapy) and conventional medicine (e.g., chemotherapy) represent the archetypes of vitalism and mechanism, the space between the ends of this spectrum is a gray area within which both naturopathic and conventional physicians operate on a continual basis. Naturopathic physicians integrate vitalistic therapies with mechanistic therapies, but it is not possible for everyone to be experts in everything. The vast majority of naturopathic or conventional physicians cannot learn and competently practice all types of health care. Consequently, to effectively meet society's health care needs, it is necessary to create an integrated health care system. Such an integrated system would have both vitalistic and mechanistic practitioners working together in the same clinical settings.

The trends of popular culture and biomedical science that are finally beginning to study alternative medicine suggest that the creation of an integrated health care system is now under way. However, it takes no great skill for a mechanistic medical doctor to switch from giving a synthetic drug for a disease to giving a natural medicinal substance (both mechanistically oriented interventions). If naturopathic medicine becomes just another mechanistic system using natural medical substances to treat disease (instead of a system identified with treating the whole person vitalistically), it will lose its unique niche in an integrated health care system. To survive and thrive in this new environment, naturopathic medicine must keep its vitalistic roots. With a thorough grounding in *vis medicatrix naturae*, modern naturopathic medicine will flourish and achieve a leadership position as the dominant health care paradigm shifts to the integrated medicine of the future.

CONCLUSION

The practice of naturopathic medicine can be summarized most simply as helping the body–mind heal itself in the least invasive, most fundamentally curative manner possible. This approach is

not tied to any particular therapy or modality, but rather is oriented to a rational blend of vitalistic and mechanistic principles working with the whole person and educating the patient in the ways of health.

As naturopathic knowledge of health and disease grows, new therapies and approaches to health care will be added as they satisfy the principle of *vis medicatrix naturae*. With integration of the larger health care system, naturopathic medicine's place is assured as the profession that truly understands each unique human being's power to heal.

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CHAPTER 6

Placebo and the Power to Heal

Peter W. Bennett, ND, RAc

INTRODUCTION

As living organisms, we have evolved with an innate capacity for self-healing. Naturopathic physicians have always relied in the clinical setting on this self-healing capability of the individual. The healing power of the body, the "life force," is a cornerstone of naturopathic philosophy and treatment. The "inner" power to heal is one of the great mysteries of medicine, and it behooves us as physicians, regardless of our licensing body, to understand the biology and physiology that surround the processes that guide and control this phenomenon. Following this logic, a central problem to be explored and considered is that placebo response has shown medical science that the mind of a patient has a powerful role in therapy. Because the definition and understanding of the human mind challenge a consensus of our collective insight and understanding, it is natural that the function and use of placebo is an area of myth and misunderstanding rather than an area of wisdom and insight.

As time marches on, medicine has failed to stimulate and utilize the subliminal healing capacity of the mind. A recent review of placebo literature in *Lancet*[1] concluded that the placebo effect has a complex physiologic multisystem dimension and should be encouraged in the clinical situation to optimize health and healing; a summary reached by this author 25 years ago. In November 2000, 17 health centers and agencies gathered together for 3 days to explore the science of self-healing hidden in the power of placebo. This conference focused on the powerful mind–brain physiology of placebo and its potential for affecting the course of human disease.[2] One of the conclusions of the conference was that the "placebo response" has potential use for medical application and needs further exploration.

Research has shown that the impressions and thoughts in a patient's mind and the attending physician's intention have a measurable effect on the health of the patient. The ability of the patient's mind to affect the process of virtually every disease has been well documented,[3,4] and the internal mechanisms and pathways by which the mind can positively or negatively affect the immune and healing processes has been investigated in the scientific literature of psychoneuroimmunology.[5,6] As the body of knowledge documenting the critical role of the patient's psyche in the therapeutic environment has grown, it has become increasingly important for all schools of medicine to teach the healing potential of the human mind.

Conventional medical thinking has turned its opinion of placebo from that of a nineteenth-century pejorative to a concept that sums up the complex mind–body interactions affecting the power of people to heal.[2] Unfortunately, the most modern abuse of the concept of placebo comes from biased critics of alternative medicine who have chosen to label the beneficial effects of these therapies as merely from placebo. These critics dismiss the science of natural healing as an imaginary phenomenon and the last resort for quack doctors who have no real medical treatments to offer their patients.[7]

The most interesting aspect of placebo literature is exploration of the extent of the potential of the mind to influence human health. The "power of placebo" draws upon the innate ability of the body to spontaneously heal itself, a fundamental principle of naturopathic medicine. This point separates the care delivered by naturopathic physicians from the pharmaceutical and surgical approaches of current medical "standard of care" procedures. If common medical texts on internal medicine or ambulatory care are examined, the word "healing" is not found in the index. Except for the diagnostic evaluation of "self-limiting diseases" and "spontaneous

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regression," the ability of the human organism to self-right and repair from a state of acute or chronic disease is not explored in modern medicine except under the designation "placebo response." The placebo response, therefore, represents all the "unknown" variables that conspire to heal a patient despite pharmaceutical and surgical intervention. Although it seems to be a natural area to develop in clinical and hospital settings, the fundamental separation of mind and body in conventional medical thinking may be slowing down a standardization of care that actively engages the hopes and beliefs of all patients undergoing treatment.

PLACEBO RESPONSE

Placebo response represents the power of the mind, through intention, to effect (1) a change in oneself, (2) a change in those around one, and (3) a change in the environment in which one lives. Intention has been observed to affect machines[8] and remote biological systems.[9] Distantly influenced systems include another person's electrodermal activity, blood pressure, and muscular activity; the spatial orientation of fish; the locomotor activity of small mammals and the rate of hemolysis of human red blood cells. Prayer, an example of intention, has been extensively studied as a therapeutic healing modality.[10] One study showed a dramatic result in cardiac intensive unit recovery when patients were prayed for by someone at a distant location.[11] Patients in this study were 5 times less likely to require antibiotics, 3 times less likely to experience pulmonary edema, 12 times less likely to require endotracheal intubation, and significantly less likely to experience cardiac mortality.

Our biological systems must conform to the laws of physics. Modern physics has investigated the effect of an observer on the system observed. It has been shown that an electron will acquire a definite axis of measurement in the process of measurement. Bell's theorem supports the idea that our universe consists of particles unified instantly as an indivisible whole; our biological homeostatic systems cannot be analyzed in terms of independent parts. The interconnected nature of our biological systems has been known for thousands of years; the ancient Buddhist concept of "interdependent phenomena" accurately describes this paradigm.

Our current medical system has not shifted with the developments in modern physics. These modern ideas of biological systems are diametrically opposed to Cartesian paradigms that our internal and external environment consists of separate parts joined by local connections. Medicine must take a "quantum leap" to catch up with the knowledge we possess about our environment through quantum physics. We can see clearly that it is impossible for a doctor to observe a patient without the observation's affecting the health of the patient.

Pierre Teilhard de Chardin postulated, and Rupert Sheldrake proved, the possibility of a "morphogenetic field" for the subliminal communication to all members of our species.[12] The effect of human thought on other members of society has been described in human society since the beginning of our earliest cultures.

Naturopathic physicians believe that the body has a powerful ability to maintain health and repair to a healthy state after disease by virtue of its inherent power of vitality. This homeostatic healing mechanism has been selected by nature in the same way that the organs that we consider to be vital to our survival have been selected. Healing happens unaided by simply maintaining an environment that does not obstruct the path of cure.

Because placebo literature documents the philosophical foundations of the naturopathic health care model, it is important to review the full scope of this subject. Integrating known placebo initiators in clinical practice is essential for good patient care.

WHY STUDY THE PLACEBO EFFECT?

For hundreds of years, physicians have watched their patients respond to therapies with a wide range of results. Some patients recover fully, whereas others, with apparently identical diseases and therapies, wither and die. Today, a skilled physician can correctly diagnose the condition of a patient by applying the sophisticated techniques of modern medicine. Then, an appropriate therapy, the efficacy of which has been thoroughly proven in research and clinical trials, can be prescribed. Through this process the patient will have received the best care available through current medical technology. However, if the diagnosis, therapy, and therapeutic interaction do not stimulate the hope, faith, and belief of the patient, the chances of success are measurably diminished. It has been repeatedly demonstrated in the literature on the placebo effect,[13] psychoneuroimmunology,[5] and psychosomatic,[14] behavioral,[15,16] and psychiatric[17] medicine, that the beliefs of both the patient and the doctor, and their trust in each other and the process, generate a significant portion of the therapeutic results.[18]

The placebo and its effect are not separate from any aspect of the therapeutic interaction, nor are they "nuisance variables" muddying a clear clinical picture. Rather, they send the physician a strong message: it is a patient's own belief system that mobilizes the inherent healing powers of the mind. By studying the placebo effect, a physician is better able to fully harness this power to trigger internal healing mechanisms. Yet, despite the quantity of documentation, the placebo effect remains one of the most misunderstood areas in modern medicine.

The physician should always strive to stimulate self-healing, or the placebo effect, as fully as possible to maximize its potential for healing. Someday physicians will be able to explore the deepest recesses of the unconscious to directly access therapies that assist the body in restoration of internal homeostasis. The optimal model for health care is the marriage of appropriate medical technology with the factors that have been shown to generate the placebo effect. This exciting scenario shines on the horizon as the health care of the future.

Because the doctor–patient relationship is such fertile ground for stimulating the healing response,[19-21] it serves a physician well to comprehend the nature of the placebo phenomenon to fully realize this potential for healing.

HISTORY OF PLACEBO

Both the modern physician and primitive medicine men and shamans of the past used ineffective therapies to stimulate healing in their patients. As Shapiro observed, "the true importance of placebo emerges with a review of the history of medical treatment."[22] It was noted that the historic therapies of the medical profession and traditional healers, "purging, puking, poisoning, puncturing, cutting, cupping, blistering, bleeding, leeching, heating, freezing, sweating, and shocking,"[23] worked because of the placebo effect. Although in retrospect, these practices might seem ludicrous, all of these therapies were once considered effective. As an embarrassing epilogue, placebo literature showed that ineffective procedures are just as pervasive in modern medicine as in the jungle hut of the shaman. We must therefore ask ourselves how unfounded medical therapies can survive peer-reviewed literature and centuries of cultural acceptance.

The power of the patient's belief in the potential for cure has been consistently observed throughout history. Both Galen and Hippocrates recognized the strong effect of the mind on disease and recommended that faith, treatment ritual, and a sound

doctor–patient relationship could provide important therapeutic results.[24] Recognition of the power of positive expectation was recorded frequently in the medical literature of the seventeenth and eighteenth centuries. It was in the eighteenth century that placebo was first defined as a "commonplace method of medicine."[25] As the importance of drug therapy grew in the nineteenth century, the term placebo became identified with medicines involving substances that resembled drugs. However, in the 1940s, because of the increase in double-blind research, it became associated with inert substances that were used to replace active medication.

ORIGIN OF THE TERM PLACEBO

The original Latin meaning of *placebo* is "I shall please."[26] Although the term had a purely medical application in the first half of the twentieth century, its meaning has been subject to various interpretations throughout the last several hundred years.

Before the 1940s, placebos were pharmacologically inactive substances, such as saline and lactose pills, used to satisfy patients that something was being done for them—in other words, the doctor was "pleasing" the patient. The 1940s and 1950s saw an explosion of the use of double-blind experimental procedures to evaluate the growing number of new drugs and medical procedures. Suspicion arose that all medical therapies contained an element of placebo phenomena.[27] This new understanding pressed the scientific community to offer new, far broader definitions.

Shapiro[23] offered the classic definition of a placebo:

> *Any therapeutic procedure (or that component of any therapeutic procedure) which is given deliberately to have an effect, or unknowingly has an effect on a patient, symptom, syndrome, or disease, but which is objectively without specific activity for the condition being treated. The therapeutic procedure may be given with or without the conscious knowledge that the procedure is a placebo, may be an active (non-inert) or inactive (inert) procedure, and includes, therefore, all medical procedures no matter how specific—oral and parenteral medications, topical preparations, inhalants, and mechanical, surgical, and psychotherapeutic procedures. The placebo must be differentiated from the placebo effect which may or may not occur and which may be favorable or unfavorable. The placebo effect is defined as the changes produced by placebos. The placebo is also used to describe an adequate control in research.*

A more accurate definition would be: "Placebo effect is the process of a physician working with the self-healing processes of a patient. Placebo response means healing that results from the patient's own natural survival and homeostatic defense mechanisms."

Modern placebo definitions extend to its nature, properties, and effects. Placebo can be known or unknown, active or inactive, positive or negative in results (placebo effect vs nocebo effect), and can extend to all forms of diagnostic or therapeutic modalities[28] as further defined in Box 6-1.

BOX 6-1 Types of Placebo

Known placebo: Placebo used in a single-blind experiment. The doctor knows it is placebo but the patient does not.

Unknown placebo: Double-blind use of placebo. Neither the doctor nor the patient knows that the medication is a placebo.

Active placebo: Any substance that has an intrinsic physiologic effect that is irrelevant to the ensuing placebo effect. The vasodilating effect of niacin would make it a good active placebo.

Inactive placebo: Any substance that is used with medicinal intent but that has no inherent physiologic effect. Aside from the glucose effect in a sugar pill (or, to complicate things, an allergic reaction to some component of the supposedly inert substance), it has no physiologic effect.

Placebo effect: Any changes that occur in a patient as the result of placebo therapy.

Nocebo effect: Any changes that occur as a result of placebo therapy that are perceived as negative or counterproductive to the path of cure.

CLINICAL OBSERVATIONS OF "KNOWN" PLACEBO THERAPY

One of the more dramatic examples of the placebo effect reported in the medical literature involved a patient with advanced lymphosarcoma, which Klopfer[29] reported was highly susceptible to the patient's faith in an experimental drug called Krebozion. When the patient was started on the drug injections, his enthusiasm was so intense that "The tumor masses had melted like snowballs on a hot stove, and in only a few days, they were half their original size!"[29] The injections were continued until the patient was discharged from the hospital and had regained a full and normal life, a complete reversal of his disease and its grim prognosis.

Within 2 months of this recovery, reports that the drug Krebozion was ineffectual were leaked to the press. Learning of this report, the patient quickly began to revert to his former condition. Suspicious of the patient's relapse, his doctors decided to take advantage of the opportunity to test the dramatic regenerative capabilities of the mind; a single-blind study was performed on the patient using pure placebo. He was told that a new version of Krebozion had been developed that overcame the difficulties described in the press, and some of the drug was promised to him as soon as it could be procured.

With much pomp and ceremony, saline water placebo was injected, increasing the patient's expectations to a fevered pitch. Recovery from his second near terminal state was even more dramatic than the first. Tumor masses melted, chest fluid vanished, he became ambulatory, and even went back to flying again. At this time he was certainly the picture of health. The water injections were continued, since they worked such wonders. He then remained symptom free for over two months. At this time, the final American Medical Association announcement appeared in the press—"nationwide tests show Krebozion to be a worthless drug in the treatment of cancer." Within a few days of this report, the patient was readmitted to the hospital in extremis. His faith was now gone, his last hope vanished, and he succumbed in less than two days.[29]

Other famous placebo case studies are one reported by Cannon[30] on "voodoo death" caused by belief, and one reported by Kirkpatrick,[31] who documented the spontaneous regression of lupus erythematosus resulting, in part, from the patient's belief in the removal of a curse.

Other Clinical Observations

Belief sickens, belief kills, belief heals.[32]

Evans[33] and Beecher[34] reviewed, between them, 26 double-blind studies on the efficacy of active analgesic drugs in the treatment of pain. Independently, they concluded that 35% of patients with pain experienced a 50% reduction in their symptoms after placebo medication. These were particularly remarkable results when viewed in the context of Evans's observation that

BOX 6-2 Symptoms and Side Effects of Placebo Response

- Anger[35]
- Anorexia[36]
- Behavioral changes[37]
- Depression[38]
- Dermatitis medicamentosa[36]
- Diarrhea[36]
- Drowsiness[38]
- Epigastric pain[36]
- Hallucinations[39]
- Headache[40]
- Lightheadedness[36]
- Palpitation[36]
- Pupillary dilation[34]
- Rash[36]
- Weakness[36]

with a standard dose of morphine, only 75% of the patients experienced a 50% reduction in pain. In calculating the efficiency index of placebo analgesia, a method often used to determine the relative efficiency of drugs, placebo was 0.56 as effective as a standard dose of morphine. This prompted Evans to remark, "Thus, on average, placebo is not a third as effective as a standard injection of morphine in reducing severe clinical pain of various kinds but is in fact 56% as effective."[33]

As discussed previously, placebo has been evaluated in a wide variety of clinical settings in addition to pain management (Box 6-2). When a phenomenon such as placebo has been observed to be active in diverse clinical situations, such as surgery, drug therapy, psychotherapy, and biofeedback, and over a range of physical and mental symptoms, the conclusion that it must be a factor in all aspects of medicine is inescapable.

In addition to the variety of positive effects that placebo produces are the *nocebo effects*, perceived as counterproductive to the therapeutic goals. These side effects are frequently consistent with those of the medication that patients believe they are getting. For example, the studies that measure the effects of a supposed aspirin usually show nocebo effects of ulcerlike pain.[41]

In homeopathy, aggravations and ameliorations are commonly seen when a placebo is given to fend off a patient's need to take a medication while the homeopathic physician is waiting to see whether a high-potency remedy will effect a cure. Homeopathic doctors report that placebos can cause anxiety and loneliness as well as calmness and immediate relief from insomnia.[42]

PLACEBO MYTHS

Investigation of the understanding of placebo found in the current medical literature revealed the misconceptions that prevail about the nature of placebo therapy and its effectiveness.[42] A study undertaken to examine doctors' and nurses' attitudes about the efficacy and use of placebos showed that both groups underestimated the number of patients who could be helped by placebo.[43] Physicians showed a consistent pattern of placebo use, as follows:

- Placebos were used to prove the patient wrong through diagnosis of psychogenic symptoms in patients who were thought to be exaggerating, imagining, or faking their symptoms.
- Placebos were used in the treatment of alcoholic, psychotic, and demanding patients who were disliked by the staff of the hospital.
- Placebos were used as treatment in situations in which standard treatments failed or the patient was getting worse.

These misconceptions regarding the nature of the placebo accounted for its widespread misuse in patients who were perceived as uncooperative or who were suspected of malingering.

TABLE 6-1 **Physiologic Changes Induced by Placebo**

PHYSIOLOGIC FUNCTION	PHYSIOLOGIC CHANGES
Heart	Improved exercise tolerance[45,46] Decreased serum lipoproteins[47] Improved T waves[48] Decreased pulse rate and arterial pressure[49]
Sympathetic stimulation	Decreased tremulousness, sweating, and tachycardia[36]
Claudication	Increased walking distance[50]
Opiod dependence	Addictive drug withdrawal[51]
Postsurgical trauma	Decreased facial swelling[52]
Diabetic blood sugar dyscrasias (NIDDM)	Lowered fasting blood sugar[53,54]
Gastrointestinal secretion and motility	Decreased gastric acid secretion[55] Changes in gastric motility[56,57] Healing of duodenal ulcers[58]
Hypertension	Lowered blood pressure[59-61] Reduced urinary catecholamines[62]
Motor dysfunction	Improved tremor magnitude[63]

NIDDM, non–insulin-dependent diabetes mellitus.

Myths about placebos continue to hinder full understanding about the power inherent in this aspect of health care. The most common myths are discussed here.[44]

Myth 1

"Since placebos tend to be physiologically inert, it is not possible for them to have an effect on physiologic homeostasis."

Fact. Research showed that placebos have a wide range of effects (Table 6-1) that are found throughout all aspects of human physiology.

Myth 2

"Placebos are useful only with symptoms that are associated with psychological or psychosomatic complaints. Patients who need a placebo are hypochondriacs with vivid imaginations and need to be palliated with something 'to please them'."

Fact. Placebos have been shown to be effective in the care of all types of patients, with a consistent level of positive results for a wide variety of accurately diagnosed diseases.

Beecher[18] was one of the first to compile a listing of the therapeutic effectiveness of placebo, thereby uncovering the wide range of therapeutic applications that were previously thought to be limited to only pain control. He concluded, "there is too little scientific as well as clinical appreciation of how important unawareness of these placebo effects can be and how devastating to experimental studies as well as to sound clinical judgement lack of attention to them can be."[18]

The large and ever-growing number of studies on placebo and double-blind research (Box 6-3) supports the following assertion made by Beecher[18] 30 years ago:

> *Many "effective" drugs have power only a little greater than that of placebo. To separate out even fairly great true effects above those of placebo is manifestly difficult to impossible on the basis of clinical*

BOX 6-3 Conditions That Have Been Shown to Respond to Placebo

- Angina[45,46,64-66]
- Anxiety[36,67,68]
- Arthritis[41,69,70]
- Asthma[71-74]
- Behavioral problems[75]
- Claudication, intermittent[50]
- Common cold[76-79]
- Cough[80]
- Depression[81,82]
- Diabetes (non–insulin-dependent diabetes mellitus)[53,54]
- Drug dependence[36]
- Dysmenorrhea[83]
- Dyspepsia[84]
- Gastric ulcers[85]
- Hayfever[86,87]
- Temporal and vascular headaches[88-90]
- Hypertension[91,92]
- Labor and postpartum pain[93]
- Premenstrual syndrome[94]
- Ménière's disease[95]
- Nausea of pregnancy[36]
- Pain[96,97]
- Psychoneuroses[98,99]
- Rhinitis[100]
- Sleep disturbances[101]
- Tremor[64]

impression. Many a drug has been extolled on the basis of clinical impression when the only power it had was that of a placebo.

Myth 3

"The placebo effect is found only in substances that are inert."

Fact. Placebo phenomena have been observed across a wide spectrum of medical disciplines, including surgery,[102] drug therapy,[103] and biofeedback.[104]

Myth 4

"The patient who responds to placebo can be characterized as someone who is of a typical neurotic disposition."[43]

Fact. Although many studies have tried to impute a personality type, disposition,[104,105] or certain epidemiologic class[106] to the patient who responds to placebo, this has yet to be well demonstrated, because given the right circumstances, any person can become a placebo reactor.[107,108]

After reviewing the bulk of the research on this subject, Bush[109] and Wolf and Pinsky[36] concluded that the attempts to pigeonhole personalities into a clinical profile ignored the complexity of the human mind. Gliedman et al[98] similarly reported that age, sex, marital status, social class, and intelligence were unimportant factors in determining a patient's response to placebo. Wolf summarized that attempts to identify placebo reactors need to

> *"identify the nature of the symptom being treated, the motivation of the patient and physician, the nature of the test agent, its mode of administration and the life situation of the subject at the time he is tested. The significant point here is not the apparently conflicting findings of investigators with respect to placebo reactors, but rather that in any given situation, responses to a placebo may vary as compared to any other situation and the significance of situations to human subjects cannot be precisely duplicated."*[36]

PHARMACODYNAMICS

The physiologic response of the "inert and inactive" placebo extends into the realm of drug pharmacodynamics. Dose–response time curves, cumulative effects (increasing therapeutic efficacy with repeated doses),[110] variable strengths of analgesia based on a patient's drug expectation,[64] drug interactions,[36,111] and carryover effects[39,105] have all been demonstrated. The effects of placebo are so pronounced that some observers have suggested that they can exceed the effects attributable to potent pharmacologic agents.[36]

Packaging and Delivery

Several studies found that the effectiveness of placebo therapy depends on the mode of delivery.[48] For example, one study found that green tablets improved anxiety and yellow tablets improved depression,[112] whereas another study found that blue capsules were more sedative and pink capsules were more stimulating.[49] Placebo injections appeared to be more effective than oral administration after oral placebo failed to relieve the symptoms.[41]

Placebo Interactions

Benson[113] wrote that the patient's belief was also a powerful force in determining the level of relief afforded by the placebo. An increase in patient expectation enhances the physician's ability to elicit a placebo response. Even if patients know that they are receiving placebos, the expectation and relief brought about by the therapeutic interaction provides positive results.[114] The importance of expectation was further demonstrated by the observation that the greater the stress level of the patient and the greater his or her need for assistance, the greater the effectiveness of placebo.[38] This was seen even in patient responses to psychotropic drugs: D-lysergic acid diethylamide tartrate 25 (LSD-25) could have no effect if the patient was told that the drug was a placebo.[104,115]

Patients, such as war heroes, who had severe injuries but did not have great mental suffering attached to their pain needed less pain medication than persons with similar injuries who had pain that engendered anxiety and connoted disaster.[116]

PLACEBO HEALING MECHANISMS

When animals or humans can react to their own deviations from homeostasis and when these deviations set off restorative processes, therapeutic intervention, including placebo, has an already existing substrate of recovery for exploitation.[15]

A human being has an intrinsic ability to "self-right"—*vis medicatrix naturae* (the healing power of nature). This is the keystone of a philosophy that has been held for thousands of years by naturally oriented physicians (see Chapter 5). The concept of a homeostatic, self-regulating mechanism is central to the understanding of basic concepts of physiology: negative feedback loops control virtually all systems of the body. According to Guyton,[117] "the body is actually a social order of about 75 trillion cells organized into different functional structures.… [E]ach cell benefits from homeostasis and in turn each cell contributes its share toward the maintenance of homeostasis."

The body can maintain health and reestablish a healthy state after disease by virtue of its inherent vitality. This is part of the definition of a homeostatic mechanism; it has been selected by nature in the same way that organs vital to our survival have been selected. The surviving species are those most fitted and best able to cope with dysfunction. Those organisms that can tolerate the greatest stresses and still maintain a normal physiology are the hardiest survivors and ensure the species' ability to increase the limits of its adaptation. Therefore, given that an organism is self-maintaining when in an environment that it has been selected for, healing happens unaided through simply maintaining an environment that does not obstruct the path of cure. As Norman

Cousins[118] observed, "without any help, the human body is able to prescribe for itself. It does so because of a healing system that is no less real than the circulatory system, the digestive system, the nervous system, or any of the other systems that define human beings and enable them to function."

The Role of Emotions

Starting in the 1970s and early 1980s, review articles began to examine the effect of the mind on the immune system, emphasizing mechanisms and pathways that gave rise to a new field called psychneuroimmunology.[4] Reviews of studies that explored how specific emotions can increase cancer susceptibility,[119,120] examined the effect of emotions and recovery from cancer,[121] investigated the increased incidence of sudden and rapid death during psychological stress,[122] and monitored the changes in immune function during emotional stress[123,124] all confirmed that emotions play a powerful role in the prognosis of a patient. Cannon[30] and Tregear[125] documented dramatic case histories of pioneering anthropologists who witnessed the power of taboos and curses to kill strong healthy men and women in third world cultures throughout Africa, South America, and the South Pacific. Tregear[125] wrote, "I have seen a strong young man die the same day he was tauped [tabooed]; the victims die under it as though their strength ran out as water."

The *Vis Medicatrix Naturae*

The healing process described as *vis medicatrix naturae* demonstrates the significant power and potential of the self-generated healing capacity. For a physician, there is no more powerful stimulator of this healing mechanism, the placebo effect, than a strong doctor–patient interaction. Just walking through the door of the physician's office nudges a patient's internal homeostatic mechanisms into seeking higher levels of health, healing, and adaptation. The placebo effect is a result or effect of the patient's seeking the assistance of the doctor's ability to heal and cure. As Benson[113] noted:

> *When we dissected the placebo effect a number of years ago, we found three basic components: One, the belief and expectation of the patient; two, the belief and expectation of the physician; and three, the interaction between the physician and the patient. When these are in concert, the placebo effect is operative.… Perhaps nothing is being transmitted from the healer to the patient, but rather it's the belief the patient has in the healer that's helpful.*

Conscious Control Over Homeostasis

The body has two internal forces to maintain homeostasis: a lower drive and a higher drive. The lower drive is the inherent internal healing mechanism, the vital force, or the primitive life support and repair mechanism that can operate even in a person who is asleep, unconscious, or comatose. The higher drive is the power of the mind and emotions to intervene and affect the course of health and disease by depressing or stimulating the internal healing capacities. The effect of this drive can be seen in the clinical observation of patients who move toward spontaneous remission of a life-threatening disease through positive emotional support[13,121] and in patients who fail to express emotions compatible with the body's attempts to survive.[121]

In any disease process, the consciousness of the patient decides the effectiveness of any therapy. It has been suggested that a wide range of nondrug stimuli has the capacity to modulate human functioning.[126] It is emerging in medical literature that any sensor stimuli or mental activity is able to alter disease progression. This extends to the thoughts and intentions of those connected to the patient. Experiments in remote intention-generated healing and prayer showed that the intention of others was a factor in the homeostatic capabilities of the mind and body. The fact that the homeostatic mechanism can sense and respond to these remote intentions is a reflection of the power of the human mind. Some authors believe that there is a physiologic basis for the unlimited possibility of human voluntary control.[127] The conclusion that awareness or "mind," anyone's mind—the patient, the doctor, or someone who is aware of the patient—can alter the patient's physiology is testament to the "holos" concept in different schools of alternative and complementary medicine. This idea flies so deeply in the face of our mechanistic model of medicine, it forces a complete paradigm shift in the conventional social ethos of medical care.

The ultimate control of psyche over soma demonstrates the priority of the conscious mind over physiologic processes such as immunity and pain control.[128] This puts an enormous responsibility on the physician. He or she must take full account of a patient's mental and emotional states when treating chronic or life-threatening disease.

Physiologic Mechanisms

Identification of a biochemical mechanism for placebo analgesia has done more to change the image of placebo than any amount of arguing about the importance of beliefs and the mind.[129]

The mechanisms of placebo response have been suggested to be a mixture of psychological interactions mediating physiologic responses.[17] Psychological components of the patient's placebo effect have been shown to include decreased anxiety and increased relaxation,[64] conditioning,[16] expectation,[21] and well-being generated by the establishment of a sound doctor–patient relationship.[130,131]

Review articles summarized a wide range of receptor agonist mechanisms driving the neural pathways in different parts of the brain.[132] To date, endorphin, dopamine, cholecystokinin, interleukins, growth hormone, and cortisol have been implicated. The physiologic mechanisms of the placebo effect were suggested to include chemicals, catalysts, and enzymes. It is believed that steroids, catecholamines,[13] the autonomic nervous system,[17,133] neuropeptides, and endorphins[134] are also involved. These physiologic mechanisms interrelate synergistically and are rapidly being researched within the rapidly developing field of psychoneuroimmunology,[6] through which the links between depression, affective disorders, emotions, and the immune system and central nervous system (CNS) are being explored. Susceptibility to depression and sensitivity to pain have now been found to be mediated through neurotransmitters such as catecholamines, serotonin, and dopamine.

The current model for explaining the mechanism by which emotions, mood, and psychological stress suppress immune function involves cerebral–hypothalamic and pituitary interaction, which translates stress and anxiety into an autonomic–endocrine response. This response adversely affects the immune function, particularly after chronic stimulation. Stressful stimulation is received in the sensory cortex of the brain and is then referred to the limbic system and the hypothalamus. This interface of higher brain functions and homeostatic regulating centers provides the communication link between the psyche and soma. According to Rossi,[17] "The hypothalamus is thus the major output pathway of the limbic system. It integrates the sensory-perceptual, emotional, and cognitive function of the mind with the biology of the body."

The nerve centers that control both branches of the autonomic nervous system (both parasympathetic and sympathetic), nerve cells that secrete endocrine-releasing factors, and neural pathways that release hormones directly into the posterior pituitary are in the hypothalamus. The corticosteroids and catecholamines from sympathetic stimulation are key factors in the alteration of disease susceptibility in response to stress. Corticosteroids inhibit the function of both macrophages and lymphocytes, as well as lymphocyte proliferation.[135] Corticosteroids also cause the thymic and lymphoid atrophy noted by Hans Selye in his experiments on stress-induced immune dysfunction.[136]

The autonomic release of catecholamines stimulates receptors on the surface of lymphocytes, thereby increasing their maturation rate. When lymphocytes are in a mature state, their ability to kill bacteria and cancer cells and produce interferon seems to become paralyzed.[137] Thus a population of mature lymphocytes develops, ready to defend the body from infection and inflammation, yet remains paralyzed until the "red alert" signal of sympathetic fight or flight is turned off, signaling the appropriate time to rest and repair.

A number of other peptides, E-type prostaglandins, somatotropin, histamine, insulin, endorphins, antidiuretic hormone, and parathyroid hormone all have receptor sites on lymphocytes and can stimulate the same cyclic adenosine monophosphate mediated response resulting in lymphocyte maturation and inhibition.[135] A study of the effect of catecholamines on the human immune system showed that when a physiologic dose of epinephrine was injected into a healthy volunteer, there was an increase in the number of circulating suppressor T lymphocytes and a decrease in the number of circulating helper T lymphocytes (changes similar to those found in acquired immunodeficiency syndrome [AIDS]).[135]

Neurophysiology of Placebo Response

Medical research has continued to expand the understanding of placebo healing response, expanding the understanding of the complexity of the brain functions that control healing in the body.[138] One review article did an excellent job of summarizing the psychobiological mechanisms involved in the wide array of medical conditions observed in placebo response literature.[1] Imaging techniques such as positron emission tomography and functional magnetic resonance imaging (MRI) have literally illuminated the areas of the brain involved in generating placebo.[139] One fascinating development is the indication that the placebo effect may be especially useful in depression, anxiety, substance abuse, and neurodegenerative diseases like Parkinson's disease and Alzheimer's disease. Research has indicated that conditioning and anticipation of the patient has a potent effect of stimulating specific brain region activity associated with pain modulation and neurohormonal regulation.

Brain Region Activity

Some of the most interesting research on placebo has evolved out of the new MRI technology. This functional MRI (fMRI) can measure blood flow into specific areas of the brain. One study showed that expectation or hope was able to stimulate a certain part of the brain that is activated by pain medications and is associated with pain relief. Placebo analgesia was found to be related to decreased brain activity in pain-sensitive brain regions, including the thalamus, insula, and anterior cingulate cortex. It was also associated with increased activity during anticipation of pain in the prefrontal cortex, providing evidence that placebos alter the experience of pain.[140]

In another study, researchers found that empathy could activate a portion of the brain. They showed that some of the brain regions involved in feeling physical pain became activated when someone empathized with another's pain. Using fMRI, study participants were observed when they experienced a painful stimulus, and the results were compared with those elicited when the participants observed their spouses receiving a similar pain stimulus. The bilateral anterior insula, rostral anterior cingulate cortex, brainstem, and cerebellum were activated when participants received pain and also by a signal that a loved one experienced pain.[141] A group of researchers at University of California at Los Angeles, using a new technology called quantitative electroencephalography, showed that "effective" placebo treatment induced changes in brain function that were different from those associated with antidepressant medication. Placebo responders (those who showed a response to placebo) showed a significant increase in prefrontal activity starting early in treatment that was not seen in medication responders or in participants who showed no response to medication or placebo. Because a high percentage of antidepressant medication represents the placebo effect, it is important to be able to predict who will be placebo responders.[142]

Placebo and Stress Physiology

Stress "letdown" of a patient in the therapeutic environment is one of the mechanisms that produces the placebo effect. It results from the patient's perception that a transition from a stressful situation to a nonstressful situation has occurred. Mowrer[137] observed that with a decrease in anxiety there is a concomitant increase in hope, signifying that the period of suffering is over. Certain familiar images and signals, such as white coats, syringes, behavioral procedures, and clinical protocol, create a conditioned response—relief now that help has arrived. Evans and Hoyle[64] similarly observed that "the reduction of fear through the shared expectations that the doctor's medicine will work—even if unknown to the patient it is placebo—mediates powerful therapeutic effects."

The placebo effect in the clinical environment transforms the emotional and mental stress of the patient. These effects, also observed and described by Franz Alexander,[14] Hans Selye,[136] George Solomon,[143] and Walter Cannon,[144] allow the patient to escape the "fight or flight" response that can cause and maintain the state of illness.

Physiologic and Psychological Stress

Selye[136] demonstrated that physiologic stress can have a dramatic effect on the immune and endocrine systems of the body. Laudenslager[145] went on to show that it is not just stress that creates these physiologic changes, but also the perception that stress is "inescapable" that is critical to the response. More recently, studies on the effects of psychological stress demonstrated significant changes in immune capability. Maladjustment to "life-change stress" correlated with reduced activity of natural killer cells,[143] decreased T- and B-cell responsivity,[123] and diminished lymphocyte cytotoxicity.[146] For example, Riley[147] observed increased tumor activity in a controlled stress environment and concluded:

> *Emotional, psychosocial, or anxiety-stimulated stress produces increased plasma concentrations of adrenaline, corticosteroids and other hormones through well-known neuroendocrine pathways. A direct consequence of these increased corticoid concentrations is the injury to elements of the immunologic apparatus, which may leave the subject vulnerable to the action of the latent*

oncogenic viruses, newly transformed cancer cells, or other incipient pathologic processes that are normally held in check by an intact immune system.

The damage to the immune system by stress, mediated through the hypothalamic–pituitary axis, has been shown to be due to the increase in serum levels of cortisol. In one study, elderly caregivers were shown to have higher cortisol levels and poor antibody response to influenza vaccine.[148] The impact of cortisol on immune and other regulatory functions like blood sugar, dehydroepiandrosterone (DHEA), insulin, testosterone, and bone resorption, flag it as having highly destructive potential. Anxiety, depression, heart disease, AIDS, and osteoporosis have all been linked with elevated cortisol levels. DHEA, another adrenal hormone, is also modulated by stress physiology, although it seems to have the opposite effect to cortisol. High levels of DHEA seem to protect the body from the damaging effects of elevated cortisol. Ratios of DHEA to cortisol are highly predictive of the individual's ability to tolerate stress.[149]

Current reviews of the literature relating psychological stress and immune dysfunction support the hypothesis that homeostatic immune mechanisms, both humoral and cellular, are significantly impaired by both natural and experimental stress.[4,114,134,150] Hypertension,[151] common colds,[152] coronary artery disease,[153] and myocardial ischemia[154] were linked to adverse stress physiology. Stress even has the ability to increase permeability of the blood–brain barrier.[155] The implications of stress-related alterations in the blood–brain barrier exposes important insights into enigmatic diseases like chronic fatigue syndrome and stress-induced neurologic disorders.

Endorphins, Hormones, and Neuropeptides

… one rapidly activated psychoneuroendocrine mechanism through which a placebo stimulus may reduce both depression and pain is produced by stimulating the endorphin system.[16]

Research on endorphins is a relatively new area of study in the field of psychoneuroimmunology. Original research by Levine et al[96] suggested that the pain relief noted in placebo studies could be explained by the simple mechanism of endorphin-mediated actions. The original emphasis on endorphins and enkephalins was plausible, considering their known modulation of pain and mood functions. This position was further supported by later observations that depression increased chronic clinical pain[156] and that decreased activity in endogenous opioids may be part of the pathophysiology of depression.[157] With the information that placebo can stimulate endorphins, Levine et al[96] believed that an explanation for the action of placebos had finally been found. Furthermore, research showed that a endorphin-mediated, pain-suppressant placebo effect could be abolished with the use of Nalaxone, an opiod antagonist.[158] The same authors went on to further show that endorphin-mediated placebo effects penetrated other physiologic systems besides pain management.[159] However, this hypothesis failed to account for the broad spectrum of placebo effects as well as for the fact that the analgesia associated with hypnosis was not affected by an opioid antagonist.[160,161] It is important to note that later literature suggested that Levine et al[96] were not entirely wrong in implicating the role of endorphins in the placebo mechanism; rather, these researchers were right for the wrong reason.

Endorphins are mainly derived from three precursor proteins (by separate biochemical processes).[162] These opioid peptides are released from central and peripheral areas in response to pain, stress, and emotions and perform many physiologic functions, of which analgesia is but one.[163] However, it is becoming evident that the boundaries between the CNS and the immune system are not as clear as once thought. The several known effects of endorphins on immune system function are listed in Table 6-2.[164]

TABLE 6-2 **Effects of Endorphins on the Immune System**

IMMUNE SYSTEM FUNCTION	ENDORPHIN EFFECT(S)
Lymphocyte production	Increased and decreased
Chemotaxis	Increased
T-cell sensitivity to prostaglandin E_2	Increased
Antibody production	Increased and decreased
Complement	Binding of fractions C5B-C9
T-cell proliferation	Modulation of
Natural killer cell function	Modulation of
B-cell differentiation	Modulation of

When the functions of neurotransmitters such as endorphins are found to have such an intimate relationship with immune integrity, the paradigm of a body with functions performed independently by its parts—a Newtonian type of thinking—begins to lose credibility. To further blur the already hazy distinction between the CNS and the immune system, research demonstrated that endorphins and peptide hormones, such as adrenocorticotropic hormone, thyroid-stimulating hormone, human chorionic gonadotropin, and luteinizing hormone, are produced by lymphocytes.[164]

It is clear that the demarcation between the CNS and the immune system is impossible to distinguish. The brain and the immune system are the only tissues in the body that have a memory, and the level of communication between the two argues a taxonomy that identifies them as one. Evidence of the innervation of the thymus gland, bone marrow, spleen, and lymph nodes supports the finding that the immune system is subject to efferent CNS information.[164] In addition, studies demonstrating the atrophy of the thymus and lymphatic tissues in the absence of growth hormone,[165] adrenocorticotropic hormone, and increased steroid production by adrenal cells after interferon stimulation, indicate that "in the future it will be difficult to distinguish the receptors and signals that are used within and between the neuroendocrine and immune system."[164]

CLINICAL APPLICATION

Whether a clinician intends to initiate a placebo effect in a clinical setting or not, the mind of the patient will initiate some subliminal healing effects according to their hope, expectation, conditioning, anxiety reduction, and meaning around the disease and treatment. A recent article in *Lancet*[1] on placebo concluded, "Any ethical assessment of efforts to promote placebo effects in clinical practice first requires knowledge as to the clinical relevance and importance of placebo effects."

A physician with an interest in psychopharmacologic treatment, which can be expensive, elaborate, detailed, time consuming, esoteric, and dangerous, usually has considerable knowledge about such treatment. He or she is interested in the symptoms of the patient and the differential response to various drugs and is careful to observe side effects, which may be dangerous. The physician may encourage the patient to call at any time if side effects develop.[24]

BOX 6-4 Six Principles of Optimizing Placebo Response in Clinical Practice

Prima non nocerum: Prioritize a hierarchy of therapeutic intervention.
Tollem causum: Remove the obstacles.
Support the therapeutic relationship.
Enhance positive emotional states.
Implement therapeutic conditioning or learning.
Use altered states of consciousness.

The application of placebo phenomena in clinical practice should not be a vague attempt to replace the skill of the medically trained physician with obscure "hand waving," incantations, and inert lactose pills. In primary care and specialty clinical practice, the physician's intent should be to optimize patient care by engaging restorative defense mechanisms. To effectively apply current placebo research, the physician must understand several principles (listed in Box 6-4 and discussed here).

Prima Non Nocerum: Prioritize a Treatment Program and Establish a Hierarchy of Care

Prima non nocerum is the Hippocratic injunction dictating that a physician care for the patient so that self-healing mechanisms can engage. This ancient phrase means "Do not disturb the organism's ability to heal itself." The body must be given the full range of possibilities in allowing the power of homeostasis, *vis medicatrix naturae*, to have its optimum capability. "Doing no harm" means that a patient is supplied with the level of medical intervention that is appropriate to his or her ability to maintain life support. The job of the physician is to determine when homeostasis or the defense mechanism has lost the ability to respond to disease.

Acute traumatic swelling and inflammation and shock are examples of the human defense mechanism responding in a way that threatens the health of the organism. It is most interesting that the organism would make choices, as in shock and inflammation, that could kill it. To practice the principle of *prima non nocerum,* a physician must learn when to act and when to let the body heal itself. This is the highest art of medicine; each case and situation is different and it is up to the physician to interpret the needs of the moment. By implication, the physician who seeks to apply this principle understands the principles of physiology upon which human life depends for homeostasis.

Prima non nocerum does not necessarily mean that a physician withholds invasive therapy: it is the physician's responsibility to determine when the body is unable to reestablish homeostasis and therapy is indicated. If an arm must be severed to save the patient's life, there is no violation of *prima non nocerum*.

However, to enhance the principle of *prima non nocerum*, a physician sometimes must withhold therapies and must be content to leave the patient to self-heal. Hippocrates understood the wisdom of letting the body heal on its own, which is implicit in the "do no harm" injunction. The following account of the treatment of Charles II of England is a case in point[166]:

> *A pint of blood was extracted from his right arm and a half pint from his left shoulder, followed by an emetic, two physics, and an enema comprised of fifteen substances; the royal head was shaved and a blister raised; then sneezing powder, more emetics, and bleeding, soothing potions, a plaster of pitch and pigeon dung on his feet, poisons containing ten different substances, chiefly herbs, finally forty drops of extract of human skull and an application of bezoar stone; after which his majesty died.*

When this treatment is compared with modern procedures, such as mammary artery ligation for the relief of angina—a procedure that has no more benefit than sham artery ligation—it appears that physicians continued throughout the centuries to rely on the placebo effect for the care and cure of their patients. Because this effect plays such an important role in health care, simple, noninvasive, and effective treatments should be the goal of all therapeutic approaches. Robert Burton[167] wrote in 1628, "an empiric oftentimes, and a silly chirurgeon, doth more strange cures than a rational physician… because the patient puts confidence in him."

The rational physician will also recognize that healing and curing are not necessarily the same. If a patient is helped in any way by the doctor, with or without the use of placebo, the path of cure has been assisted, although the specific disease may not have responded. Not all patients can be cured, but most patients can be helped.

Tollem Causum: Remove the Cause of Disease

Tollem causum is the principle that seeks to remove the obstacles to cure. The forces "inhibiting the floodgates of health from opening" must be removed for the full force of the patient's beliefs to effect the path of cure. This concept is fundamental to the philosophy of naturopathic medicine with its strong emphasis on diet, detoxification, and a pattern of living that is consistent and compatible with the context in which humans evolved. Obstacles to cure block the self-healing capacity of the organism. Contamination with heavy metals and xenobiotics (see Chapter 35), focal infections, electromagnetic pollution, scar tissue, genetic metabolic abnormalities, and parenchymal organ damage defeat the best therapeutic intentions and must be addressed.

The patient's habitat is an important aspect of the therapeutic protocol, not only in the diagnosis and care of internal mental and physiologic dysfunction, but also in determining which environmental factors may be contributing to dysfunction and disease. These factors might include diet, lifestyle, and living environment. It is of the utmost importance to remove a patient from surroundings that are associated with illness or to assist the patient in creating an environment more conducive to health.

Factors that provide conditioning that reinforces the disease process can be associated directly or indirectly with one's environment. For example, if animals are returned to situations where their experimental neuroses were induced, their pathologic behavior reactivates.[168] When a patient leaves the offending environment to receive treatment from a physician, the prognosis is correspondingly more favorable.[15] The physician has the added advantage of a patient's heightened expectation during an office visit; a patient's positive associations with the "healing" environment increases his or her receptivity to treatment.[169] If the home or work environment is a source of "disease" and an obstacle to cure, providing an alternative environment may be a most helpful way to remove the obstacles to cure.

Support the Therapeutic Relationship

Confidence should surround all aspects of the therapeutic interaction. The patient must have confidence in the doctor's ability to assist a cure, the doctor must have confidence in the efficacy of his or her therapy,[170] and there must be an understanding or

relationship between the doctor and patient that is mutually conducive to respect, trust, and compassion.

The quality of the doctor–patient relationship is paramount. The therapeutic approach to a patient that optimizes the confidence of the patient in the skill of the doctor stimulates the inherent self-regulating healing mechanisms by relaxing the anxiety the patient has about the illness. Anxiety is a well-known immunosuppressant and aggravates the body's defense mechanism. An optimum therapeutic relationship, when combined with the clinical skill to remove the cause of homeostatic dysfunction, is the height of therapeutic acumen. As Lewith[171] so accurately stated, "The general practitioner may therefore wish to employ all his knowledge, enthusiasm, consultation technique and sympathy, to create the best possible atmosphere in which to elicit a placebo response from the patient."

Current research on factors contributing to the genesis of the placebo effect consistently document the importance of the doctor–patient relationship.[172-174] The healing power of the therapeutic interaction has been demonstrated by the commencement of the placebo effect even before the actual administration of the pill.[175]

The physician facilitates the cultivation of a sound relationship by developing good communication skills. The art of the bedside manner has been recognized throughout history as the primary skill a successful physician needs.[176] The history of medicine is as much a history of the relationship between doctor and patient as the evolution of medical technology and techniques. Through centuries in which doctors were doing more harm than good, little more than the esteem of their clientele sustained the medical profession. But however little real help the doctor had to offer, it was to him that people turned when illness struck.[177]

Bedside manner has been found in clinical studies to entirely alter the course of double-blind studies, and the quality of a therapeutic encounter has been found to facilitate or disrupt the efficacy of a treatment.[178] Listening to the patient,[178] verbal and nonverbal communication of the physician, amount of time spent with the patient,[179] patient education,[180] demeanor of the physician,[181] and interview skills[179] have been suggested as factors and components of effective physician communication skills.

Touch is an important form of communication and is sometimes forgotten as a key aspect of the doctor–patient relationship. Highly skilled clinicians with many years of experience, such as now deceased Dr. John Bastyr (whose remarkable healing abilities inspired the founding of Bastyr University by those privileged to have been his students), frequently impressed upon clinicians the importance of always using diagnostic and therapeutic touch during a patient visit. The doctor's touch can be diagnostic, therapeutic, and, perhaps most important, a means of communicating that he or she is deeply attuned to the problems, needs, and fears of the patient.[181] Touch can heal by increasing tissue mobility and fluid exchange, as in massage, or by relieving pain, as demonstrated by research on healers who use their hands.[183] Touch has also been documented in well-designed double-blind research to extend an unusual healing power that can be transmitted through the hands to plants and animals.[184]

Among other methods of enhancing confidence between the doctor and patient, the setting in which a doctor provides therapy to a patient also determines its effectiveness. The doctor's office setting is very important for optimum and effective treatment: tools and support systems are more accessible, and a heightened patient response results from seeking out the "healing" environment. In a clinical trial with hypertensive patients, placebo alone was not as effective as when it was administered in conjunction with hospitalization. The visit to the physician represents a search for changes that cannot be found through "self-care" or over-the-counter medicines. According to Frank[185]:

> *In short, it appeared that the placebo situation relieved chiefly anxiety and depression, that the degree of relief was unrelated to personality and autonomic measures, and that the patients who responded strongly to a placebo at one time might not at another. In conjunction, these results suggest that the extent of responsiveness to a placebo depends on the interaction of the patient's state at a particular time with certain properties of the situation. The finding that administration of tests and questionnaires seemed to have at least as beneficial an effect as had the pill implies that any interaction between patient and situation that heightens expectations of help may lead to symptom reduction and improvement in mood. The aspects of the situation producing this effect include not only presentation of a symbol of the physician's healing powers (a pill), but any attention and interest shown by professional personnel.*

This phenomenon was also observed in industry and termed the "Hawthorne effect." As a direct result of the greater attention factory workers received during investigation, the quality of their work improved.[186] In conclusion, the importance of a doctor–patient relationship and the confidence that it engenders shows that all human beings need to share their feelings and experience the therapeutic benefits of touch: the doctor–patient relationship provides an ideal way to meet these fundamental needs.

Enhance Positive Emotional States

> *Love in all its subtleties is nothing more, and nothing less, than … the psychical convergence of the universe upon itself.*
> ***—Pierre Teilhard de Chardin, The Phenomenon of Man***

For optimum enhancement of the psychoneuroimmune system, the physician must assist the patient in developing practices that amplify positive emotional states and reduce a negative emotional state. A negative mental state (anxiety, stress, panic, anger, depression, neurotic behavior, self-deprecation, self-destructive feelings and tendencies, and a weak will to live) hinders the ideal functioning of the psychoneuroimmune endocrine axis, disrupting homeostasis. Engle[187] termed this the *giving-up/given-up complex*:

> *Study of the life settings in which patients fall ill reveals that illness is commonly preceded by a period of psychological disturbance, during which the individual feels unable to cope. This has been designated the giving-up/given-up complex and has the following five characteristics: a feeling of giving up, experienced as helplessness or hopelessness; a depreciated image of the self; a sense of loss of gratification from relationships or roles in life; a feeling of disruption of the sense of continuity between past, present, and future; and a reactivation of earlier periods of giving-up. It is proposed that this state reflects the temporary failure of the mental coping mechanisms with a consequent activation of neurally regulated biologic emergency patterns. Changes in body economy so evoked may alter the organism's capability to deal with concurrent pathogenic processes, permitting disease to develop.*

The importance of reducing negative mental states in acute and chronic conditions has been discussed extensively.[122] Acute psychological stress is documented to cause various forms of cardiopulmonary dysfunction and even death.[114]

Chronic mental and emotional strain causes breakdown of the immune system and disease. The homeostatic processes become

overwhelmed by autoimmune, microbial, or neoplastic invasion. Major writers on the subject of acute and chronic stress emphasized the high priority of managing the physiologically and immunologically destructive effects of the human body's response to stress. Pelletier[188] listed hypertension, arteriosclerosis, migraine headache, cancer, chronic bronchitis, emphysema, asthma, and arthritis as disease processes that are caused or exacerbated by stress physiology. A study researching the relationship between resistance to streptococcal infections in families and stress load in the family found a positive correlation.[189] Another study on the psychosomatic susceptibility to infectious mononucleosis found that two psychosocial factors, high motivation and poor academic performance, significantly increased the risk of "disease" infection.[190] In still another, anticipation of mood and menstrual discomfort were positively correlated and manipulated, thereby supporting the suspicion that expectations act as a determinant of mood.[191]

The conclusion that there is no acute, chronic, or degenerative disease that is not affected by a patient's mental and emotional state must be drawn from the pervasive immunoendocrine effects generated by the mind and emotions. Wolf[192] and Cousins[193] wrote of the power of panic as a factor in myocardial infarction, Marbach et al[156] described depression as a component in myofascial pain dysfunction, and Shekelle et al[194] noted, in a 17-year follow-up study, a twofold increase in the incidence of cancer in depressed patients. The clinical scenarios these observers described imply that the placebo effect can control the onset and advance of a disease by shutting down the destructive thoughts, images, and feelings that mediate stress.

Enhancing positive emotions is the corollary to controlling the damaging effects of negative mental and emotional states. Laughter,[21] hope,[195] acceptance,[116] and the reduction of suffering[196] have been shown to speed the course of healing and reduce the level of pain and distress reported by patients. Although pain is sometimes the only language nature can use to adequately communicate to the patient that something is in need of healing, "the relief of suffering and the cure of disease must be seen as twin obligations of a medical profession that is truly dedicated to the sick."[196]

Acceptance has been observed to be a key factor that assists patients in better understanding their pain.[116] Acceptance does not mean complacency in the face of disease, but a rational understanding of the situation and the limitations that can sometimes accompany a disease process.

The importance of cultivating hope in a patient also cannot be underestimated.[197] The fact that a patient seeks the help of a physician or "caregiver" already implies a substrate of hope and is a signal that the patient can visualize the potential for recovery. The treatment needs to merely stimulate this willingness to envision a future of health. Hope is an embodiment of the patient's and the doctor's ability to visualize an image of healing and recovery. This process is a recurrent theme in imagery therapy,[198] visualization therapy,[199] therapeutic touch,[200] and psychic healing.[201] Hope is both an active and a passive placebo. *Passive hope placebo* is that which brought with the patient as the act of seeking help generates a level of unspoken faith in an image or potential for cure. *Active hope placebo* is generated by the physician, who consciously instills a vision or image of cure in the patient as an adjunct to therapy.

Frank[185] performed a double-blind study in which patients were divided into control and induction groups. The induction group was led through a process whereby their hope was strengthened to conform with the expectations of the therapist[185]:

> *It introduces some perceptual clarity into the process of treatment; and to the extent that all our therapists adhered roughly to the insight model of therapy, it helped to bring the patient's expectations in line with what actually occurred in treatment, and also helped him behave in accordance with the therapist's expectations of a good patient.*

The induction group was actually being consciously strengthened to a level of optimal response but was not being led into false expectations.[202]

This type of patient education or active placebo is a necessary and useful tool for framing and directing a positive outlook and prognosis. If a patient can conceive of a state of wellness, then that state of wellness can be achieved. It is the job and domain of the physician to discover those images, emotions, and perceptions that reside in the conscious and subconscious mind of the patient that block the image of a positive state of health. He or she must actively work to control these with the same level of intent as with any presenting gross complaint or physiologic dysfunction. Finding these dysfunctional mental substrates and working with the patient to try to change them is fundamental to treating the true cause of disease (see earlier discussion of *tollem causum*).

Research demonstrated the importance of positive and negative thinking in heart disease and cancer, the two areas of disease that cause the highest death rate: doctors' health care management protocols should reflect this research in the same way that attention to proper diet is part of a management approach to high serum cholesterol. It is now clearly established, for instance, that even low levels of stress trigger the onset of myocardial ischemia.[203] We also know from the work of Steven Greer[204] and David Spiegel[205] that attitude and emotional exploration are critical to breast cancer survival. Knowing these scientific facts, all doctors must have strategies for helping their patients explore the areas of stress management, group therapy, and support groups and skills in building positive attitudes.

Implement Therapeutic Conditioning or Learning

> *Those who remain at least dimly aware that everything they say or do to a patient conveys a major or minor, positive or negative, and helpful or harmful psychological impact are likely to be more effective physicians.*[206]

Conditioning of the mind has been suggested as a mechanism by which the placebo effect becomes a learned response.[15,17,185] The future of therapeutic application of placebo will probably hinge primarily on the use of conditioning. A doctor who can understand this will pay close attention to the stimuli of his or her patients and modify these stimuli in a scientific way to help treat immune-related and neurologically related diseases.

Modern psychology acknowledges two models of conditioning or reinforcement of learning behavior, operant and classical. Operant conditioning is a behavior response that theoretically occurs in the presence of some stimulus that is a positive reinforcement; for example, a rat will learn to press a conditioning bar if a food pellet is dispensed as a result. Classical conditioning is a behavior response created by the simultaneous pairing of unconditioned and conditioned stimuli before an evoked response. This is best illustrated by the experiments of Pavlov and his "salivating dog." In Pavlov's experiment with the conditioning of a dog's salivary response to the ringing of a bell, the bell ring is the conditioned stimuli and the food is the unconditioned stimuli. The salivation is the unconditioned response to the food that becomes the conditioned response.

When the dog finally associates the bell ring with the food, the ringing alone causes salivation, the conditioned response.

The principle of classical conditioning has far-reaching implications for the diagnosis and treatment of disease because of the pervasive and permeating implications that conditioning has in all the sensory stimuli of daily existence, in sickness and in health: "Pavlov's teachings, concepts and basic notions afford the real and ultimately scientific basis for the recognition of the potentialities of medical science attacking diseases from both the psychic and somatic sides."[207]

For the purposes of this discussion, one must recognize that classical conditioning happens randomly in our environment and is closely linked to health and healing phenomena. Subconsciously, we note random events and associate them with previous events and observations, independent of an intended learning behavior. Operant conditioning happens in the context of reward, and classical conditioning happens in the context of associated stimuli. There is a much greater predominance and range of associated stimuli (classical conditioning) than operant conditioning for the genesis of the placebo effect. This is because the operant depends on reward, although operant conditioning can happen in the medical mode: "Pain-killing drugs that I have taken in the past kills pain; therefore this capsule, which is a painkiller, will kill my pain."

Gliedman et al[15] noted that drugs that affect the CNS are readily conditioned, whereas drugs that affect the peripheral nervous system and are secretory stimulators (e.g., atropine and pilocarpine) do not result in the establishment of a conditioned response. The primary importance of psychological states to CNS excitation demonstrates that the pivotal loci of command for conditioning reside within the hypothalamus and the limbic system. Therefore, a doctor who can induce a state of central excitation in the patient can encourage and condition the patient to make those changes that are deemed necessary for the recovery of health.

The conditioning of a patient to a placebo response is modified by learning stimuli associated with the illness, the stimuli of the doctor and the therapeutic setting, the stimuli of the therapy, previous health, medical therapy, and authority-related experiences.[208] The way that all of these factors interact in the psyche of the patient determines the nature of the placebo response that is achieved.

Satiation obscures the conditioned response, whereas situations of increased stress seem to potentiate the responsiveness of the placebo effect.[116] Placebo, conditioning, and learning may therefore be subject to the nature of central excitatory states as well as levels of stress and distress.

The physiologic breadth of the placebo response in humans can now be understood in terms of the variety of interactions and effects that drugs, therapeutic procedures, and sensory phenomena of the medical environment have on the psychosomatic matrix of a patient's consciousness. Rossi[17] noted that this complicated web of sensory processing revealed how any facet of therapy "that alters any aspect of the body's sensory, perceptual or physiologic responsiveness on any level can disrupt the more or less fragile state-dependant encoding of symptoms and thereby evoke a 'nonspecific' but real healing effect that we call the placebo response."

The scientific basis of therapeutic applications of psychoneuroimmunology is based on classical conditioning. Ader and Cohen[209] performed research to show that the immune system could be conditioned for therapeutic purposes. They conditioned immunosuppression in rats by injecting them with a conditioned stimulus of cyclophosphamide (a potent immunosuppressing agent) while feeding them a saccharine solution as an unconditioned stimulus.[209] The idea of conditioning for immunomodulation in human patients is therefore a promising therapeutic modality. Applying conditioning techniques for the treatment of systemic lupus erythematosus involving a dosage that normally had minimal results resulted in a delay in the development of the disease.[210]

To fully account for the extent of previous and future conditioning in a patient, the physician must take a complete and exhaustive history to explore the influences of family, work, accidents, emotional predispositions, medical history, and neutral stimuli as contributing factors during the onset of an illness. Lifestyle and emotional, behavioral, or physiologic factors might contribute to maintaining the state-dependent learning pattern of disease and dysfunction or give clues to a successful therapeutic intervention. A good example of this is the demonstration by Batterman and Lower[211] of increased analgesics effectiveness based on similar previous therapy. A physician who knows which therapies succeeded and which failed can take advantage of the patient's conditioning and encourage biochemical pathways that the body has learned. Drug or therapeutic interventions are not procedures that can be predicted in the same way that in vivo experimental results can.

The variables involved in human responses to therapy are clearly underestimated in the current rush of research-oriented therapeutic evaluation.[56] Therefore, a patient who has been treated by a number of physicians or practitioners for a complaint and has received no results or relief has been conditioned to believe that consultation and treatment by a physician will provide no positive changes. When the patient visits the next practitioner, even if this practitioner can offer a diagnosis and treatment that are correct answers to the long-sought cure, there are very real patient conditioning factors that must still be considered.

Consider the case of a young woman who underwent treatment for breast cancer and the clinical course of the ensuing metastases. Each time she had a positive response to therapy, she experienced a subsequent re-manifestation of the cancer. The result of this conditioning was that she came to equate each new course of chemotherapy as a herald of some new manifestation: she "was torn between a desire to live and the fear that allowing hope to emerge again would merely expose her to misery if the treatment failed."[212]

The parameters of conditioning in a clinical setting extend to all aspects of the patient's sensory perceptions. Consciously or unconsciously, the physician provides an environment for patient learning. Lipkin[213] pointed out that every drug, every apparatus, every injection, and every piece of information or advice carries a suggestion of help and hope, regardless of the physiologic effects that may accompany it. The physician must realize that patients are taking in all the information about the surroundings, interactions, and therapy and are making associations that can potentially affect the course of their responsiveness to therapy.

Mowrer[136] observed that the "safety signals" of syringes, lab coats, and behavioral procedures were all retained in the patient's psyche for future association. A physician can skillfully take advantage of these signals by encouraging and cultivating response generalization or by associating previous therapeutic situations with subsequent treatments by means of unconditioned stimuli, such as office music, odors, and images. Giving patients some sort of unconditioned stimulus that can be taken home allows them to associate with the conditioned response, eliciting the memory of the therapeutic interaction while patients are away from the doctor's office. These unconditioned stimuli or placebos can be given in multiples at one time,[131] changed for more powerful stimuli,[69] and delivered at the end of an induction, suggestion, or imagery procedure. They should not be limited to pills or other apparent

medicaments, but should extend to sounds, smells, visualizations, and feelings.

It should be remembered that therapeutic conditioning depends on a perceived physiologic shift or change in the patient as described in the theory and research of biofeedback.[214] This shift can be experienced as a sense of relaxation, increased warmth or circulation, altered autonomic tone, or change in some sensory perception. Patients know immediately when there is no change in their disease or dysfunction after they have been given placebo.[215] Therefore, some patients need a more active form of therapeutic management that allows for some level of perceived change. Ideally this perception would be a sense of being free from pain or alteration from a state of abnormal physiologic function to a state of improved physiologic function. Acupuncture, spinal manipulation, drug therapy, physiotherapy, hydrotherapy, and surgery are all therapies that can create an immediate biochemical impact perceived by the patient.

The optimum model to apply to the concept of conditioning therapy and the selection of an appropriate therapy or modality was proposed by Greene and Laskin[216] in their evaluation of myofascial pain dysfunction. During an 11-year follow-up study of patients with myofascial pain dysfunction, these researchers concluded that, when comparing the effectiveness of a wide variety of reversible and nonreversible (surgical) therapies, conservative and reversible therapies were the most important and appropriate treatment factors for the patient's health and well-being. Focusing on patient communication, educating patients about reversibility of the condition and the nature of muscle dysfunction as it relates to stress–pain–spasm, developing a therapeutic strategy based on increasing patient awareness and self-management skills, and selecting a flexible treatment strategy were all found to be essential for achieving a good initial response that could lead to long-term wellness. Greene and Laskin[216] believed that the specifics as to which therapy was most indicated were not as important as the need to focus on the nature of presenting musculoskeletal problems and the factors and complexity of the treatment environment.

Routine use of active pharmacologic substances reinforces the relationship between conditioned and unconditioned stimuli. However, routine use of unconditioned stimuli in the absence of a conditioned response weakens the therapeutic efficacy of the practitioner and has been described as "placebo sag."[16] Therefore, the learning of a conditioned response from unconditioned stimuli could diminish if the conditioned stimuli fail to produce an adequate or reliable conditioned response. Without the intermittent demonstration of active strength, the placebo effect will get weaker and weaker.

The implications of placebo sag for practitioners of alternative medicine, who try to work with the body's own defense mechanisms without overwhelming medical intervention, are that periodic use of perceptually active therapy is needed to support a patient who is not able to respond or responds too slowly to a gentler therapeutic nudge. In this case, the physician must recondition the vital force to open a path to homeostasis.

In a sense, this may be a paradigm of the therapeutic situation, in which changes toward health are induced in the patient by a doctor who is able to cultivate a basic state of arousal, presumably central in nature. This state of arousal causes the patient to become accessible to the doctor's expectations of the patient.[15]

The typical placebo burst, in which a therapy is initially effective after a short period but then wanes, is now understood in terms of the placebo sag from lack of effective unconditioned stimuli to maintain the conditioned framework.[69] Physicians who lack the ability to extract themselves from a series of unsuccessful therapies risk eventual placebo sag[16]:

> *[T]herapists who primarily use their active strengths (or unconditioned stimuli) paradoxically will get stronger placebo effects than quacks, will enjoy escalating credibility, and will seem as miracle men—when in fact perhaps only half their miracles can be traced to their active ingredients while the other half is a function of the anticipatory (or conditioned) response elicited by their conditioned features.*

Because the visit to a physician is often initiated by the physical pain of the patient, it stands to reason that skillful pain management is a high priority in establishing a therapeutic conditioned response. Pain management by hypnosis, transcutaneous electrical nerve stimulation, therapeutic touch, direct or indirect manipulation, imagery, acupuncture, meditation,[217] and an understanding that aims to elicit the nature of suffering[212] can all be valuable therapeutic adjuncts to establishing a therapeutic environment that conditions the patient for full potentiation of his or her healing capabilities. (See Chapter 42 for a full discussion of these techniques.)

With the recent development of standardization of, research into, and concentration of the active components of plant medicines, vitamins, and biochemical precursors, naturopathic medicine as well as other forms of alternative medicine stand on a stronger therapeutic base because of an ever-growing verification of its pharmaceutical and therapeutic armamentarium. These therapeutic modalities are characterized by safe yet physiologically active substances and procedures; therefore, they provide some defense against placebo sag.

Use Altered States of Consciousness

Since ancient times, aboriginal humans have recognized the tremendous therapeutic power that lays dormant in the subconscious mind. For thousands of years, shamans and medicine men used trance states to engage the most subtle aspects of the patient's subconscious to affect factors in disease pathogenesis and prognosis.[218] In modern medicine, it has been documented that shamanistic healing involving altered states can offer dramatic "spontaneous remissions"[31]; the mechanisms of this process have been explored in the theory and application of hypnosis.[3,128]

Most currently accepted techniques employed to trigger the subconscious to effect positive changes in somatic or psychic health involve hypnosis. Placebo effect has been linked with hypnosis, or "low arousal states," which are therefore believed to be critical factors in the evaluation of the mechanisms and perimeters of placebo.[207] A review of the literature documenting the potency of hypnosis and the observed results of placebo clearly demonstrated that these two areas yielded remarkably similar clinical results. The inquiry into hypnosis grew out of the simple intent to validate the effectiveness of the mind in healing processes, whereas most placebo literature grew out of the intent to demonstrate a certain percentage of chance, fluke, spontaneous remission, or psychosomatic illness as a factor to be ruled out in the delivery of intelligent, scientific health care. Using these antiquated definitions of placebo and hypnosis, one is led to believe that hypnosis describes a process of healing based on the skillful guidance of a qualified practitioner, and that placebo describes a process based on chance, regardless of the professional circumstances. On closer inspection, the distinction between the two blurs: they appear to be much the same process.

Illness, healing, and health states shift constantly in the homeostatic system, a system that is affected by stimuli received through the different levels of awareness and can be accessed, investigated, and modified by a variety of techniques. These include placebo, hypnosis, and induced altered states of consciousness. Rossi[17] noted that because memory depends on and is limited to the level of awareness in which the memory was acquired, it is "state bound information":

> *State dependent memory, learning, and behavior phenomena are the missing link in all previous theories of mind body relationships.… The major thrust of these hypotheses is that mind-body information and state-dependent memory, learning and behavior mediated by the limbic-hypothalamic system, are the two fundamental processes of mind-body communication and healing.… The new approach to mind-body healing and therapeutic hypnosis may be conceptualized as processes of accessing and utilizing state-dependent memory, learning and behavior systems that encode symptoms and problems and then reframing them for more integrated levels of adaptation and development.*

Some psychosomatic phenomena are coded into the behavior of an individual through state-induced patterning. Until the patient can access the state in which somatic complaints are induced, possibly through hypnosis or other methods that break the sympathetic dominance of "encoded" shock,[219] the psyche cannot clear them from the soma[17]:

> *A person in a traumatic car accident experiences an intense rush of the alarm reaction hormones. His detailed memories of the accident are intertwined with the complex psychophysiological state associated with these hormones. When he returns to his usual or "normal" psychophysiological states of awareness a few hours or days later, the memories of the accident become fuzzy or, in really severe cases … the victim may be completely amnesic. The memories of the accident have become "state-bound"—that is, they are bound to the precise psychophysiological state evoked by the alarm reaction, together with its associated sensory-perceptual impressions.*

In accessing these psychosomatic state-dependent areas of homeostatic dysfunction, the physician must use techniques that relax the conscious mind and allow access to subconscious content for reframing. The nature of the visit to a physician encourages a patient into more accessible unconscious states as demonstrated by higher placebo effects when patients present in a hospital setting.[169] These labile states of consciousness are quite natural; humans constantly cycle in and out of different consciousness states.[169] These cycles, or ultradian rhythms, are described as alternating cycles of hemispherical dominance that change every 1-½ hours.

When these cycles are interrupted by behavioral stress, psychosomatic behavioral responses such as ulcers, gastritis, asthma attacks, and rashes develop.[220] A change in these rhythms manifests as a period of psychic repose. If an individual is in the midst of performing a task, daydreaming or the perceived need for a rest or coffee break may be the external manifestation of an internally sensed signal of a change in rhythm. This is also a period when one is highly susceptible to hypnotic suggestion. Because these rhythms are very flexible and labile, they can be invoked through hypnosis, or if the physician senses a natural lull indicating a hemispherical switch, a "natural" trance can be induced.

Centuries ago in India, practitioners of hatha yoga observed the effect of mental states on the breathing patterns of an individual. With anger, frustration, and mental instability, the breath reflects a short, arrhythmic pattern that mirrors the disturbed psyche of the person. Conversely, when a person is in a peaceful, relaxed, deep meditative state, the breath is long, rhythmic, and barely perceptible. Their discovery formed the basis for the development of breathing exercises called *pranayama* (literally, regulation or restraint of the vital energy), which aimed to calm the breath so that deep states of meditation and focused concentration could be attained. Current research has affirmed the powerful effect these exercises have on asthma, diabetes, chronic gastrointestinal disorders, and psychosomatic and psychiatric dysfunction.[221]

Therapeutic exercises that use somatic stimuli to effect changes in the psyche create fertile environments for stimulating the placebo response. A breathing technique used to decrease sympathetic tone or alter nostril predominance for causing shifts in hemispherical activity,[222] an exercise to release fascial muscle tension and thereby effect mood-enhancing blood flow in the brain,[223,224] and a biofeedback treatment that aids in slowing the heart rate and decreasing negative emotional states[214] are all examples of how the psyche can be accessed by the soma. The whole process of eliciting the placebo response involves an attempt to marshal all the reserves and potential for healing through a doctor–patient interaction, engaging both the patient's mind and body to reestablish homeostatic equilibrium.

Health care professionals can use the wisdom of psychosomatic therapies as a central part of their therapeutic protocol. In addition to the specific therapeutic regimen, treatment of the whole patient can be achieved through these harmonious techniques. If physicians could persuade patients to care daily for their emotions, minds, and spirits the way they care for their hair or teeth, the effectiveness of any prescribed treatment would be greatly enhanced. As a primary therapeutic adjunct and important basis for preventive medicine, this line of treatment is all too often ignored.

ETHICS

It is important to remember that there are two forms of "conscious" placebo use by the physician. The use of placebo as a gentle therapeutic agent by a practitioner is very different from the use of placebo in a controlled trial in which the possibility of a known therapy is withheld in a treatment group. Some researchers believe that use of placebo in clinical trials breeches the Declaration of Helsinki, which states that every patient should be assured of the best proven diagnostic and therapeutic method.[225] The ethical problems of delivering health care in a research design, in which there is a possibility of favorable outcome and half of the group is denied access to this possible favorable outcome, make it a troubling issue.

The ethical use of placebo has also been questioned in an attempt to determine whether a physician should be deceiving patients during the process of healing.[226] Although some writers advocate a restricted use of pure and impure placebo because of its "deceptive" nature,[214] it becomes clear in a brief review of the current literature[5] that any argument for or against the use of placebo assumes the existence of medical procedures that are free of potential placebo effect. Brody[27] concluded that placebo can be called the "lie that heals." However, closer examination shows that it is not the lie that does the healing, but rather the relationship between the patient and doctor that stimulates a natural self-healing mechanism via psychological, symbolic, and biological intervention[27]:

> *For some time, medical science has looked almost exclusively at technical means of diagnosis and treatment; the doctor/patient*

relationship that forms the setting for their application has been naively viewed as a noncontributory background factor, relegated to the amorphous realm of the "art of medicine," or simply ignored. In this setting, the placebo effect has inevitably been viewed as a nuisance variable, interfering with our ability to elicit "clean data" from clinical trials; and deception in medicine has been seen either as an unimportant side issue or as a tolerated means toward an end. But as the doctor/patient is rediscovered as a worthy focus for medical research and medical education, the placebo effect assumes center stage as one approach to a more sophisticated understanding of this relationship.

A physician's correct understanding of the nature of placebo therapy has been observed as able to coexist with its inaccurate use and abuse.[43] It has been recommended, however, that: (1) pure placebo should not be prescribed unless the physician has examined the exact indications even more carefully than when prescribing specific therapy, and (2) to avoid missing a disease process that can be easily treated with an empirically proven protocol (e.g., vitamin B_{12}–deficient peripheral neuropathy), the physician should not relax a diagnostic protocol because a patient seems to be responding to placebo.[226]

The final ethical hurdle of placebo use, or for that matter any medical treatment, is the abuse of hope in the patient's path of healing. It is one thing to make a harmless recommendation that provides no therapeutic value, but another to subject a patient to known consequences of a dangerous procedure in the pursuit of a dubious outcome. Hope can be abused, leading the patient to experience unreasonable suffering.[227]



CONCLUSION

Health practitioners must be equipped with a better understanding of placebo therapeutics.[9,228] For many years now, the study of placebo has been recommended to doctors and other health care professionals. The ideal environment for the dissemination of the therapeutic implications of the doctor–patient relationship is in medical schools as a required part of the curriculum. After finding a pattern of misuse and misunderstanding about the nature and efficacy of placebo, Goodwin et al[43] recommended that better education might result in more effective placebo use.

In 1938, Houston[176] wrote of the need to reaffirm the art of medicine because he perceived a trend in medicine that invested in a concept of the therapeutic doctor–patient interaction as "undisciplined thought." Houston's remedy for the intellectual bias that viewed medicine as a "tight, fast-set science" was to emphasize the importance of psychobiology in medical schools[177]:

One of the most hopeful moves in medical education is teaching to first-year students the elements of psychobiology. A system of belief is implanted best in the young. It would be my suggestion that psychobiology be taught in the premedical years, that the doctor/patient relationship be the beginning of medical studies. A deep insight into this fundamental philosophy is a chief concern of the internist.

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CHAPTER 7

Positive Mental Attitude

Michael T. Murray, ND

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INTRODUCTION

A positive mental attitude is one of the important foundational elements of good health. This axiom has been contemplated by philosophers and physicians since the time of Plato and Hippocrates. In addition to simple conventional wisdom, modern research has also verified the important role that attitude—the collection of habitual thoughts and emotions—plays in determining the length and quality of life. Specifically, studies using various scales to assess attitude, including the Optimism–Pessimism (PSM) scale of the Minnesota Multiphasic Personality Inventory (MMPI), have shown that individuals with a pessimistic explanatory style have poorer health, are prone to depression, are more frequent users of medical and mental health care delivery systems, exhibit more cognitive decline and impaired immune function with aging, and have a shorter survival rate compared to optimists.[1-8] One of the most recent studies involved a large cohort of 5566 people who completed a survey at two time points, aged 51–56 years at Time 1 and 63–67 years at Time 2. This survey included a questionnaire to determine positive psychological well-being by measuring self-acceptance, autonomy, purpose in life, positive relationships with others, environmental mastery, and personal growth. The results showed that people with low positive well-being were 7.16 times more likely to be depressed 10 years later.[9] This research highlighted the fact that although life is full of events that are beyond one's control, people can control their responses to such events. Attitude goes a long way toward determining how people view and respond to the stresses and challenges of life.

Attitude is reflected by *explanatory style*, a term developed by noted psychologist Martin Seligman to describe a cognitive personality variable that reflects how people habitually explain the causes of life events.[8] Explanatory style was used to explain individual differences in response to negative events during the attributional reformulation of the learned helplessness model of depression developed by Seligman (described in Chapter 142).

To determine a patient's level of optimism, have him or her take the Attributional Style Questionnaire developed by Seligman or use the PSM scale of the MMPI. Techniques to help patients learn to be optimistic are given in the following discussion.

ATTITUDE, PERSONALITY, EMOTIONS, AND IMMUNE FUNCTION

The importance of attitude to human health has been examined in the link among the brain, emotions, and the immune system. Research in the field of psychoneuroimmunology indicates that every part of the immune system is connected to the brain in some way, either via a direct nervous tissue connection or through the complex language of chemical messengers and hormones. What scientists are discovering is that every thought, emotion, and experience sends a message to the immune system that either enhances or impairs its ability to function. A simplistic view is that positive emotions, such as joy, happiness, and optimism, tend to boost immune system function, whereas negative emotions, such as depression, sadness, and pessimism, tend to suppress it.

Studies examining immune function in optimists versus pessimists have demonstrated significantly better immune function in the optimists. Specifically, studies have shown that optimists have increased secretory immunoglobulin-A function, natural killer cell activity, and cell-mediated immunity, which is demonstrated by better ratios of helper to suppressor T-cells than those of pessimists.[5,10-13]

The immune system is so critical to preventing cancer that, if emotions and attitude were risk factors for cancer, one would expect to see an increased risk of cancer in people

who have long-standing depression or a pessimistic attitude. Research supports this association; for example, smokers who are depressed have a much greater risk of lung cancer than smokers who are not depressed.[14]

Depression and the harboring of other negative emotions contribute to an increased risk of cancer in several ways. Most research has focused on the impact of depression and other negative emotions on natural killer cells. Considerable scientific evidence has now documented the link between a higher risk of cancer and negative emotions, stress, and a low level or activity of natural killer cells.[15] Negative emotions and stress paralyze many aspects of immune function and literally can cause natural killer cells to burst.[15,16] Furthermore, the prototypical cancer personality—an individual who suppresses anger, avoids conflicts, and has a tendency to have feelings of helplessness—has lower natural killer cell activity than other personality types.[12,13] These studies also indicate that individuals with a personality type that is prone to cancer have an exaggerated response to stress, which compounds the detrimental effects stress has on natural killer cells and the entire immune system.

Depression and stress not only affect the immune system but also appear to hinder the cell's ability to repair damage to DNA. Most carcinogens cause cancer by directly damaging DNA in cells, thereby producing abnormal cells. One of the most important protective mechanisms against cancer in the cell's nucleus is the enzymes responsible for the repair or destruction of damaged DNA. Several studies have shown that depression and stress alter these DNA repair mechanisms; for example, in one study, lymphocytes (a type of white blood cell) from depressed patients demonstrated impairment in the ability to repair cellular DNA damaged by exposure to x-rays.[17,18]

Just as research has identified personality, emotional, and attitude traits that are associated with impaired immune function, likewise the field of psychoneuroimmunology has identified a collection of "immune power" traits that include a positive mental attitude, an effective strategy for dealing with stress, and a capacity to confide traumas, challenges, and feelings to oneself and others.[15,19]

ATTITUDE AND CARDIOVASCULAR HEALTH

In addition to the brain and immune system, the cardiovascular system is another body structure intricately tied to emotions and attitude. The relationship of an optimistic or pessimistic explanatory style with incidence of coronary heart disease was examined as part of the Veterans Affairs Normative Aging Study, an ongoing cohort study of older men.[7] These men were assessed by the MMPI PSM scale. During an average 10-year follow up, 162 cases of incident coronary heart disease occurred: 71 cases of incident nonfatal myocardial infarction, 31 cases of fatal coronary heart disease, and 60 cases of angina pectoris. Men reporting high levels of optimism had a 45% lower risk for angina pectoris, nonfatal myocardial infarction, and coronary heart disease death than men reporting high levels of pessimism. Interestingly, a clear dose–response relationship was found between levels of optimism and each outcome.

To illustrate how closely the cardiovascular system is linked to attitude, one study showed that measures of optimism and pessimism affected something as simple as ambulatory blood pressure.[20] Pessimistic adults had higher blood pressure levels and felt more negative and less positive than optimistic adults. These results suggest that pessimism has broad physiologic consequences.

Excessive anger, worrying, and other negative emotions have also been shown to be associated with an increased risk for cardiovascular disease; however, these emotions may simply reflect a pessimistic explanatory style.

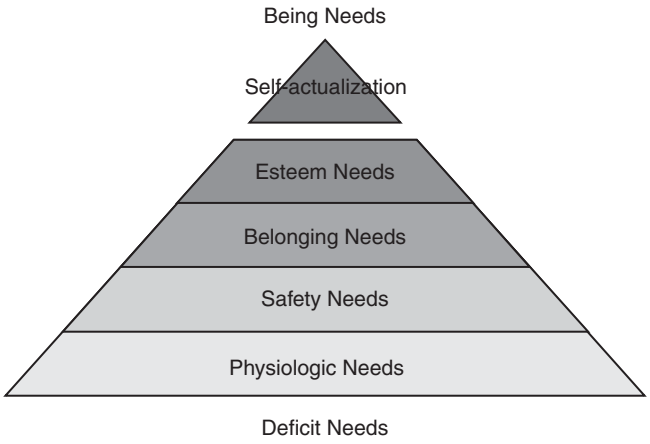


FIGURE 7-1 Maslow's hierarchy of needs.

ATTITUDE AND SELF-ACTUALIZATION

A physician's role should include not only facilitating the health of the patient but also helping the patient achieve *self-actualization*, which is a concept developed by Abraham Maslow, the founding father of humanistic psychology. His work and theories were the result of intense research on psychologically healthy people over more than 30 years. Essentially, Maslow was the first psychologist to study healthy people. He strongly believed that the study of healthy people would create a firm foundation for the theories and values of a new psychotherapy.

Maslow discovered that healthy individuals are motivated toward self-actualization, a process of "ongoing actualization of potentials, capacities, talents, as fulfillment of a mission (or call, fate, destiny, or vocation), as a fuller knowledge of, and acceptance of, the person's own intrinsic nature, as an increasing trend toward unity, integration, or synergy within the person."[21]

Maslow developed a five-step pyramid of human needs in which personality development progresses from one step to the next. The needs of the lower levels must be satisfied before the next level can be achieved. When needs are met, the individual moves toward well-being and health. Figure 7-1 displays Maslow's hierarchy of needs.

The primary needs that form the base of the pyramid are basic survival or physiologic requirements: the satisfaction of hunger, thirst, sexuality, and shelter. The second step consists of the needs for safety, which are essential for dealing with the world: security, order, and stability. The individual then progresses to the third step, which involves the ability to love and be loved: belonging. The fourth step involves self-esteem and self-respect: approval, recognition, and acceptance. The final step is self-actualization: the use of one's creative potential for self-fulfillment.

In modern life, a person's occupation often correlates with the ability to achieve these needs. Table 7-1 provides an application of Maslow's hierarchy of needs in an occupational environment.

Maslow studied and noted that self-actualized people had strikingly similar characteristics. Here are some of Maslow's key findings in an abbreviated form:

- Self-actualized people perceive reality more effectively than others and are more comfortable with it. They have an unusual ability to detect the spurious, the fake, and the dishonest in personality. They judge experiences, people, and things correctly and efficiently. They possess an ability to be objective about their own strengths, possibilities, and limitations. This self-awareness enables them to clearly define values, goals, desires, and feelings. They are not frightened by uncertainty.

TABLE 7-1 **Practical Application of Maslow's Hierarchy of Needs**

LEVEL OF NEED	GENERAL REWARDS	OCCUPATIONAL FACTORS
Self-actualization	Growth	Challenging job
	Achievement	Opportunities for creativity
	Advancement	Achievement in work
	Creativity	Promotion
Self-esteem	Self-respect	Social recognition
	Status	Job title
	Prestige	High status of job
		Feedback from the job itself
Belonging	Love	Work groups or teams
	Friendship	Supervision
	Belongingness	Professional associations
Safety	Security	Health and safety
	Stability	Job security
	Protection	Contract of employment
Physiologic	Food	Pay
	Water	Working conditions
	Sleep	
	Sex	

- Self-actualized people have an acceptance of self, others, and nature. They can accept their own human shortcomings without condemnation. They do not have an absolute lack of guilt, shame, sadness, anxiety, and defensiveness, but they do not experience these feelings to unnecessary or unrealistic degrees. When they do feel guilty or regretful, they do something about it. Generally, they do not feel bad about discrepancies between what is and what ought to be.
- Self-actualized people are relatively spontaneous in their behavior and even more spontaneous in their inner life, thoughts, and impulses. They are unconventional in their impulses, thoughts, and consciousness. They are rarely nonconformists, but they seldom allow convention to keep them from doing anything they consider important or basic.
- Self-actualized people have a problem-solving orientation toward life instead of a self orientation. They commonly have a mission in life, some problem outside themselves that enlists much of their energies. In general, this mission is unselfish and is involved with the philosophical and ethical.
- Self-actualized people have a quality of detachment and a need for privacy. Often it is possible for them to remain above the battle, to be undisturbed by what upsets others. They are self-governing people who find meaning in being active, responsible, self-disciplined, and decisive rather than being pawns or helplessly ruled by others.
- Self-actualized people have a wonderful capacity to appreciate the basic pleasures of life, such as nature, children, music, and sex, again and again. They approach these basic experiences with awe, pleasure, wonder, and even ecstasy.
- Self-actualized people commonly have mystical or "peak" experiences, times of intense emotions in which they transcend the self. During a peak experience, they have feelings of limitless horizons and unlimited power while simultaneously feeling more helpless than ever before. There is a loss of place and time, and feelings of great ecstasy, wonder, and awe. The peak experience ends with the conviction that something extremely important and valuable has happened, so that the person is transformed and strengthened by the experience to some extent.
- Self-actualized people have deep feelings of identification with, sympathy for, and affection for other people despite occasional anger, impatience, or disgust.
- Self-actualized people have deeper and more profound interpersonal relationships than most other adults, but not necessarily deeper than children's. They are capable of more closeness, greater love, more perfect identification, and more erasing of ego boundaries than other people would consider possible. One consequence is that self-actualized people have especially deep ties with relatively few individuals, and their circle of friends is small. They tend to be kind or at least patient with almost everyone, yet they speak realistically and harshly of those who they feel deserve it, especially hypocritical, pretentious, pompous, or self-inflated individuals.
- Self-actualized people are democratic in the deepest possible sense. They are friendly toward everyone, regardless of class, education, political beliefs, race, and color. They believe it is possible to learn something from everyone. They are humble, in the sense of being aware of how little they know in comparison with what could be known and what is known by others.
- Self-actualized people are strongly ethical and moral. However, their notions of right and wrong and good and evil are often unconventional. For example, a self-actualized person would never consider segregation, apartheid, or racism to be morally right although it may be legal.
- Self-actualized people have a keen, unhostile sense of humor. They do not laugh at jokes that hurt other people or are aimed at others' inferiority. They can make fun of others in general or of themselves when they are foolish or try to be big when they are small. They are inclined toward thoughtful humor that elicits a smile, is intrinsic to the situation, and is spontaneous.
- Self-actualized people are highly imaginative and creative. The creativeness of a self-actualized individual is not of the special talent type, such as Mozart's, but rather is similar to the naive and universal creativeness of unspoiled children.

CLINICAL ASPECTS OF LEARNED OPTIMISM

The new psychology that Maslow's work referred to may turn out to be "positive clinical psychology".[22] This field of practice was born in 1998 when Martin Seligman chose it as the theme for his term as president of the American Psychological Association.[23] Positive clinical psychology aims to change clinical psychology to have an equally weighted focus on both positive and negative functioning.[24] The approach is based on five key bodies of empirical findings: (1) the absence of positive well-being leads to the development of disorder over time[9]; (2) the absence of positive characteristics predicts disorder above and beyond the presence of negative characteristics[9]; (3) positive characteristics interact with negative life events to predict disorder (so studying only negative life events would produce misleading results)[25]; (4) many aspects of well-being range from extremely negative functioning, through a neural midpoint, to positive well-being (possibly including happiness to depression and anxiety to relaxation continuums),[26] making it impossible to study exclusively negative or positive well-being; and (5) positive interventions can be as effective as other more commonly used approaches such as cognitive therapy.[27]

Positive clinical psychology ultimately involves helping patients become optimistic, which according to Martin Seligman, the world's leading authority on attitude and explanatory style, is our natural tendency.[28] Optimism not only is a necessary step toward achieving optimal health, as emphasized in the preceding, but is also critical to happiness and a higher quality of life.

In many instances, it is not what happens in one's life that determines one's direction; to a large degree, it is the response to those challenges that shapes the quality of life and determines one's level of health. Surprisingly, it is often true that hardship, heartbreak, disappointment, and failure serve as the sparks for joy, ecstasy, compassion, and success. The determining factor is whether these challenges are viewed as stepping stones or stumbling blocks.

A person's attitude is like his or her physical body: it must be conditioned to be strong and positive. Conditioning an attitude to be positive and optimistic requires adopting specific healthy habits. Here are four key areas of focus for helping patients develop a positive mental attitude:

- Help them become aware of self-talk. Tell them that all people conduct a constant running dialogue in their heads. In time, the things people say to themselves and others percolate down into their subconscious minds. Those inner thoughts, in turn, affect the way people think and feel. Naturally, a steady stream of negative thoughts will have a negative effect on a person's mood, immune system, and quality of life. The cure is to become aware of self-talk and then to consciously work to feed positive self-talk messages to the subconscious mind.
- Help them ask better questions. The quality of a person's life is equal to the quality of the questions habitually asked. For example, if a person experiences a setback, does he or she think "Why am I so stupid? Why do bad things always happen to me?" or "Okay, what can be learned from this situation so that it never happens again? What can I do to make the situation better?" Clearly, the latter response is healthier. Regardless of the situation, asking better questions is bound to improve one's attitude. Some examples of questions that can improve attitude and self-esteem when asked regularly include:
 "What am I most happy about in my life right now?"
 "What am I most excited about in my life right now?"
 "What am I most grateful about in my life right now?"
 "What am I enjoying most in my life right now?"
 "What am I committed to in my life right now?"
 "Who do I love? Who loves me?"
 "What must I do today to achieve my long-term goal?"
- Help them set positive goals. Learning to set achievable goals is a powerful method for building a positive attitude and raising self-esteem. Achieving goals creates a success cycle: a person feels better about himself or herself, and the better he or she feels, the more likely he or she is to succeed. Some guidelines for helping patients set health goals follow:
 State the goal in positive terms and in the present tense; avoid negative words. It's better to say, "I enjoy eating healthy, low-calorie, nutritious foods" than to say "I will not eat sugar, candy, ice cream, and other fattening foods."
 Make the goal attainable and realistic. Start out with goals that are easily attainable, like drinking six glasses of water a day or switching from white to whole-grain bread. Initially choosing easily attainable goals creates a success cycle that helps build a positive self-image. Little things add up to make a major difference in the way a person feels about himself or herself.
 Be specific. The more clearly the goal is defined, the more likely it will be achieved. For example, if a person wants to lose weight, he or she should define the desired weight and the body fat percentage or measurements to be achieved.
- Help them experience gratitude. A large body of recent work has suggested that people who are more grateful have higher levels of well-being, are happier, less depressed, less stressed, and more satisfied with their lives and social relationships.[29,30] Gratitude appears to be one of the strongest links with mental health of any character trait. Helping to instill a sense of gratitude has been shown to be a very successful intervention. In one study, participants were randomly assigned to one of six therapeutic interventions designed to improve the participant's overall quality of life.[31] Of these six interventions, it was found that the biggest short-term effects came from a "gratitude visit," where participants wrote and delivered a letter of gratitude to someone in their life. This simple gesture showed a rise in happiness scores by 10% and a significant fall in depression scores, results which lasted up to 1 month after the visit. The act of writing "gratitude journals," in which participants wrote down three things they were grateful for every day had longer lasting effects on happiness scores. The greatest benefits with this practice were usually found to occur around 6 months after it began. Similar practices have shown comparable benefits.

Counseling is necessary for the severely pessimistic individual. Forms of cognitive therapy appear to be the most useful therapy at this time. Cognitions comprise the whole system of thoughts, beliefs, mental images, and feelings. Cognitive therapy can be as effective as the use of antidepressant drugs in the treatment of moderate depression; in addition, there tends to be a lower risk of relapse—the return of depression—with cognitive therapy.[32] One reason for this is that cognitive therapy teaches people practical skills they can use to combat depression any time, anywhere, and every day for the rest of their lives. Cognitive therapy avoids the long, drawn out (and expensive) process of psychoanalysis. It is a practical, solution-oriented psychotherapy that teaches skills a person can apply to improve quality of life.

Mental health specialists trained in cognitive therapy seek to change the way the depressed person consciously thinks about failure, defeat, loss, and helplessness. To do so, they employ five basic tactics that help patients to do the following:

- Recognize the automatic negative thoughts that flit through consciousness at the times when they feel the worst.
- Dispute the negative thoughts by focusing on contrary evidence.
- Learn a different explanation to dispute the automatic negative thoughts.
- Avoid rumination (the constant churning of a thought in one's mind) by helping the patient better control his or her thoughts.
- Question depression-causing negative thoughts and beliefs, and replace them with empowering positive thoughts and beliefs.

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CHAPTER 8

Research in Natural Medicine

Carlo Calabrese, ND, MPH

CHAPTER CONTENTS

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WHAT IS NATURAL MEDICINE?

For the purposes of this chapter, *natural medicine* is defined as a paradigm of healing found throughout the world and guided by several distinguishing principles. Care is patient-centered and individualized. Emphasizing self-care, natural medicine supports the body's own healing processes and treats causes rather than simply alleviating symptoms. Natural medicine distinguishes itself by an affinity for medicines and health aids from the natural environment (e.g., those with which human beings have co-evolved). Despite the preference for remedies from nature, natural medicine is a practice. Much of what is now called complementary and alternative medicine (CAM) fits the definition of natural medicine. This chapter addresses those CAM practices and systems that have a discernable set of strategies and observable health outcomes. Under proper social cultivation, such practices may evolve to be internally coherent and efficient, although the theories governing them may not be well articulated. The skills are distributed over numerous professional groups (e.g., naturopathic doctors, traditional eastern and southern Asian medical systems, mixer chiropractors, and practitioners of many indigenous medicines), and are also practiced widely among conventional medical doctors (as integrative or functional medicine) and other eclectic healers. Some traditional practices have evolved parallel to what modern medicine has become, resulting in regulated disciplines. Natural medicine may be of aid to ameliorate disease and improve health, perhaps in a revolutionary way. By contrast, some practices may be harmful sociocultural delusions. How does one tell the difference?

There have been a great many published reviews of natural medicine practices, especially of its substances and approach to diseases, including the present volume.[1-3] Nevertheless, many of its practices have not borne the level of scrutiny of standard modern medicine. Some within CAM ranks have resisted the usual scientific evaluation as reductionistic and an inappropriate means to the understanding of healing.* This chapter addresses needs in the development of relevant original data in natural medicine.

PURPOSE OF RESEARCH

The improvement of healing practices is the general purpose of health research. An improvement could be clinical (with which individual patients may be helped) or economic (in which society's abilities to reduce total suffering and maximize health are enhanced). Various parts of the community (e.g., consumers, practitioners, government, industry) hope for research to respond to the questions "Does it work?" "Does it work better?" and "What works best?" To respond, one should know what "it" is (learned through observation and qualitative research) and what "works" means (the measures of the reduction of suffering and improvement of performance).

Research tools such as descriptive statistics and hypothesis testing are epidemiologic techniques; they lead to generalizations about populations. They have limitations in clinical practice, in which the focus is on one patient at a time. Current biomedical research increasingly focuses on strategy developed from molecular (lately genetics and the "-omics") and physical (surgical and prosthetic) models. In

*Editor Joseph Pizzorno comments, "I have asserted for over 30 years now that we do research not to prove ourselves, but rather to get better. How do you know if your therapy, no matter how natural, is actually helping rather than harming the patient unless you do objective research?"

research practice, hypothesis testing is usually most sensitive to a selected outcome and most internally valid (able to answer the precise question it set for itself) when it is most reductionistic. The more discrete variables of chemistry and mechanics lend themselves to more reductionistic hypothesis testing. In turn, the validity of the reductionistic approach depends on the precision (narrowness) of the question. Natural medicine is ecologic and holistic in its orientation, with numerous broad analog inputs and outputs with what might appear to be intuitive discriminations. The common models in research that emphasize transferability, internal validity, replicability, and generalizability in molecular and physical systems may conflict with model validity when studying natural medicine systems.[4] Model validity ensures that the study design reflects the structure and logic of the practices of interest. Thus, one might ask whether alternative medicine calls for alternative science. It may be so; some philosophers of science and mathematicians are working toward methods that may be better suited to the evaluation of natural medicine systems.[5,6] Although the development of accepted research methods that incorporate more complex and subtle biomedical quanta are awaited, much can be done with the currently available biomedical research tools.



METHODOLOGICAL PROBLEMS AND STRATEGIES

Medical research rightly results in a generalizable approach to human degeneration and injury. Thus, one can expect to do research only with medical practices that are defined and transferable to other practitioners and patients. Successful research determines whether it is true that interventions produce benefit and how reliable they are in their effects. Research needs to be replicable to evaluate a therapy for potential promulgation and thus qualify for social support. The obvious is stated here because studies of natural medicine may have difficulty achieving these well-accepted research ideals.

What does replicability mean for a medicine that may offer individualized treatment to every patient? How does individualized treatment map onto an evaluative system in which outcomes typically refer to populations? Better tools are needed to understand and evaluate these practices, particularly informational tools that go beyond the more commonly used physiologic, psychological, pharmaceutical, and epidemiologic methods.[5] Many accommodations within clinical study methodology can be made that will reduce the apparent contradictions of the different medical value systems. Research methods from other fields like psychology, ecology, and anthropology can also be used. When performing research studies in natural medicine that might lead to improved practice, issues that are different from or need more emphasis than those in conventional biomedicine will need to be addressed. This chapter touches on some of the methodological issues for clinical trials, observational studies, and basic science studies in natural medicine.

Clinical Trials

Properly performed clinical research in conventional medicine is a demanding discipline that encompasses study design; determination of sample size and population characteristics; ethics; clinical care; definition and sensitive measurement of diseases and outcomes; project management, recruitment, and participant adherence and retention; and data management and statistics, analysis, and interpretation. All of these are secondary to establishing the research questions—the purposes—of the trial which will differ, for example, in explanatory (development and discovery: Could this work in controlled circumstances? How?) versus pragmatic (application and policy: Does this work in everyday practice? Which treatment is better?) study.[7] Different designs can be usefully applied in research approaches to different aspects of natural medicine practice. For any type of clinical trial of natural medicine, the following issues bear additional attention beyond those required for pharmaceutical trials:

1. Standardization
2. Individualization of treatment: nosology and indications
3. Combination therapies: effect size and safety
4. Nonspecific healing effects
5. Outcomes and measures
6. Controls and blinding
7. Whole practice models

Different clinical trial methods should also be considered, including for fit with currently important questions in natural medicine: (1) efficacy trials that are randomized and placebo controlled, (2) comparative trials that test treatments against each other, and (3) pragmatic trials where conditions model everyday practice to the extent possible.

Standardization

Replicability is a hallmark of the scientific method. Specifically what is tested (e.g., a substance, treatment procedure, or system of practice) must be defined, described, and stabilized so that it can be delivered reliably from patient to patient and study to study. Standardization is a great strength of modern medicine's pharmacotherapeutics. Natural medicine does not have as definitive a codex. Rather, its practices evolve over time, with some areas highly dependent on current scientific discovery, whereas others are used empirically, rather than rationally, in procedures that are hundreds or thousands of years old.

The organized natural medical professions have variably definitive articulations of philosophy and clinical strategies. What constitutes a competent practitioner in a given discipline often remains uncertain,[8] and many natural medicine approaches, like those of indigenous practices, are unlikely ever to be codified. Even with the licensed practices (e.g., naturopathic medicine, acupuncture, and chiropractic), health insurance coverage with regulation by practitioner-review panels is recent. It is only in the last two decades that coding systems for alternative practices have begun to describe the array of interventions available in the United States.[9] The current emphasis on research in CAM practices calls for speeding up the process of standardization toward replicability.

Communication about natural medicine research issues can be problematic when using standard clinical practice and biomedical research metaphors. One way to understand the problem is to say that natural medicine's critical practices lack articulation and operationalization of accepted and, within the respective practitioner groups, widely understood memes. Memes are collective concepts: ideas, behaviors, or skills that are transferred from one person to another by imitation and replicable on a population basis (see Richard Dawkins' book *The Selfish Gene*, from 1976)[9a]. A meme, as a phrase, invokes meaning beyond those of the words themselves, such as in the principle *vis medicatrix naturae* (the healing power of nature). Dictionaries of memes may be needed for the collective concepts of natural medicine practice that may be identified as the practices are investigated. The development of memes through which to express the syncretic concepts of natural medicine and which may have broad applicability is one of the benefits of researching the practices.[5] The dearth of articulation of natural medicine's concepts accounts in part for its remarkable variation among practitioners. Its transfer from mentor to student may be imprecise or misinterpreted even before practitioner

preferences and personalities are brought into play. This is not to say that the concepts of natural medicine practice are not reliably transmitted from mentor to student, only that they are not yet always articulated in ways that have been operationalized for clinical trials.

Standardization of natural remedies is becoming better understood. To perform a single-agent controlled trial of herbs in a specific disease, numerous choices should be made about the intervention. The Policy Announcement on the Quality of Natural Products of the National Institutes of Health (NIH) National Center for Complementary and Alternative Medicine (NCCAM) has brought some clarity to the botanical standards for NIH sponsored trials (http://www.nccam.nih.gov/research/policies/naturalproducts.htm). Studies should begin with verification of plant species used, growth and harvesting conditions, and the stability of purported active compounds. Selections should be made among plant parts, various crude extracts, or specific chemical constituents that may be concentrated in various ways and to varying degrees of purity. Crude fresh extracts, which traditional herbalists prefer, are highly susceptible to deterioration. In more sophisticated systems of botanical medicine preparation, a product is standardized to guarantee the minimum or maximum concentration of a number of ingredients for a given period, for example, EGb 761 (Schwabe GmbH, Karlsruhe, Germany), the *Ginkgo biloba,* which has been the most researched botanical and is standardized on four constituents. Standardizing on particular constituents has its challenges. Active ingredients in plants are often classes of molecules (e.g., polysaccharides, saponins, terpenes) that are difficult to distinguish in biological activity. Different compounds in a single species may have similar, possibly complementary effects, such as the polysaccharides and isobutyramides in *Echinacea* species. During in vitro assays, which guide fractionation of the crude extract toward a single active molecule, it is not uncommon for activity to increase but then diminish as greater purity of an identified molecular species is reached, as was the case of the terpenes of *Andrographis paniculata* (AndroVir, Paracelsian, Inc., Ithaca, NY) in cell signaling. A few botanicals are standardized on an in vitro biological activity. The industry standard, porously applied, is chemical standardization on actives and certified Good Manufacturing Practices.

Nutrition can be divided into dietary practices and nutritional supplements. Studies in dietary interventions are demanding. The gold standard for dietary intervention is a residential facility to maintain adherence to the therapeutic regimen, but this solution is expensive and recruitment is difficult. A long observation time is frequently needed in dietary studies because diets are often intended as preventives or restoratives.

Some nutritional supplements are cultures, such as probiotics (live bacteria taken to normalize commensal bacterial populations) and algae. Studies in these types of interventions have some of the same complications as botanical medicine studies, as well as the issues of organism viability and interactivity with commensal microorganisms and the internal conditions for proliferation.

Homeopathy is a special case in standardization, in that chemical standards are largely irrelevant for remedies that rely on ultradilutional remedies that may contain no molecules of the material originally potentized. Biological testing of homeopathics is in its infancy, and reliability is not ensured. Thus, only the manufacturing process can be standardized at this time.

"Body, mind, spirit" is a leitmotif of natural medicine. The interplay of psychodynamic and spiritual phenomena and physical health are only partially encompassed by the behaviorist approach of most health psychology research, but this has been greatly augmented by recent studies in "mind–body" medicine with numerous reviews in various specialties in publication. Advances have been made in the neuroscience of expectancies in the placebo effect, with the size of the placebo effect recognized as different in different conditions, but despite the ubiquitous use of placebo in practice,[10] operationalization and manipulation of placebo effects remain fraught methodologically and ethically. Placebo use in medical encounters continues to be explored, but raises more questions than answers;[11] however, hope remains for advances in future studies.[12]

While they represent a small proportion of all health studies, questions about spirituality remain of investigative interest, although with few authoritative and widely used research methods. Operationalization of spiritual experience is likely to be idiosyncratic or culture specific. The 4th edition of the *Diagnostic and Statistical Manual* (DSM-IV, 1995) reinstated the possibility of a religious or spiritual problem. Definitions of spirituality in the medical literature may refer to hope and meaning or to a personal relationship with God, serenity, or connectedness, all perhaps related to states of the patient's consciousness.[13,14] A number of thinkers continue to bemoan the lack of definition in the area.[15] Although efforts to present cogent, broadly acceptable definitions have been made, they have not been successful.[16,17] Better approaches to specifying spiritual interventions may be needed before they will be accessible to replicable research. Recent reviews of the health effects of intercessory prayer, an observable phenomenon, have been equivocal.[18]

Individualization of Treatment

Natural medicines' disease taxonomies (classifications of human illness) are not always congruent with those of Western molecular biomedicine. Primary variance (differences in outcome) of efficacy is more likely to vary with the conditions of a practice's native taxonomy than with a foreign one. For example, "strengthening the immune system," "decreasing toxicity," and "fortifying the will to health" are common goals in natural health therapeutics but are rare in conventional practice. Treatment response would be expected to have a different profile because different diseases are being treated. Thus, the speed to healing, as well as the disease being treated, may be confounded in the evaluation of one system by the other's definitions and rules. These concepts are themes to be described more explicitly in natural medicine diagnosis.

Some natural medicine concepts may no longer have or may never have had a biomedical equivalent. An example is the concept of "constitution" used in naturopathy, homeopathy, and Asian medical systems. This is a patient's given biological potential, tendencies, and patterns of long-standing psychophysical strengths and weaknesses that are genetically and embryologically determined. Others are the "biological terrain" (the background physical health and individual context for the immediate medical problem) and the "vital force" (the motive plan or spirit animating mind and body expressed as physiologic and psychological functionality and adaptability). Biomedical equivalents exist in some parameters for system control concepts; however, they are therapeutically exploited more thoroughly by holistic practitioners. Such concepts are balance (as in the immune system, among microbial symbionts, hormones, and neurotransmitters); deficiency (not just nutritional but organ deficiencies, such as hypochlorhydria and hypothyroidism); functional reserves; endogenous and exogenous toxicities; and dysmetabolisms (e.g., syndrome X). An important concept is that a disease syndrome may be an attempt by the body to adapt to ecologic stress and so should not be unnecessarily suppressed. This is of interest not only because it is

an independent variable (baseline factor), but also because it influences the measurement of the dependent variable (outcome).

A skilled natural medicine practitioner necessarily expects success through individualization of treatment regimens. Individualization means that remedies are prescribed not solely on the basis of disease entities but also according to other characteristics of the patient. Such characteristics may be transient, constitutional, or representative of the entire constellation of the patient's health problems, strengths, and his or her capacity for self-care. The lack of fit of a person's health syndrome with a conventional disease model, expressed perhaps in the inability or reluctance of a conventional practitioner to diagnose a particular health problem, may be the very reason a patient turns to natural medicine. A medical system that does not recognize an entity is unlikely to have an effective therapy for it. The complaint will be managed as something else, resulting in ineffective treatment while exposing the patient to the side effects of the "remedy." Conversely, a medical system that provides an adequate explanatory model for a patient's symptoms—their origin, aggravators, and ameliorators—has a better chance of effective treatment or management of the condition. Thus, individualization of treatment is a strength of natural medicine rather than merely a research problem. Compromises may be made in practice to make a trial of specified therapy possible, such as by semi-protocolized treatments, but they may alter therapeutic effect. If the need for individualization is neglected in natural medicine research design, the design will fail to apply the medicine as practiced and thus to evaluate its potential benefit.

Combination Therapeutics: Effect Size, Response Rate, and Safety

Combination treatment is almost a rule among natural medicine practitioners, who use multiple remedies individualized for each case. This complicates the design of clinical trials, yet the evaluation of combination interventions is critical to assessing an examined practice. Single natural agents may have a true effect small enough that a very large patient sample size is necessary to detect a treatment difference. However, the size of the effect of several agents acting together, especially if they act by different mechanisms, may work by cumulative or synergetic interactions. Combination treatment may also afford the practitioner latitude in choosing the correct remedies for a patient's condition, thereby increasing the treatment responder rate. Another strategy in choosing elements of combinations is tailoring them to a case to efficiently address multiple conditions simultaneously, thereby achieving better global outcomes. Yet another is to use some agents as "governors" (the term in Chinese herbal medicine) to ameliorate potential side effects of primary remedies.

The possibility of adverse events could theoretically rise with combinations. Although the problems of additive and synergetic actions, inhibition, and toxicity associated with multiple synthetic and novel pharmaceuticals in combination are both formidable and ubiquitous, the history of use of natural remedy candidates and the experience of clinicians in using combinations of natural products in various clinical populations mitigate these problems in everyday practice. For example, when whole botanicals are used at a traditional use dose, early toxicity is most likely to result in nausea and vomiting or diuretic action. More serious adverse events (e.g., anaphylactoid reactions) are rarer with nutrients and botanicals of traditional medicinal use than with novel drugs of a single molecular species. Modern practitioners of natural medicine also combine modalities (e.g., homeopathy and counseling, or manipulation and herbs) that are extremely unlikely to lead to a deleterious interaction, but that, if successful, could each stimulate improvement by a completely different route. Because of the breadth of options for affecting a condition, a skilled practitioner can avoid remedies that pose a risk in a particular case while still attaining the targeted pharmacologic action. There is no systematic study of the safety of combinations, but data from licensing authorities and professional liability companies for practices covered show modest levels of adverse experience.

Nonspecific Healing Effects

A confounder in a clinical trial is an apparent therapeutic effect that can be attributed not to the test treatment but to a factor associated with the treatment, disease, or population studied. This is a risk inherent to all research and is the reason why randomization, blinding, and objective measures are valuable in distinguishing true differences in effect among medications. The most honest scientists may have conscious or unconscious behaviors that could bias study results if differentially applied to study groups. Yet similar behaviors are at work in everyday clinical practice to induce affiliation, confidence, commitment, and satisfaction in patients and are the responsibility and *sine qua non* of skilled healers.

An important confounder that may be integral to treatment is intentionality. (See Chapters 6, Placebo and the Power to Heal and 7, Positive Mental Attitude.) The potential therapeutic action of pure intention, which is not mediated by language or any well-known material force, might be espoused explicitly by only a minority of holistic practitioners, although actually it might be widely practiced among them. This may be called "psychic healing" or simply "healing". If the intent is to determine whether these techniques have effect on disease, surprisingly, there may be no particular difficulties in conducting studies than those already addressed here. Trials of intercessory prayer may provide a model.[19] Design differences may be called for if the therapists are special (gifted) versus ordinary people, or if the healing energy is directed or willed versus invoked (as from God or spirits). Little has been written on the capacity of intention to influence physical outcomes; there is implicit rejection of the idea based on cartesian mind–body duality. Nevertheless, a number of studies suggest its existence.[20,21] Studies of the effect of prayer or other spiritual practices also may be relevant here and raise the possibility that specific kinds of intentionality may make a difference.[22]

Intuition is a similarly nebulous practitioner-associated quality that may have an influence on outcome. It might be thought to bear on diagnosis as a source of data or on therapeutics as a guide among possible alternative strategies. Although intentionality and intuition are not typically listed in the educational catalogs of natural medicine academic institutions as requisite health care skills to be acquired, they may be common concepts in the culture of the institutions. Generally they are not considered antiscientific concepts that should be expunged from the awareness of students. They might be acknowledged and even honored as possible sources of data and therapeutic direction as long as their "discoveries" are not contradicted by harder evidence. The informality of the inclusion of intention and intuition in practice compounds the difficulty of including these concepts in some reproducible way in research protocols.

Health care is practiced within a culture whereby practitioners and patients have roles and expectations that reinforce belief in expected outcomes. Some studies have indicated that good practitioner–patient communication results in better health outcomes. Thus, some of the magnitude of effect may depend on the setting in which care is offered. Differences in outcome between medical practices may also hinge on the difference between research and nonresearch settings. For example, it is possible that research

participants who refuse random assignment have a psychological orientation that may work synergistically with the physical effects of the practices of a medical culture that they prefer or to which they are native. If this is true, the evaluation of systems of practice relative to each other would preclude simple randomization. Trials that should be of real interest to policymakers are those that determine not simply whether a practice works for anyone to whom it is applied, but whether it works (and is cost effective) among those who choose it. A study design that could determine the added value of the availability of some form of natural health care in those who choose it would be one that randomly assigns patients to either a group that undergoes further randomization to strict assignment of alternative or conventional care or a group offering them a choice of alternative or conventional care.[23] Such a four-group trial including randomization with choice would compare the effect of the different practices among those patients who discriminatively select among them versus those who are simply assigned to them.

Natural medicine has little language for placebo and other nonspecific healing effects despite the fact that many conventional scientific authorities think this is an area in which there is much to offer. Both unintentional nonspecific healing effects and intentional psychospiritual medicine are areas in which the discovery and definition of important memes, especially those that may serve research, are poorly evolved not only for natural medicine, but also for Western biomedicine.

Outcomes and Measures

Because natural medicine addresses the holistic, it is expected by practitioners to have broad benefit (e.g., correcting deficiencies, strengthening and balancing metabolic processes, and "removing the obstacles to cure"). If a natural medicine intervention for a particular disease is shaped and delivered, a benefit is likely to affect more than one disease condition at a time. Randomized clinical trials (RCTs) are typically designed to provide higher validity on a few measures and tend to overlook effects on diseases other than the target disease, neglecting effects on overall well-being. (See discussion on "Cure and Suppression" in Chapter 5, Philosophy of Naturopathic Medicine.) Clients, who often use CAM for overall health and wellness,[22] expect to see positive results not only in objective disease parameters but also in general body functions (e.g., fatigue and energy, pain, inflammation, digestion, mental and emotional function) at a perceptible level. Thus, methods to assess the efficacy of the medicine should use holistic measures accounting for effects throughout the body systems and over the life cycle, if possible, and in an intervention's influence on social roles, productivity, and cost. Beyond the effectiveness of medicine for the individual patient, measures of an entire holistic practice may reasonably be expected to address public health as well as environmental, social, and economic outcomes.

Strides have been made in the development of measures that assess individual health globally.[24] There has been progress with the development and wide adoption of instruments, beginning with the Medical Outcomes Study SF-36 and its successors, and of measures such as "quality-adjusted years of life saved." However, there remains a lack of sensitivity to changes in disease at higher levels of function. The lack of sensitivity relates to the general absence of health measures (e.g., productivity) as opposed to disease measures in clinical trials. Gentle natural treatments may show smaller, more gradual improvements than may be expected from pharmaceutical and surgical interventions, and instruments sensitive to change are needed if trials are to be relatively short. Ultimately, the possibility of the superiority of natural health care in a few areas, such as longevity, the incidence of chronic disease in aging, and the incidence and prevalence of disease in progeny, ideally will require multidecade evaluation. Online tools available and in development for patient-reported outcomes hold potential for large, long-term studies with whole person measures.[24a]

Controls and Blinding

The choice of appropriate comparison controls is an important issue because every alteration of control answers different questions. The different questions in the comparison of a test intervention with placebo, a specific standard of care, usual care (the patient's baseline care), or time–attention behavior controls are all of interest. Sometimes ethical constraints may prevent a natural medicine therapy from being evaluated without a concomitant conventional therapy. Some cases of special interest are whether natural health care leads to lower overall morbidity and mortality (1) in patients who are randomly assigned to natural health care compared with those who are not; (2) in patients to whom it is equally available on the basis of cost and access compared with those to whom it is not; and (3) in patients who would actively pursue it in the presence of health system structural resistance (e.g., devoted consumers) compared with those who would choose it only if it were equally available or with those who would explore it only under special circumstances. The answers to these questions involve belief, motivation, cost, the restraint of use because of cost (from the consumer's side), the restraint of access because of cost (from the provider's side), and compliance. These answers may be fundamental to determining both the efficacy and efficiency of the inclusion of various forms of natural medicine in a rationally structured health care delivery system.

Treatments can be categorized simply into substances (drugs and remedies), procedures, and interactions (verbal and behavioral medicine). The double-blind RCT test system is easily applied with the evaluation of substances. Nonmaterial process interventions, such as manipulation, exercise, acupuncture, other forms of point work, and psychological and spiritual treatment, are more methodologically problematic in the RCT desideratum of blinding. Blinding is likely to prove difficult for most dietary manipulations, psychospiritual practices, and any whole practice intervention. In these cases, blinding often may be at least partially maintained by separating evaluation from treatment and blinding the evaluator. In considering the value of blinding, one should remember that studies that blind the practitioner and patient decrease or eliminate the possibility that intentionality will contribute to a positive outcome. However, CAM theories accommodate blinding and expectation as contributors to outcome.

Whole Practice Models

Given that individualized combinations of modalities and remedies generally are the rule in natural medicine and that their selection is guided by a health system's own principles and guidelines, evaluation of models of whole practices is most likely to reveal their potential health benefit. The main difficulty that arises is in attaining replicability of the intervention. (See Chapter 2, Functional Medicine, for a presentation of a methodology for systematizing individualization.) Although they remain both innovative and challenging, a number of intervention models are possible in approaching the ideal.

The simplest is a fixed combination of remedies, although this approach abandons individualization. If it is applied in trials with specific inclusion and exclusion criteria, however, the loss of individualization may be tolerable. A slightly more ambitious approach to whole practice is a menu of choices applied to several possible

etiologies in a symptom manifestation (disease) under study. As alternative medicines have been studied in recent years, pragmatic trials have been explored using a practitioner of given qualifications as the unit of intervention, treating the practitioner and his discipline as a "black box." A further step in sophistication is the intervention driven by guidelines or algorithms from the principles and body of knowledge of the discipline. Such guidelines may be derived through expert practitioner panels. The design and replicability of best practice protocols derived by experts from discipline principles are being studied in naturopathic[25] and Chinese medicines.[26] The complex models that have resulted may be facilitated operationally by manualization for the guidance of practitioners, who must be well trained to assess patients and deliver a standardized intervention flexibly.[27] A new question that would arise in such studies of manualized practice is the degree of adherence by the provider to the protocol. Another method is artificial intelligence programs that seek to emulate the decision-making processes of clinicians so that personalization can be standardized according to the algorithms practitioners use, often unconsciously.

The inability to distinguish the effects of single agents in pragmatic and whole practice studies frequently diminishes enthusiasm among grant review committees, since a whole practice is not easily transferable to other practitioners. However, whole practice studies are essential to determining the effectiveness and safety of natural medicine disciplines.

Observational Studies

There are essentially two components to medical research: observation and experimentation. Observation documents the natural history of clinical conditions, the approach to health, and the outcomes of treatment. In observational studies, ideas of association are formed and hypotheses are generated. Experimentation in medicine evaluates the outcomes while varying practice. Experimentation tests hypotheses generated in a variety of ways, including from observational study. In CAM, where many variants of health care of unknown safety and effectiveness are already in practice, observational study holds an important place. In medicine, research questions often involve pursuing a desired outcome by manipulating the input variables. The input variables are discovered ultimately through observation, as are the models in which to study them. Both observation and experimentation are needed to validly evaluate medical practices. With an appreciation for the appropriate place of observational study, we should not expect observational studies to provide the information nor meet the methods *desiderata* for experiments. In the relatively little examined practices of natural medicine and CAM, "until we know more about the practice, scope of practice, patient characteristics, utilization rates, and patient numbers, it is difficult to design appropriate studies or to even know which issues are worth studying."[6]

The challenge with results observed in evaluation of clinical practice is determining whether the observed association reflects a causative relationship. Although newer statistical tools, such as propensity scores and principal component analysis, may help, observational studies have been considered low on the hierarchy of validity in evaluation of medical practices. Effect sizes found in observational studies are often considered inflated, yet those from clinical trials and observational studies appear to be similar.[28,29]

Observational outcomes studies have some unique advantages in the study of natural medical practice. Outcomes research involves cohort studies wherein repeated health status evaluations in ordinary care settings compare outcomes of spontaneously arising variations of care, such as standard care and alternatives to it. Variations may be specific remedies, treatment approaches, or even whole professional practices. Advantages include the lack of ethical conflicts about withholding conventional treatment because the patients choose their practitioner. The effect of intention on the part of patient and practitioner is not abrogated. The medicine implemented is fully individualized with no constraint on the combinations considered best for a patient. The cost of research per case is a lesser constraint than in randomized trials if patients (or third parties) cover the cost of care. Costs can be included as an outcome. Mixed methods—quantitative and qualitative—in observational studies are usual and useful. More early observational studies will help to guide future trials. Best-case series, a retrospective review of selected cases, are having an effect on research directions in CAM.[30]

The care of patients currently using natural medicine is a valuable source of data for evaluating and monitoring care characteristics in different forms of practice. The growing coverage of CAM practitioners by third-party payers in health delivery systems over the past 20 years has generated much data on use and cost for currently licensed and insurance-covered natural medicine practitioners that can be used for comparison with outcomes of standard therapy.[31] The study by Cherkin et al,[32] designed on the model of the National Ambulatory Care survey, was remarkable in ascertaining the content of practice of state-licensed naturopaths, acupuncturists, chiropractors, and massage therapists.

The complexities of natural medicine (and any whole practice), with multiple inputs (patient characteristics and combination individualized treatments), broad measures, standardization data, and complex control conditions (e.g., "usual" care), both descriptive and analytical, all imply worthwhile data for exploration. For some CAM professions, the adoption of electronic medical records and the increased integration of CAM trained practitioners into conventional settings is generating rapidly growing databases in which clinical epidemiology may become common. To plan studies (including single-agent trials) and to understand results, the disciplines benefit from improving infrastructures for design, data collection, management, analysis, and interpretation. The NIH NCCAM has recognized the need and value of developing infrastructure at CAM institutions where there is clinical expertise in the practices.[33] There is a growing cadre of cross-trained and productive research CAM practitioners to engage in high priority studies with interdisciplinary expertise.

Basic Science Studies

Data from the basic sciences ensure the causal chain linking a happy clinical observation and an intervention. They help the wider community understand and use the natural medicine professions' experience. All of the natural medicine disciplines would benefit from greater exposure to the array of laboratory pharmacology and might, in turn, inform pharmacology of their own useful strategies. In the exploration of natural medical theory and in refining remedies, it would be useful to have access to a range of basic science techniques from analytical chemistry to classical microbiology to advanced molecular biology. Thousands of natural products have been screened for numerous laboratory outcomes. However, new understandings of human biology and advances in technology have made many more types of studies possible in areas such as combinatory pharmacodynamics, gene expression, proteomics, metabolomics, glycobiology, and immunology. Practitioners could guide the refinement of study questions from their best clinical judgment for future investigation.

One continuing need is in standardization of *materia medica*, not only on chemical constituents but also on biological activity. NIH NCCAM shows a sustained interest in funding the basic sciences in future CAM research centers.

Animal studies present their own complexities for the practices of interest. On one hand, acupuncture and homeopathic veterinary are common, and demonstration of the concepts of the animal study practices seems a reasonable route to improving practice. On the other hand, some CAM institutions have policies prohibiting animal research. Many vitalists and holistic practitioners hold that neither animal studies nor in vitro work appropriately reflects the human being. Their arguments may bear legitimate scrutiny. When animal work is the most fruitful way to pursue an important clinical goal, most natural medicine academic centers are willing to collaborate with animal laboratories.

Considering the salugenic rather than disease-oriented goals of most natural medicine practices, it may prove a valuable direction for natural medicine institutions to improve collective understanding through the basic science of normal and optimal physiology and the effects and mechanisms in which they are most likely to be expert. Alternative practitioners are well situated to contribute knowledge to the study of overall health, complexity in health care, and health behavior.



CRITERIA FOR A PRIORITIZED RESEARCH PROGRAM

The entire array of research design has a place in natural medicine research. There is a wide range of methodological discussion in publications and many currently ongoing studies spurred by substantial funding from the NIH. Methodologists have covered many problems in evaluation of different expressions of natural medicine, and the approaches and methods have been well summarized.[34] However, resources are always limited; therefore, research should be prioritized. Some major criteria to consider in developing programs of research to be considered are the following:

1. Focus on diseases with the highest burden of human suffering and the greatest public health significance as well as those in which standard therapy falls short of cure and effective management.
2. Evaluate first the treatments that have the greatest likelihood of reducing the burden of suffering—the low-hanging fruit among natural medicine therapeutics and preventives. Two sources for targeting decisions in this regard are the evidence already present in the scientific literature and the opinions and data of experienced natural medicine practitioners.
3. Attend to methodological evolution and the necessary sequencing of studies to achieve long range goals and to explore for and validate positive clinical experiences. Some research questions require methodological innovation because we do not yet know exactly how to answer them (e.g., in evaluating the whole-systems approach to disease, long-term safety, ultradilutional and combinatorial effects, spiritual practices, and even measures of overall health). Important questions may call for complex designs that combine observational and experimental research. Clinical research usually requires preclinical preparation. The confidence of investigators and funders and the clarity of their direction improve with preliminary pilot and observational data.
4. Attend to building a practice improvement and discovery infrastructure for the future in those practice disciplines prepared for it.

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SECTION 2

SUPPLEMENTARY DIAGNOSTIC PROCEDURES

Patrick Hanaway

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Over the past 50 years, tremendous progress has been made in the development of laboratory procedures for the diagnosis of disease. However, this work has focused primarily on pathologic processes—little has been done to help the physician recognize physiologic abnormalities before they progress to the pathologic stage. The problem is further aggravated for doctors of preventive/integrative/functional/natural medicine, who need to evaluate in an objective manner the nutritional status, lifestyle, physiology, toxic load, and health of their patients. The few widely available tests that exist tend to be oriented to measuring absolute values rather than functional indices and generally indicate abnormal values only after serious dysfunction develops.

We have compiled a number of useful assessments that we believe will greatly aid physicians who would like to utilize more objective tests in their evaluation of the pathophysiologic status of their patients. These are not meant to replace the standard, pathologically oriented, diagnostic procedures but rather to supplement them and aid in the early diagnosis of disease susceptibility and the quantification of the processes that usually precede clinical disease. Where possible, preference is given to tests that measure function rather than abstract absolute values. In keeping with the metabolic and scientific orientation of this textbook, emphasis has been placed on those procedures that have good support in the scientific literature for the evaluation of nutritional status.

Most of these laboratory procedures are on the cutting edge of our understanding of the assessment of the physiologic function of metabolically unique individuals. Because it is an emerging field, few experts exist and most are employed by the commercial laboratories performing and providing the procedures.

CHAPTER 9

Apoptosis Assessment

Lise Alschuler, ND, FABNO and Aristo Vojdani, PhD, MT

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INTRODUCTION

Apoptosis is a distinct form of cell death controlled by an internally encoded suicide program. It is believed to occur in the majority of animal cells. It is a distinct event that triggers characteristic morphologic and biological changes in the cellular life cycle. It is common during embryogenesis, normal tissue and organ involution, and cytotoxic immunologic reactions, and occurs naturally at the end of the life span of differentiated cells. Apoptosis can also be induced in cells by the application of a number of different agents, including physiologic activators, heat shock, bacterial toxins, oncogenes, chemotherapeutic drugs, various toxic chemicals, ultraviolet and γ-radiation, and hypoxia. When apoptosis occurs, the nucleus and cytoplasm of the cell often fragment into membrane-bound apoptotic bodies, which are then phagocytized by neighboring cells. Alternatively, during necrosis, cell death occurs by direct injury to cells, resulting in cellular lysing and release of cytoplasmic components into the surrounding environment, often inducing an inflammatory response in the tissue. Apoptosis may occur in one cell, leaving surrounding cells unaffected, as opposed to necrosis, which affects multiple cells simultaneously.

A landmark of cellular self-destruction by apoptosis is the activation of nucleases and proteases that degrade the higher order chromatin structure of the DNA into fragments of 50 to 300 kilobases and subsequently into smaller DNA pieces of about 200 base-pairs in length. Activation of proteases, notably aspartate-specific cysteinyl proteases, referred to as caspases, is of primary relevance to apoptosis. Caspase-3 is considered to be the key mediator of apoptosis of mammalian cells, and its expression may be measured with immunohistochemical staining. Using fluorescent-labeled reagents, it is possible to tag the DNA break and identify the percentage of apoptotic cells with a high degree of accuracy.[1–6]

Measurable Features of Apoptosis

One of the most easily measured features of apoptotic cells is the breakup of the genomic DNA by cellular nucleases. These DNA fragments can be extracted from apoptotic cells and result in the appearance of DNA laddering when the DNA is analyzed by agarose gel electrophoresis. The DNA of nonapoptotic cells, which remains largely intact, does not display this laddering on agarose gels during electrophoresis. The large number of DNA fragments appearing in apoptotic cells results in a multitude of 3'-hydroxyl termini of DNA ends. This property can also be used to identify apoptotic cells by labeling the DNA breaks with fluorescent-tagged deoxyuridine triphosphate nucleotides. The enzyme terminal deoxynucleotidyl transferase catalyzes a template-independent addition of deoxyribonucleotide triphosphates to the 3'-hydroxyl ends of double- or single-stranded DNA. A substantial number of these sites are available in apoptotic cells, providing the basis for the single-step fluorescent labeling and flow cytometric method. Nonapoptotic cells do not incorporate significant amounts of the fluorescent-tagged deoxyuridine triphosphate nucleotides due to the lack of exposed 3'-hydroxyl DNA ends.

Apoptosis can also be characterized by changes in cell membrane structure. During apoptosis, the cell membrane's phospholipid asymmetry changes—phosphatidylserine is exposed on the outer membrane, whereas membrane integrity is maintained. Annexin V specifically binds phosphatidylserine, whereas propidium

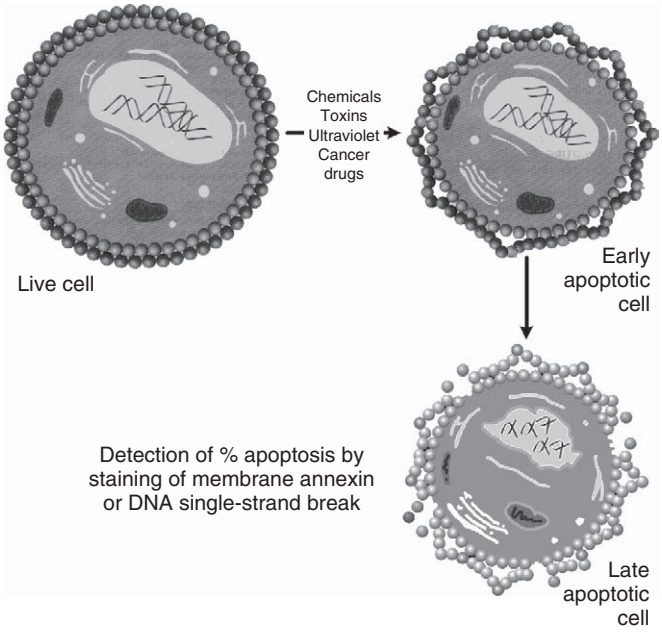


FIGURE 9-1 Detection of apoptosis using damaged membrane or DNA single-strand break and flow cytometry.

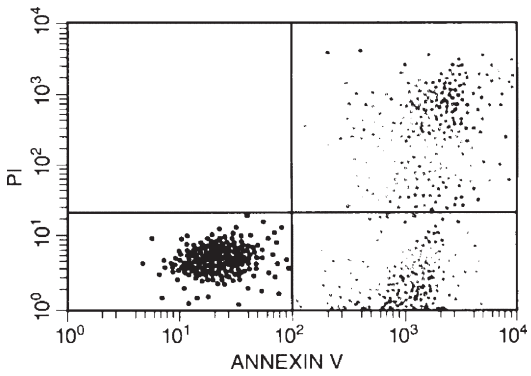


FIGURE 9-2 Separation of cells by flow cytometry and detection of apoptotic population.

iodide is a DNA-binding fluorochrome. When a cell population is exposed to both reagents, apoptotic cells stain positive for annexin V and negative for propidium iodide; necrotic cells stain positive for both, and live cells stain negative for both.[3]

This process of apoptosis and its analysis by flow cytometry are shown in Figures 9-1 and 9-2.

Another assessment of apoptosis involves ex vivo cell analysis. Specifically, the expression of active caspase-3 along with the Bcl-2/Bax ratio as markers of apoptosis can be measured. Immunohistochemical staining will reveal the expression of these apoptotic-related proteins, caspase-3 and cleaved caspase-3; the latter is indicative of apoptosis.[7] Bcl-2 is anti-apoptotic gene product that exists in ratio to Bax and Bak, which are pro-apoptotic gene products. This ratio is indicative of the degree of apoptosis, with a decreased Bcl-2:Bax ratio indicative of apoptosis. Cells from Bax (–/–) and Bak(–/–) knockout animals do not respond to apoptosis inducers. In these cells, cytochrome C is not released from the mitochondrial membrane to initiate the caspase cascade.[8] Thus, Bax and Bak are critical to apoptosis, and their expression in relation to Bcl-2 is highly correlative to apoptosis.

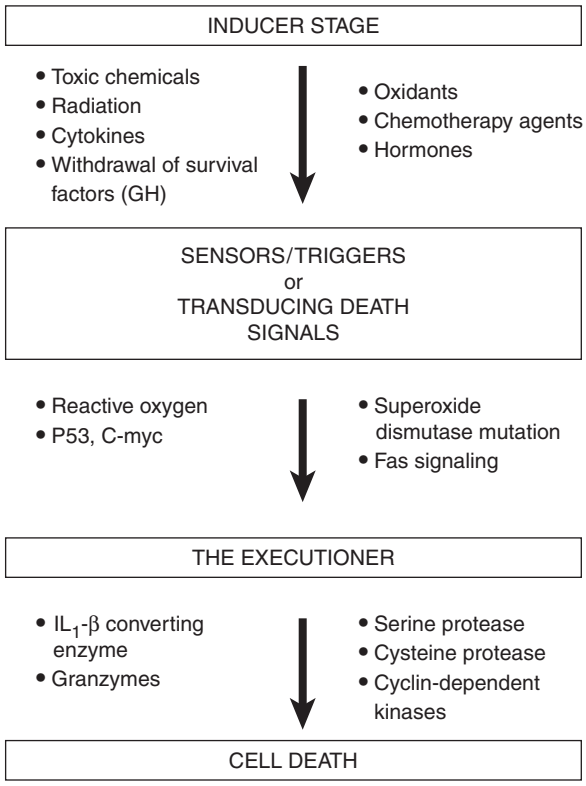


FIGURE 9-3 Various stages of "inside out" cell death or apoptosis.

Different Stages of Apoptosis

The process of apoptosis is divided into three different stages:
- Induction
- Sensing or triggering
- Execution

These stages of apoptosis are depicted in Figure 9-3. Induction represents the initial events that signal a cell so that apoptosis may begin. This induction phase may be induced by various physical agents, such as toxic chemicals, hypoxia, radiation, chemotherapy agents, hormones, and CD95 or Fas ligation. It has been proposed that the induction stage of apoptosis is prevented by many antioxidants (vitamin C, β-carotene, and vitamin E) and also by various biological response modifiers, including lentinan, thymic hormones, viral antigens, and cytokines.

The induction stage is followed by a decision on whether or not the cell will undergo apoptosis. The decision to die is under the control of a number of different pathways or cellular sensors that induce the apoptosis signal, which then triggers the central mechanisms. During this stage, enzymes such as interleukin1-β converting enzymes, serine protease, cysteine protease, granzymes, and cyclin-dependent kinases become activated. Once activated, these enzymes dismantle the cell and trigger the cell surface changes that cause direct cell recognition and engulfment of the dying cells by phagocytes. These central events are prevented by various antioxidants and biological response modifiers.

Apoptosis is Induced by Chemicals to Control Malignancy

Many chemicals have the capacity to bind to DNA, form DNA adducts, or cause DNA single-strand breaks, possibly leading to cancer. However, the body is equipped with many factors, enzymes, suppressor genes, and cellular sensors, all with the capacity to

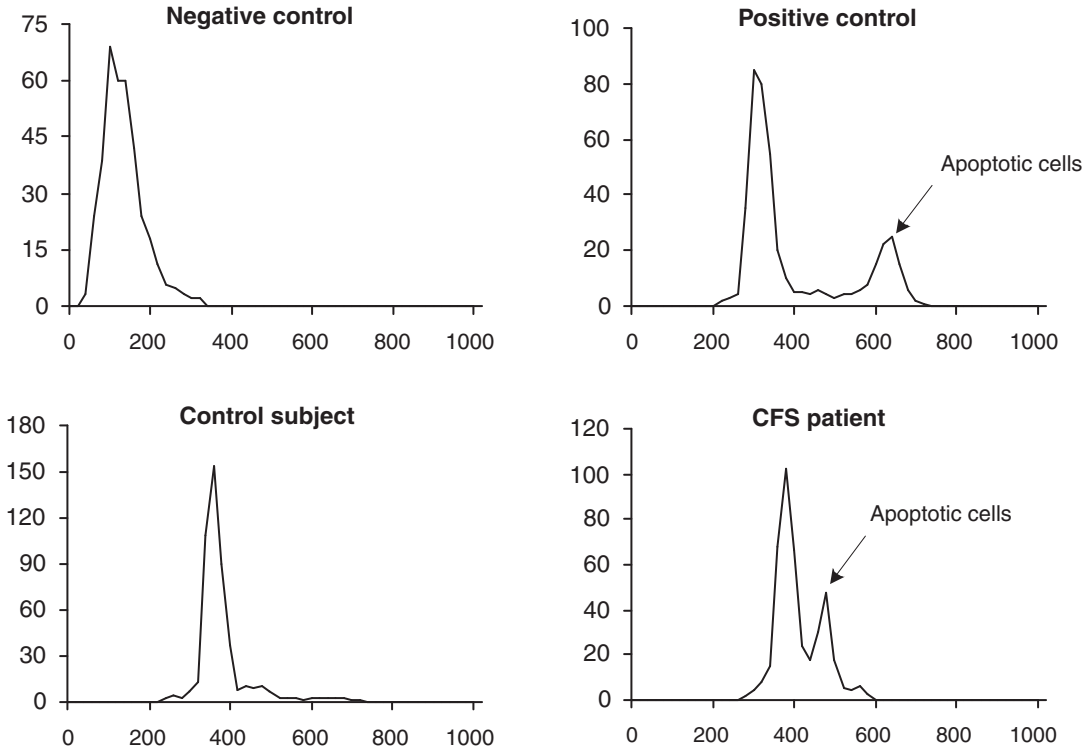


FIGURE 9-4 Enhanced apoptotic cell population in benzene-exposed individuals with chronic fatigue syndrome. Flow cytometry analysis of apoptotic cell population in negative control cells (HL-60 leukemic cell line), positive control cells (HL-60 leukemic cells treated with the Apogen camptothecin), control subjects, and benzene-exposed individuals. Peripheral blood leukocytes were isolated, cultured for 12 hours, fixed in paraformaldehyde, labeled with fluorescent-tagged deoxyuridine triphosphate nucleotides, and analyzed for apoptosis by flow cytometry.

prevent the consequences of this DNA damage by activating apoptosis-inducing signals.

The role of apoptosis in regulating tissue growth is readily apparent in the simple equation in which the rate of growth is equal to the difference between the rates of cell proliferation and cell death. Thus, tissues expand if the rate of proliferation exceeds the rate of cell death. This is one of the reasons for suggesting that defects in apoptosis may contribute to the transformed state.

An important prediction of the relevance of apoptosis to malignancy is that the rate of apoptosis versus mitosis should influence the behavior of a tumor. Recently, the relationship between the apoptotic and mitotic indexes in a tumor was demonstrated as predictive of outcome: a higher ratio of apoptosis to mitosis within the tumor correlated with positive prognosis. Further, it was found that this was not simply a function of cell death per se. Tumors with a high incidence of necrosis rather than apoptosis were correlated with poor prognosis. It therefore follows that treatments or conditions that favor apoptosis should have desirable effects, and that defects in the pathways leading to apoptosis are likely to play important roles in the process of oncogenesis.[4,5]

Many reactive chemicals and drugs such as acetaminophen, diquat, carbon tetrachloride, quinones, cyanide, polyhydroxyl polyether, methyl mercury, and organotin have been implicated in apoptosis (programmed cell death) and necrosis (toxic cell death).[9–16]

Most research on chemical induction of apoptosis is carried out with primary cultures of cell lines (e.g., neurons, thymocytes, carcinoma cells, leukemia cells, neuroblastoma, breast cancer cells, lymphoma); little has been published on the in vivo effects of chemicals on apoptotic cells in animal models and none in humans. Therefore, it was of interest to examine the effects of exposure to low levels of benzene, as well as through drinking water concentrations of up to 14 ppb on the apoptotic cell population, as well as to examine possible changes in the cell cycle progression.[9]

Evidence is sufficient for the carcinogenicity of benzene in humans; therefore, there is no safe level of exposure to this chemical or its metabolites. Published case reports, a case series, epidemiologic studies, and both cohort and case–control studies have shown statistically significant associations between leukemia and occupational exposure to benzene and benzene-containing solvents.[17,18]

It has been indicated that possibly 800,000 persons are exposed to benzene from coke oven emissions at levels less than 0.1 ppm, and 5 million may be exposed to benzene from petroleum refinery emissions at levels of 0.1 to 1 ppm. Since then, numerous chemicals have been implicated in apoptosis (or programmed cell death), which arises from damage to DNA. One of the authors, Vojdani along with collaborators, hypothesized that in individuals with a certain genetic makeup, benzene or its metabolites act as haptens, which may induce programmed cell death. The study involved a group of 60 male and female subjects who were exposed to benzene-contaminated water (at concentrations up to 14 ppm for a period of 3 to 5 years).[18a] For comparison, a control group consisting of 30 healthy males and females with a similar age distribution and without a history of exposure to benzene were recruited. Peripheral blood lymphocytes of both groups were tested for percentage of apoptotic cell population, using flow cytometry. When exposed individuals were compared with the control group, statistically significant differences between each mean group were detected (27.5 ± 2.4 and 10 ± 2.6, respectively), indicating an

increased rate of apoptosis in 86.6% of exposed individuals (P <0.0001; Mann-Whitney U-test). Flow cytometry analysis of apoptosis in a healthy control and a patient with chronic fatigue syndrome is shown in Figure 9-4.

It has been demonstrated that benzene induction of apoptosis is caused by a discrete block of the cell cycle progression.

There is a tendency for normal cells to commit "suicide" when deprived of usual growth factors or physical contact with their neighbors due to chemical exposure, which may represent a built-in defense against metastasis. Prompt activation of apoptosis in tumor cells that leave their native tissue presumably eliminates many metastatic cells before they have a chance to proliferate. In cancer, it is tumor cells that neglect to sacrifice themselves or forget to die. Researchers increasingly describe cancer as a disease involving both excessive proliferation of cells and abandonment of their ability to die. The dysregulation of apoptosis in malignant cells underlies both the initiation and progression of cancer.

Cancer develops after a cell accumulates mutations in several genes that control cell growth and survival. When a mutation seems irreparable, the affected cell usually kills itself rather than risk becoming deranged and potentially dangerous. However, if the cell does not die, it or its progeny may live long enough to accumulate mutations that enable it to divide uncontrollably and metastasize.

In many tumors, genetic damage apparently fails to induce apoptosis because the constituent cells have inactivated the gene that codes for the p53 protein. This protein can lead to activation of the cell's apoptotic machinery when DNA is injured by environmental agents, such as benzene or its metabolites. Therefore, it is important to study cell suicide in health and diseases.

CLINICAL APPLICATIONS

Apoptosis in Cancer

The failure of apoptosis in malignant cells in the context of irreparable DNA damage leads to tumor progression. Cancer therapies, namely, chemotherapy and radiation, control cancer by inflicting cell damage, which, in turn, triggers apoptosis. Unfortunately, >50% of all human cancers involve a mutation of p53, a central gene in apoptosis. p53 stimulates both the extrinsic death receptor pathway of apoptosis as well as the intrinsic mitochondrial pathway involving a decreased Bcl-2:Bax ratio. Thus, it is imperative to find therapies that promote apoptosis independent of p53. Promising therapies in this regard include curcumin,[19] derived from *Curcuma longa*, and resveratrol,[20] both of which are under investigative study for this application. Another promising cancer treatment involves the use of recombinant human apoptosis ligands to induce tumor necrosis factor-related apoptosis inducing ligand (TRAIL). These ligands induce apoptosis via TRAIL, a selective death receptor pathway in a broad range of cancer cell lines while sparing most normal cell types.[21]

The therapeutic potential for TRAIL inducing ligands is most promising in combination with cytotoxic chemotherapy agents. Advances in cancer therapy are likely to come in the arena of targeted therapies, the majority of which trigger specific receptor-driven pathways that culminate in apoptosis. The centrality of apoptosis induction in cancer cannot be overstated.

Apoptosis in Autoimmune Diseases

In cancer, it is the tumor cells that forget to die; in autoimmunity, immune cells fail to die when they are supposed to. Virtually all tissues harbor apoptotic cells at one time or another. Damaged cells usually commit suicide for the greater good of the body; when this does not occur, disease may develop. Autoimmunity occurs when the antigen receptors on immune cells recognize specific antigens on healthy cells and cause the cells bearing those particular substances to die. Autoimmune disease results from perpetuated immune-mediated tissue destruction, and can involve immune cells that are resistant to apoptosis. Under normal conditions, the body allows a certain number of self-reactive lymphocytes to circulate. These cells normally do little harm, but they can become overactive through several processes. For instance, if these reactive lymphocytes recognize some foreign antigen such as microbes on food and haptenic chemicals, then exposure to that antigen causes them to become excited. If, due to molecular mimicry, these antigens are similar to normal tissues, the activated cells may expand their numbers and attack the healthy tissue, thus causing an autoimmune disease.[1,22,23]

Autoimmune reactions usually are self-limited—they disappear when the antigens that originally set them off are cleared away. In some instances, however, the autoreactive lymphocytes survive longer than they should and continue to induce apoptosis in normal cells. Some evidence in animals and humans has indicated that extended survival of autoreactive cells is implicated in at least two chronic autoimmune syndromes—systemic lupus erythematosus and rheumatoid arthritis. In other words, the lymphocytes undergo too little apoptosis, with the result that normal cells undergo too much.[24,25]

Apoptosis During Viral Infection

Disturbance in the regulation of apoptosis is a component in various diseases. Viral illnesses are among the diseases caused by apoptosis dysregulation. After entering a cell, viruses attempt to shut down the cell's ability to make any proteins except those needed to produce more virus. This act of stalling host protein synthesis is enough to induce many kinds of cells to undergo apoptosis. If the host cell dies, the virus is also eliminated. Therefore, certain viruses have evolved ways to inhibit apoptosis in the cells they infect.

Epstein-Barr virus, which causes mononucleosis and has been linked to lymphomas in humans, uses a mechanism that has been seen in other viruses. Epstein-Barr virus produces substances that inhibit apoptosis. Papillomavirus, a major cause of cervical cancer, inactivates p53, a central mediator of apoptosis. Cowpox virus, a relative of which is used as the smallpox vaccine, is another virus that inhibits caspase activation and attendant apoptosis. Investigators interested in antiviral therapy are now exploring ways to block the activity of the antiapoptotic molecules manufactured by viruses.[24]

Apoptosis in Acquired Immunodeficiency Syndrome

Induction of apoptosis by viruses in healthy cells is believed to contribute to the immune deficiency found in patients with acquired immunodeficiency syndrome (AIDS). In these patients, infection with human immunodeficiency virus (HIV) causes T-helper cells to die. As T-helper cells gradually disappear, cytotoxic cells, such as natural killer cells, perish as well through apoptosis, because they cannot survive without the growth signals produced by T-helper cells. When the number of T cells dwindles, so does the body's ability to fight infections, especially viral and parasitic infections. Researchers have shown that many more helper cells succumb in addition to those that are infected with HIV. It is also highly probable that a large number of the cells die through apoptosis. Apparently, Fas plays a crucial role in this process.

Normally, T cells make functional Fas only after they have been active for a few days and are ready to die. However, helper cells from AIDS patients may display high amounts of functional Fas even before the cells have encountered an antigen. This display of Fas would be expected to cause the cells to undergo apoptosis prematurely whenever they encounter Fas ligand on other cells (such as on T cells already activated against HIV or other microbes). In addition, if the primed cells encounter the antigen recognized by their receptors, they may trigger their own death.

It is also possible that oxygen-free radicals trigger the suicide of virus-free T cells. These highly reactive substances are produced by inflammatory cells drawn to infected lymph nodes in HIV patients. Free radicals can damage DNA and membranes in cells. They will cause necrosis if they do extensive damage, but they can induce apoptosis if the damage is more subtle. In support of the free-radical theory, researchers have found that molecules capable of neutralizing free radicals prevent apoptosis in T cells obtained from AIDS patients.[24,25]

Therapies with antiapoptotic medication, such as Trolox, a water-soluble analog of vitamin E that prevents oxidative stress, and pyrrolidine dithiocarbamate, a potent inhibitor of nuclear factor-κB, are now the focus of AIDS and autoimmune disease studies.[26,27]

Additionally, protease inhibitors, which are the mainstay of HIV therapy, inhibit apoptosis in immune cells.[28]

The mechanism underlying the apoptosis inhibition is as of yet unknown, but interestingly, supratherapeutic doses of protease inhibitors have an opposite, pro-apoptotic, effect.

Apoptosis in the Heart and Brain

In contrast to cancer, where cells forget to die and insufficient apoptosis occurs, excessive apoptosis accounts for much of the cell death that follows heart attacks and strokes. In the heart, vessel blockage decimates cells that were fully dependent on the vessel. Those cells die by necrosis, partly because they are catastrophically starved of the oxygen and glucose they need to maintain themselves and partly because calcium ions, which are normally pumped out of the cell, rise to toxic levels.

Over the course of a few days, cells surrounding the dead zone, which initially survive because they continue to receive nourishment from other blood vessels, can die as well. Later, however, many cells die by necrosis after being overwhelmed by the destructive free radicals that are released when inflammatory cells swarm into the dead zone to remove necrotic tissue. The less injured cells commit suicide by apoptosis.

If the patient is treated by restoring blood flow, still more cells may die by necrosis or apoptosis because reperfusion leads to a transient increase in the production of free radicals. Similarly, in strokes due to inflammation, release of such neurotransmitters as glutamate lead to necrosis and apoptosis. Understanding of the factors that lead to the tissue death accompanying heart attack, stroke, and reperfusion has led to new ideas for treatment. Notably, cell death might be limited by drugs and other agents that block free-radical production or inhibit proteases.

Apoptosis also accounts for much of the pathology seen in such diseases as Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis (Lou Gehrig's disease), which are marked by the loss of brain neurons. Elevated apoptosis in these neurologic diseases seems to be related to lack of production of the nerve growth factor and to free radical damage. It seems likely that a combination of such factors could cause many cells to destroy themselves. Manipulation of this process of cell killing may help in treating these neurologic diseases. Studies in animal models imply that long-term delivery of nerve growth factors could protect against programmed cell death in these conditions. Therefore, a greater understanding of the mechanisms involved in cell death should greatly enhance those important steps.[22,26,29]

CONCLUSIONS

Apoptosis and cell proliferation play an important role in development, differentiation, homeostasis, and aging.[2–6] The balance established between these two processes depends on various growth and death signals that are influenced by diet, nutrition, lifestyle, and other environmental factors. When the equilibrium between life and death is disrupted by aberrant signals (e.g., low levels of antioxidants in the blood or tissue cells), either tissue growth or atrophy occurs.

Under normal conditions with optimal nutritional factors, tissue homeostasis is sustained by balancing the effects of mitosis and apoptosis. The importance of this balance can clearly be seen when one of these processes becomes predominant (Figure 9-5). The apoptotic potential within each cell is critical for the health of the host. Apoptosis is an elegant response to overwhelming DNA damaging stress. This seemingly heroic sacrifice of self for the greater good underpins healthy living. Imbalance of apoptosis regulators, genetic mutations, and viral infections thwarts the healing impact of apoptosis. Finding ways to restore apoptotic balance is critical to health.

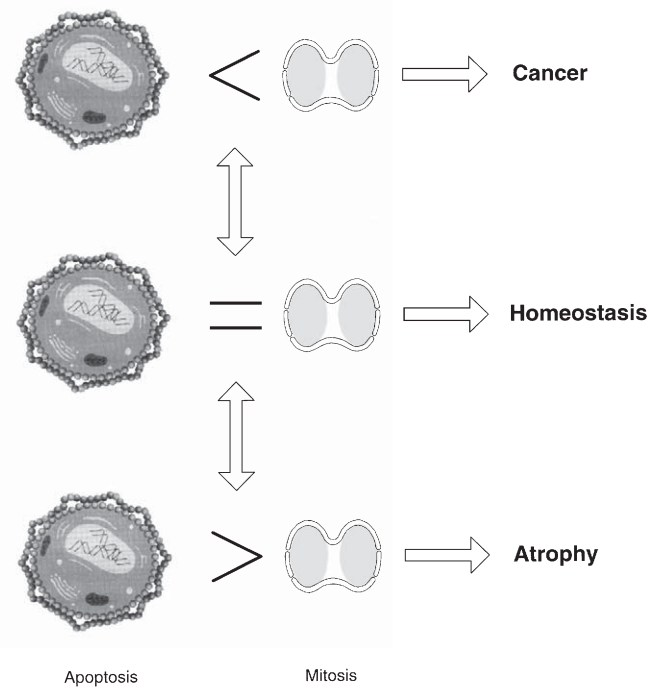


FIGURE 9-5 Balance or imbalance between the rate of apoptosis and mitosis determines tissue homeostasis, atrophy, cell proliferation, and development of cancer.

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CHAPTER 10

Bacterial Overgrowth of the Small Intestine Breath Test

Mary James, ND

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INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) is an abnormal colonization within the small bowel by bacteria normally found in the colon, mouth, or pharynx.[1] Also called bacterial overgrowth of the small intestine (BOSI), "blind-loop," or "stagnant loop,"[2] SIBO is a potentially serious disorder that leads to problems such as malabsorption, anemia and weight loss, malnutrition,[3] increased intestinal permeability, and bone loss.[4] Breath testing for hydrogen (H_2) and methane (CH_4) provides a simple noninvasive means of detecting SIBO. Once SIBO has been identified, antimicrobials are typically administered to eradicate the bacteria. Subsequent attention to underlying causes is also essential in preventing recurrence.

Frequency of Small Intestinal Bacterial Overgrowth

Bacterial overgrowth of the small intestine is an overlooked contributing factor in several common disorders.[5] Several studies, for example, demonstrated the presence of SIBO in patients with irritable bowel syndrome (IBS).[6] In one such study, in which 84% of IBS patients tested positive for SIBO (vs 20% of healthy controls), successful eradication of SIBO led to a 75% improvement (compared with a 36.7% improvement in those with incomplete eradication, and an 11% improvement in participants receiving placebo).[7] SIBO has also been observed in patients with chronic fatigue syndrome[8] and/or fibromyalgia.[9] SIBO tends to increase intestinal permeability (aka "leaky gut").[10] Investigators who found leaky gut in 37.5% of patients with fibromyalgia suggested exposure of immune cells to luminal antigens and consequent immune modulation as a likely mechanism for the pain syndrome.[11] A variety of anatomic and motor disorders of the small bowel can lead to SIBO, including surgical loops, diverticula, strictures, adhesions, tumors, fistulas,[2] scleroderma,[12] intestinal pseudoobstruction,[13] and diabetic enteropathy.[14] Jejunal diverticulosis[5] and Crohn's disease[15] have both been associated with SIBO, particularly in patients with previous intestinal surgery. Although the concentration of bacteria normally increases exponentially toward the distal end of the small intestine,[2] far fewer bacteria inhabit the small intestine than the colon.[16] A common feature of most of these disorders is stasis of small bowel contents, which allows bacterial concentrations to increasingly resemble those of the large intestine (Box 10-1).[16,17] Although many of the bacteria found in SIBO are beneficial within the colon, these same microorganisms can have deleterious effects within the delicate environment of the small intestine.

Interestingly, many patients with celiac disease whose symptoms persist despite a gluten-free diet have been shown to have SIBO, with improvement only after bacterial eradication.[18] The incidence of SIBO also increases with age.[19] It has been found that 64% of individuals more than 75 years of age with chronic diarrhea have colonic-type flora in their small bowels[5] and that SIBO is the most common cause of clinically significant malabsorption in elderly persons.[2]

Pathophysiology

Two major factors control the numbers and types of bacteria within the small bowel: intestinal peristalsis and gastric acid secretion.[2,16] Accordingly, SIBO has been associated with both intestinal stasis and hypochlorhydria.[17] Other factors that influence SIBO include pancreatic enzyme secretion,[20] disaccharidase production by

BOX 10-1 Causes of Small Intestinal Bacterial Overgrowth

- Achlorhydria, hypochlorhydria, drug-induced hypoacidity
- Chronic constipation
- Stasis resulting from structural changes (e.g., diverticulosis, blind loops, radiation damage, stricture, fistulas, intestinal pseudoobstruction, adhesions resulting from prior surgery)
- Chronic pancreatic insufficiency
- Disaccharidase deficiencies (lactase)
- Damaged ileocecal valve
- Immunodeficiency (especially of secretory immunoglobulin A)
- Diabetes mellitus
- Scleroderma
- Crohn's disease

BOX 10-2 When to Consider Breath Testing for Small Intestinal Bacterial Overgrowth

- Gas, bloating, or diarrhea, usually after eating
- Unexplained weight loss
- Evidence of malabsorption
- Chronic hypochlorhydria or achlorhydria
- Use of acid-blocking medications
- Prior intestinal surgery, chronic constipation, or other causes of intestinal stasis
- Intolerance of disaccharides (lactose)
- Unexplained vitamin B_{12} deficiency, weight loss, or bone loss
- Unexplained nutrient insufficiencies (e.g., calcium, magnesium, fat-soluble vitamins)
- Elevations of fecal short chain fatty acids
- Unexplained "leaky gut"

BOX 10-3 Signs and Symptoms of Bacterial Overgrowth

- Gas, bloating, and flatulence
- Diarrhea
- Abdominal cramping
- Steatorrhea
- Lactose intolerance
- Megaloblastic anemia

microvilli,[21] ileocecal valve function,[22] bile salts, luminal pH, and oxidation-reduction potential.[16]

For SIBO to produce clinical consequences, an adequate concentration of organisms with particular metabolic properties within specific locations of the small intestine is required. For example, a heavy concentration of strict anaerobes and coliforms in the proximal small intestine is more likely to be associated with malabsorption than a flora consisting of fewer strict anaerobes or coliforms or when strict anaerobes or coliforms are located in the distal small intestine.[16] For this reason, SIBO may be asymptomatic in some individuals yet produce signs and symptoms in others. Box 10-2 outlines clinical signs and symptoms that alert the practitioner to consider testing for SIBO.

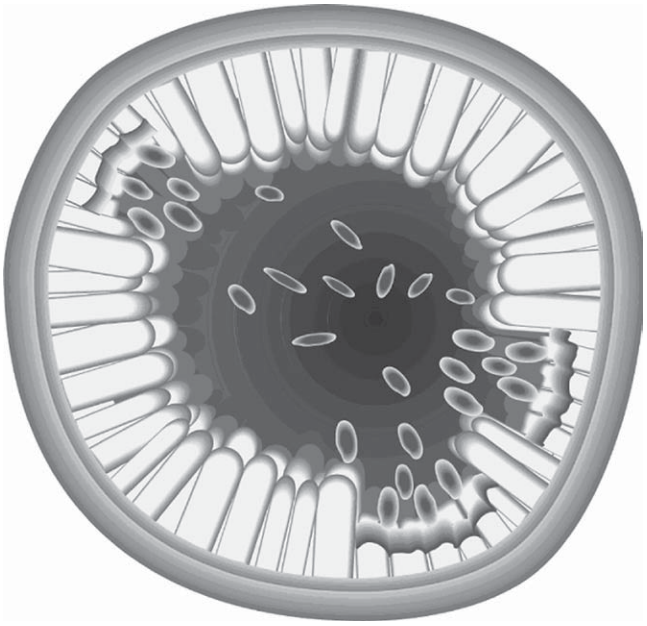


FIGURE 10-1 In small intestinal bacterial overgrowth, free bile acids can damage the brush border, resulting in reduced enzyme activity and maldigestion. (Courtesy Genova Diagnostics, Asheville, NC.)

Diagnosis

Signs and Symptoms

The classic SIBO syndrome is characterized by megaloblastic anemia resulting from vitamin B_{12} deficiency and weight loss and diarrhea secondary to fat malabsorption.[16] However, many patients present with nonspecific symptoms 1 to 2 hours after a meal, including bloating, flatulence, and abdominal pain resulting from bacterial fermentation of intraluminal sugars and associated gas production (Box 10-3).[8,18]

Via secretory and osmotic processes, diarrhea may occur even in the absence of significant steatorrhea. Unabsorbed fats and bile salts are modified by bacteria in the colon to hydroxylated fats and free bile acids, respectively, which stimulate colonic secretion of water and electrolytes.[16]

Bile salts, essential to fat emulsification and assimilation, must be conjugated with taurine or glycine to function properly. In SIBO, bacteria in the proximal small intestine deconjugate bile salts to form free bile acids.[16] This can have two major clinical repercussions: (1) free bile acids can promote mucosal damage (Figure 10-1), resulting in reduced brush-border enzyme activities (especially lactase),[23] defects in mucosal uptake of sugars and amino acids, enteric blood loss, and protein-losing enteropathy; or (2) the conjugated bile salt concentration may fall below the

concentration necessary for effective micelle formation, resulting in fat malabsorption, steatorrhea,[16,17] and deficiencies of fat-soluble vitamins.[3]

Fat malabsorption in SIBO can also result from mechanical interference, specifically formation of a pseudomembrane, thought to represent a maladaptive defense mechanism against the bacterial overgrowth.[24]

Unabsorbed fatty acids can form insoluble soaps with calcium and magnesium, rendering them unavailable.[3] Osteomalacia, night blindness, hypocalcemic tetany,[2] or metabolic bone disease[4] may develop as a consequence of lipid malabsorption in patients with SIBO. Although rare, iron deficiency anemia may result from blood loss.[3]

SIBO may also lead to vitamin B_{12} deficiency, with megaloblastic anemia and low serum cobalamin levels.[2,16] Although intrinsic factor is not altered by anaerobic bacteria, microbes are capable of detaching vitamin B_{12} from the intrinsic factor, as well as directly using B_{12}.[22] Either mechanism has the effect of making the vitamin unavailable. Paradoxically, serum folate values are usually normal or even elevated in SIBO, a result of bacterial synthesis of the vitamin.[25]

Hypoproteinemia may also occur in SIBO, secondary to protein-losing enteropathy and protein malabsorption.[3,17] In addition, bacteria may metabolize proteins to ammonia and fatty acids, thereby rendering them unavailable to the host.[23]

LABORATORY ASSESSMENT

The composition of bacterial populations contaminating the small bowel is complex and variable.[2] However, the diagnosis of SIBO tends to be oriented less to the identification of specific microorganisms and more to overall bacterial concentrations.[2]

Endoscopy

Culture of a small bowel aspirate via endoscopy is a direct method for diagnosing SIBO; abnormally high bacterial counts confirm the diagnosis.[17] This method offers good sensitivity but low specificity. Because the aspirate is typically taken from only one location, SIBO in the more distal end of the small bowel or concentrated in a large diverticulum or blind loop may be missed.[26] Intubation methods are invasive, time consuming, uncomfortable, and expensive.

Breath Testing

Breath tests were devised as less invasive alternatives to intubation and culture, offering greater patient comfort and convenience. They also offer good sensitivity[27]; a meta-analysis suggested that lactulose breath testing identifies SIBO in approximately 54% of IBS patients compared with only 4% of patients via jejunal aspirate and culture.[28]

Breath tests are based on the ability of intestinal microbes to ferment carbohydrates, producing H_2 or CH_4 in the process. A fraction of these gases naturally diffuse from the bowel to the circulation and are excreted with expired air. Because there is no other metabolic source of H_2 and CH_4, pulmonary excretion of these gases is used as a measure of bacterial fermentation during the passage through the bowel.[29]

A lactulose breath test is commonly employed to diagnose SIBO. Typically, patients ingest a challenge dose of lactulose (a synthetic, nonabsorbed disaccharide) after two days of fiber restriction and a 12-hour fast.[30] Glucose has also been used as a challenge agent, although its rapid absorption reduces the test's sensitivity in the distal ileum[27] and the agent is not suitable for patients with blood sugar disorders such as diabetes. In all cases, intestinal bacteria modify the challenge substance, producing an early peak in breath gas values in patients with SIBO. In the case of lactulose, which offers the advantage of traveling the full length of the small intestine, the early H_2 and CH_4 peak is typically followed by a prolonged peak representing colonic bacterial activity (approximately 90 minutes into the collection process).[27,31]

In the lactulose breath test, breath specimens are collected by exhaling into a special mouthpiece connected to a vacuum-sealed collection tube. A fasting (prechallenge) breath sample is collected, 10 g of lactulose are ingested, and then five more breath specimens are collected at timed intervals over a 2-hour period. Breath levels of H_2 and CH_4 are plotted over time; earlier rises in breath gas values correlate with more proximal portions of the small intestine.

Hydrogen Versus Methane

Many studies using carbohydrate challenges have measured only breath H_2. However, 30% to 50% of H_2 producers also produce CH_4,[32] most likely a result of "methanogenic" bacteria, which consume H_2, producing CH_4 in the process.[30] Individuals whose intestines harbor methanogenic bacteria typically produce greater amounts of breath CH_4 during the test, thus being potentially missed on a test examining only H_2.[33]

Clinical correlations have been noted between various disorders and the production of H_2 versus CH_4. In one study, individuals producing higher amounts of H_2 relative to CH_4 reported significantly increased bloating and cramping after carbohydrate ingestion, whereas individuals producing high CH_4 reported no significant increase in these symptoms.[34] Specific IBS symptoms also vary with breath gas values. For example, CH_4 production has been associated with constipation-predominant IBS, whereas H_2 production has been associated with diarrhea.[35] SIBO, in general, appears to be more common in diarrhea-predominant IBS than in constipation-predominant IBS.[28]

Interpretation

Lactulose is normally not fermented until it reaches the colon. As a result, the typical fasting breath sample contains less than 20 ppm of H_2 or CH_4. An increase in breath gas levels in the later breath specimens (90 and 120 minutes) usually reflects colonic bacterial fermentation and is considered normal. Lack of the expected colonic peak can result from antibiotics or an acidic colonic pH.[36,37] In patients with SIBO, the lactulose is fermented in the small intestine, resulting in an early peak in breath gas values.[27]

A positive test result (indicating SIBO) is defined by either (1) the presence of a total H_2 and CH_4 gas peak more than 15 ppm above baseline levels, occurring less than 90 minutes after lactulose ingestion, or (2) an elevated baseline (fasting) breath gas concentration, even if there is no large increase from baseline over the next few samples.[38] Elevated baseline values occur in up to one-third of patients with SIBO[36] and are thought to relate to the fermentation of endogenous brush-border glycoproteins.[39]

False-Positive and False-Negative Results

Various factors may interfere with the breath test, resulting in false-negative or false-positive results. Detailed instructions for breath collection help to minimize this interference.

False-Positive Results. The following factors may account for a false-positive result on a breath test:

- Failure to fast for at least 12 hours before the test or to avoid dietary fiber the day before collection can result in excessive "background noise" that contributes to the overall concentration of breath gases.[29]

- Sleeping, smoking, or eating shortly before or during sample collection can increase concentrations of breath gases.[40]
- Fermentation by oropharyngeal flora can lead to early, transient elevations in breath gases after carbohydrate ingestion.[41] As a result, teeth and tongue brushing before specimen collection is recommended.

False-Negative Results. False-positive results on a breath test can be caused by the following factors:

- Diarrhea or the recent administration of antimicrobials can temporarily reduce the concentration of gut bacteria,[42] thus obscuring SIBO. Laxatives and enemas pose a similar risk.[43] Patients are advised to wait at least 1 week after antibiotic therapy before performing the test.
- SIBO confined to the distal ileum may go undetected if the breath gas peak produced in the ileum merges with the breath gases produced by the colonic flora.[27]
- Rapid intestinal transit may cause delayed increases in breath gases, leading to a rise only after the lactulose has already reached the cecum.[44] This is particularly relevant for patients with SIBO who have undergone small bowel resection.

TREATMENT OF BACTERIAL OVERGROWTH

Bacterial Eradication

Unfortunately, addressing only the contributing factors to SIBO usually fails to reverse it; therefore, the primary treatment of SIBO is directed at altering the intestinal flora with antimicrobials.[17] Conversely, investigation and treatment of the root cause is necessary to prevent chronic recurrence of SIBO.

Most patients with clinically significant SIBO host an intestinal flora consisting largely of anaerobes; however, some patients harbor a predominance of gram-negative aerobes, such as *Escherichia coli*, *Klebsiella*, and *Pseudomonas*.[45] As a result, the most effective antimicrobial agent is one targeting both aerobic and anaerobic microorganisms.[2]

Antibiotics

The first-line antibiotic for SIBO has been tetracycline (250 mg four times daily for 7 days).[2] However, the high prevalence of bacterial resistance to this drug (up to 60% of patients with SIBO)[2] has led to the use of alternative antibiotics. Common alternatives include the quinolones, amoxicillin with clavulanic acid (Augmentin), clindamycin, and metronidazole.[46,47] Although included in some of these lists, antibiotics with poor activity against anaerobes might best be avoided in the treatment of SIBO (e.g., penicillin, ampicillin, and the oral aminoglycosides kanamycin and neomycin).[2]

The minimally absorbed antibiotic, rifaximin, is particularly effective while also minimizing the risk of side effects. In one study, a 7-day course of rifaximin (Xifarxan) at 400 mg three times daily normalized breath hydrogen excretion in 70% of patients with SIBO, whereas tetracycline normalized H_2 excretion in only 27% of patients.[48] More recent studies of rifaximin utilized 550 mg twice daily for 14 days and demonstrated equivalent resolution of SIBO, as well as elimination of IBS symptoms.[49]

A poor response to antibiotics may indicate mucosal disease, antibiotic resistance, antibiotic-associated diarrhea, or an incorrect diagnosis.[22,50] Recurrence of symptoms after treatment suggests the need for follow-up testing and possible re-treatment. Older age, history of appendectomy, and chronic use of proton pump inhibitors increase the likelihood of recurrence.[51] Because prolonged antibiotic therapy significantly raises the risk of diarrhea, *Clostridium difficile* infection, and bacterial resistance,[2] the administration of probiotics is advised to minimize such side effects.[21]

Antibiotic Alternatives

Peppermint oil, which has been used successfully in patients with IBS, is a volatile oil with antimicrobial properties.[52] Enteric-coated peppermint oil (dose of 0.2 mL three times a day) dramatically reduced gastrointestinal symptoms in a patient with SIBO.[53] Follow-up breath testing suggested some persistent bacterial overgrowth; the addition of an established antimicrobial agent such as berberine might help improve the results.[54] Further research on the use of botanical agents in SIBO is clearly needed.

A small double-blind study examined the effect of oral probiotics (combined *Lactobacillus acidophilus* and *L. casei* strains) on SIBO. A significant decrease in breath H_2 concentration was noted as early as 1 week into treatment, providing evidence that *Lactobacillus* strains might be useful in SIBO.[55]

Addressing the Underlying Cause

Bacterial overgrowth of the small intestine may easily recur if root causes are not addressed.

Restoration of Gastric Acidity

Because gastric acidity is a critical deterrent to SIBO, restoration of normal stomach pH in patients with hypochlorhydria or achlorhydria is essential. This may include the use of betaine hydrochloride with meals or the discontinuation of antacid medications. SIBO has been found in both healthy subjects and patients with an ulcer after even short-term (5-week) administration of omeprazole.[56] Alterations in gastric pH affect digestive capacity, leading to incompletely digested proteins providing substrate for bacteria in the terminal ileum.

Normalization of Intestinal Motility

As mentioned, intestinal stasis is another major contributing factor to SIBO. When not resulting from anatomic or organic causes, reduced motility may be improved with measures such as increased dietary fiber, water, probiotics, stress management, and exercise. Surgical correction of anatomic causes of intestinal stasis, such as small bowel diverticula, may be warranted.[57]

Supportive Measures

SIBO patients may become lactose intolerant as a result of disaccharidase deficiency. This is often ameliorated with bacterial eradication[58]; however, temporary avoidance of all disaccharides can also help to "starve" the excess bacteria and allow healing of the intestinal lining.[59]

Substituting more easily absorbed medium-chain triglycerides for most dietary fat may be helpful in patients with diarrhea and steatorrhea.[2]

Probiotics and prebiotics are recommended to help restore normal balance of intestinal flora, especially in patients with a history of antibiotic use.[21,55]

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CHAPTER 11

Cell Signaling Analysis

Lise Alschuler, ND, and Aristo Vojdani, PhD, MT

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INTRODUCTION

Signaling pathways in normal cells consist of growth and controlling messages from the outer surface deep into the nucleus. In the nucleus, the cell cycle clock collects different messages, which are used to determine when the cell should divide. Cancer cells often proliferate excessively because genetic mutations cause induction of stimulatory pathways and issue too many "go ahead" signals, or the inhibitory pathways can no longer control the stimulatory pathways.[1]

Over the past 5 years, impressive evidence has been gathered with regard to the destination of stimulatory and inhibitory pathways in the cell. These pathways converge on a molecular apparatus in the cell nucleus that is often referred to as the *cell cycle clock.* The clock is the executive decision maker of the cell; apparently, it runs amok in virtually all types of human cancer. In a normal cell, the clock integrates the mixture of growth-regulating signals received by the cell and decides whether the cell should pass through its life cycle. If the answer is positive, the clock leads the process.

THE CELL CYCLE

A scheme of the classic cell cycle is shown in Figure 11-1. The cell cycle compartments are drawn such that their horizontal position reflects their respective DNA content. Cells that contain only one complement of DNA from each parent (2C) are referred to as *diploid cells.* Cells that have duplicated their genome, and thus have 4C amounts of DNA, are called *tetraploid cells.*

The cell cycle is classically divided into the following phases:

- G_0
- G_1
- S
- G_2
- M

The cell cycle phase of G_1 was historically considered to be a time when diploid (2C) cells had little observable activity. Because this time precedes DNA synthesis, the term *Gap 1 (G_1)* was coined. It is known that there is quite a bit of transcription and protein synthesis during this phase. At a certain point in the cell's life, the DNA synthetic machinery turns on. This phase of the cell's life is labeled *S* for synthesis. As the cell proceeds through this phase, its DNA content increases from 2C to 4C. At the end of S, the cell duplicates its genome and now is in the tetraploid state. After the S phase, the cell again enters a phase that was historically thought to be quiescent. Because this phase is the second gap region, it is referred to as *G_2.* In the G_2 phase, the cell produces the necessary proteins that play a major role in cytokinesis. After a highly variable amount of time, the cell enters mitosis (*M*). DNA content remains constant at 4C until the cell actually divides at the end of telophase.

The enlarged parent cell finally reaches the point where it divides in half to produce its two daughters, each of which is endowed with a complete set of chromosomes. The new daughter cells immediately enter G_1 and may go through the full cycle again. Alternatively, they may stop cycling temporarily or permanently.[2–4] Telomeres, condensed chromatin caps on the ends of chromosomes, dictate the ultimate number of cell divisions that can occur. With each cell division, the telomeres shorten, ultimately to the point that disallows further mitosis. Thus, telomeres are

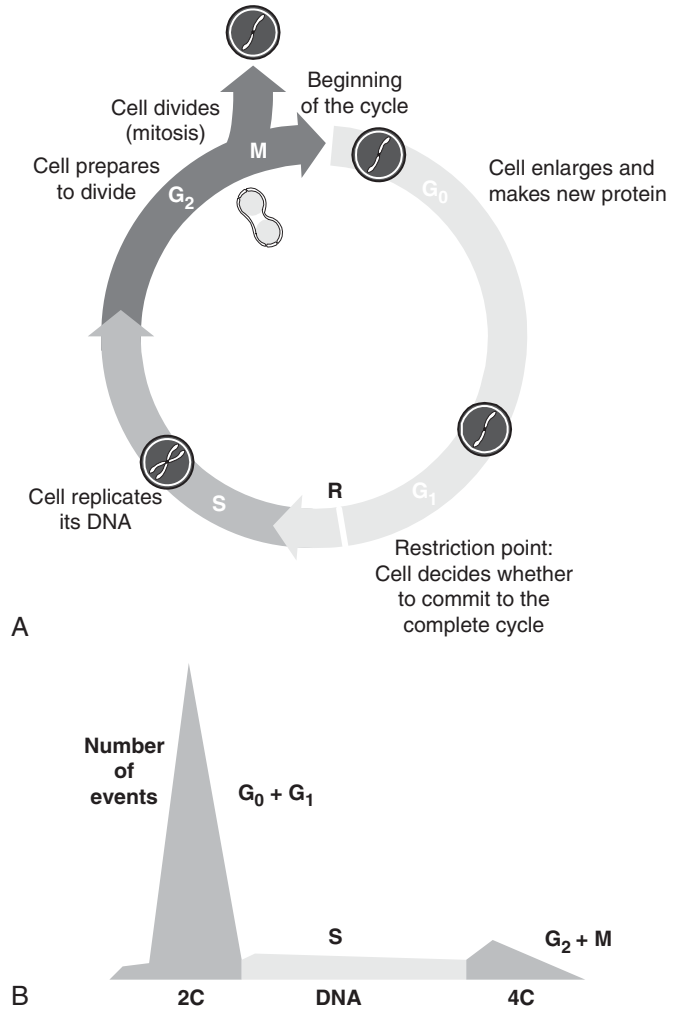


FIGURE 11-1 Stages of cell cycle (G_0, G_1, S, G_2, and M phases) (A) and DNA histogram (B) generated by flow cytometry.

considered to be the "mitotic clock." Telomere shortening is linked to aging, age-associated diseases, including cancer, coronary artery disease, and heart failure. Cell proliferation capacity, the cellular environment, and epigenetic factors affect telomere length and therefore cells' mitotic capacity.

Telomere length can be assessed and is available as a clinical test. The telomere length is reported as a telomere score, which is a calculation of the telomere length derived from nucleated white blood cells. This result is then compared with the average telomere length of similar aged sample population. This information can be utilized to prioritize interventions that increase telomere length, such as dietary, stress reduction, antioxidant, and vitamin therapies.[5]

Another influence on the cell cycle clock is circadian rhythms, or circadian clock. The circadian clock is the result of molecular clocks in each cell, circadian physiology, and ultimately, the suprachiasmatic nuclei in the hypothalamus. The circadian clock regulates the activity and expression of cell cycle check point related proteins and, in turn, these check points regulate circadian clock proteins. This has significant clinical implications, particularly in the area of cancer treatment. Both the toxicity and efficacy of cytotoxic agents can vary by more than 50% as a function of when they are dosed in experimental models.[6] The administration of cytotoxic agents in accordance with the circadian induced activity of the target cells is gaining ground as a reasonable therapeutic approach.

FLOW CYTOMETRY TO ASSESS CELL CYCLE STATUS

Flow cytometry is a method of measuring cell properties as they "flow" through a detector while being illuminated with intense light. Tissues are generally disaggregated into single-cell suspensions and stained with one or more fluorescent dyes. The cells are forced to flow within a sheath of fluid, eventually being intersected and interrogated by an intense light source, such as a laser beam. As the cell enters the laser beam, it scatters light in all directions. The measurement of light scattered in the forward direction yields information on the particle's size. Scattered light at right angles to the incident light beam provides information on the internal granularity of the cell. If the cell has been stained with one or more fluorescent dyes, a correlated measurement of more than one cellular parameter can be achieved.

CLINICAL APPLICATION

Patients Exposed to Carcinogenic Chemicals and Patients with Chronic Fatigue Syndrome

To determine whether peripheral blood lymphocytes (PBLs) isolated from individuals with chronic fatigue syndrome (CFS) and chemically exposed patients represent a discrete block in cell cycle progression, PBLs isolated from CFS and control individuals were cultured, harvested, fixed, stained with propidium iodide, and analyzed by flow cytometry. The nonapoptotic cell population in PBL isolated from CFS individuals consisted of cells arrested in the late S and G_2/M boundaries, compared with healthy controls. The arrest was characterized by increased S and G_2/M phases of the cell cycle (from 9% to 33% and from 4% to 21%, respectively) (Table 11-1 and Figure 11-2) at the expense of G_0/G_1. Such an abnormality in cell cycle progression indicates abnormal mitotic cell division in patients who have been exposed to chemicals and who have CFS. From these results, we concluded that PBLs of patients with chemical exposure and CFS grow inappropriately, not only because the signaling pathways in cells are perturbed, but also because the cell cycle clock becomes deranged and stimulatory messages become greater than the inhibitory pathways.[7,8]

However, to limit cell proliferation and avoid cancer, the human body equips cells with certain backup systems that guard against runaway division. One such backup system present in lymphocytes of CFS patients provokes the cell to undergo apoptosis. This programmed cell death occurs if some of the cell's essential components are deregulated or damaged. For example, injury to chromosomal DNA can trigger apoptosis.[1,7,8]

TABLE 11-1 **Percentage of Different Phases of Cell Cycle in Healthy Controls and Patients Exposed to Chemicals**

PHASE	HEALTHY CONTROLS	CHEMICALLY EXPOSED
G_0/G_1	88.6 ± 1.4	51.7 ± 2.4
S	8.6 ± 1.2	33.2 ± 4.3
G_2/M	3.6 ± 0.82	21.0 ± 2.6

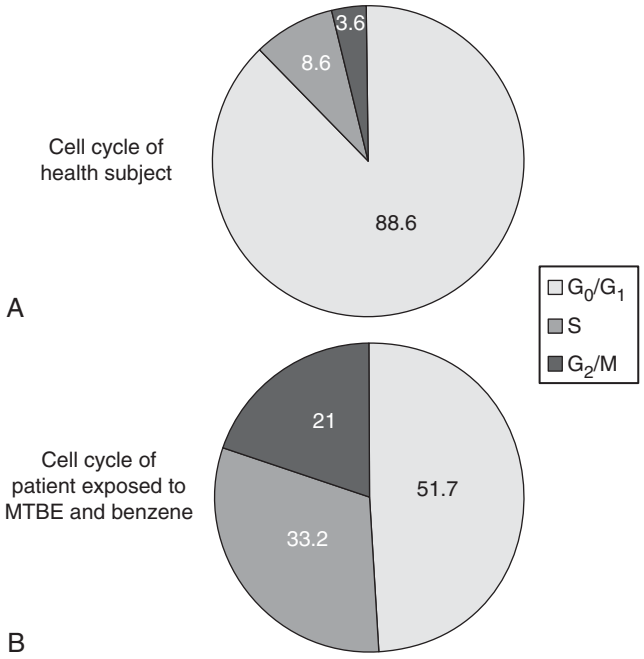


FIGURE 11-2 Cell cycle analysis of peripheral blood lymphocytes from healthy controls (A) and patients exposed to benzene (B). Note that in patients' samples, the majority of cells switched from G_0/G_1 to S and G_2/M phases.

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CHAPTER 12

Erythrocyte Sedimentation Rate

Michael T. Murray, ND

CHAPTER CONTENTS

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INTRODUCTION

The erythrocyte sedimentation rate (ESR), the rate at which erythrocytes settle out of nonclotted blood in 1 hour, has been one of the most widely performed laboratory tests in the past 65 years. Used primarily to detect occult processes and monitor inflammatory conditions, the ESR test has changed little since 1918 when Fahraeus discovered that erythrocytes of pregnant women sedimented in plasma more rapidly than they did in nonpregnant women. Since its incorporation into standard laboratory diagnosis, the ESR has been shrouded with medical myths and is often misinterpreted or misused. This chapter provides a rational guideline for its use as a nonspecific measure of inflammatory, infectious, neoplastic, and cardiovascular diseases.[1-4]

ERYTHROCYTE AGGREGATION

Normally, erythrocytes settle quite slowly as the gravitational force of the erythrocyte's mass is counteracted by the buoyant force of the erythrocyte's volume. However, when erythrocytes aggregate, they sediment relatively rapidly because the proportional increase in their total mass exceeds the proportional increase in their volume.[1-4]

Therefore, the major determinant in the sedimentation rate of erythrocytes is erythrocyte aggregation, which usually occurs along a single axis (rouleaux formation). The aggregation of erythrocytes is largely determined by electrostatic forces. Under normal circumstances, erythrocytes have a negative charge and therefore repel each other. However, many plasma proteins are positively charged and neutralize the surface charge of erythrocytes, thereby reducing repulsive forces and promoting aggregation.[1-3]

The relative contribution of the various "acute phase" reactant proteins to aggregation is shown in Table 12-1. One protein that has no direct effect on the ESR in physiologic concentrations, but which is associated with certain inflammatory, degenerative, and neoplastic diseases, is C-reactive protein (CRP). Its major function is facilitation of the complement system. Like ESR, measurement of CRP is used in the monitoring of patients with chronic inflammatory conditions.[1] An elevated CRP provides evidence of an inflammatory process despite a normal ESR. Therefore, when used in conjunction with the ESR, it greatly increases the sensitivity in detecting inflammatory and/or infectious processes, especially when variables such as anemia confound the ESR.

The ESR is also elevated in patients with proteinemias (myeloma, macroglobulinemia, cryoglobulinemia, and cold agglutinin disease).[1-4] Disorders of erythrocytes such as various anemias will alter the ESR and may interfere with accurate interpretation.[1-4] Because the ESR is directly proportional to the mass of the erythrocyte and inversely proportional to its surface area, large erythrocytes sediment more rapidly than smaller cells. Therefore, in macrocytic anemia, there is an increased ESR, and in microcytic anemia, there is a decreased ESR.

Although the usefulness of ESR determination has decreased as new methods of evaluating disease have been developed, it remains quite helpful in the diagnosis of some diseases, such as temporal arteritis and polymyalgia rheumatica. Perhaps more useful is its ability to monitor these conditions as well as others, including chronic inflammatory diseases such as rheumatoid arthritis (RA), Hodgkin's disease, and other cancers. Although the use of the ESR as a screening test to identify patients

TABLE 12-1 **Relative Contribution of Acute-Phase Reactant Proteins to Erythrocyte Aggregation**

BLOOD CONSTITUENT	RELATIVE CONTRIBUTION
Fibrinogen	10
β-Globulin	5
α-Globulin	2
Albumin	1

who have serious disease is not supported by the literature, it does provide a general gauge of inflammatory processes in the body. It is well accepted that an extreme elevation of the ESR is strongly associated with serious underlying disease, most often infection, collagen vascular disease, or metastatic malignancy. Recently, there has been a growing appreciation of the value of the ESR as a marker for atherosclerosis and coronary artery disease.[5,6] In addition, as a sign of chronic low-grade inflammation, it may be helpful as a marker for other conditions as well. For example, in a study of 49,321 Swedish males aged 18 to 20 years, screened for general health and for mental and physical capacity at compulsory conscription examination before military service, there was an inverse correlation between ESR and performance on an IQ test.[7] This result indicated that low-grade inflammation, as indicated by the ESR, was associated with reduced cognitive abilities at ages 18 to 20 years.

PROCEDURES

Various methods for determination of the ESR have been developed. Currently, the Westergren method is recommended by the International Committee for Standardization in Hematology.

Westergren Method

In the standard Westergren method, the following procedure is used:

1. Dilute venous blood 4:1 with anticoagulant sodium citrate.
2. Put in a 200-mm long, 2.5-mm internal diameter, glass tube (Westergren tube).
3. Allow to stand in a vertical position for 1 hour.
4. At the end of 1 hour, the distance from the meniscus to the top of the column of erythrocytes is recorded as the ESR.

The modified Westergren method uses ethylenediaminetetraacetic acid rather than sodium citrate as an anticoagulant and is more convenient because the same tube of blood can be used for other hematologic studies. The standard and modified methods give identical results.[1-4]

Wintrobe Method

The second most commonly used method is the Wintrobe method. This method is performed with a 100-mm tube (Wintrobe tube) containing oxalate as the anticoagulant. It is more sensitive than the Westergren method in the "normal" to "mildly elevated" range; however, in the more highly elevated ESR, the short tube leads to relatively insensitive readings due to packing of cells.[2]

Results

The results of both the Westergren and Wintrobe methods are listed in Box 12-1.

BOX 12-1 **Results of Westergren and Wintrobe Methods**

Westergren (normal results)
- Men: 0-10 mm/h
- Women: 0-15 mm/h
- Children: 0-10 mm/h

Wintrobe (normal results)
- Men: <6.5 mm/h
- Women: <16 mm/h

INTERPRETATION

Several factors may result in false-positive or false-negative ESR values; the more significant of these are listed in Box 12-2. In addition, it is important to recognize that in acute disease, the change in sedimentation rate may lag behind the temperature elevation and leukocytosis for 6 to 24 hours, and in unruptured acute appendicitis the rate may be normal. In convalescence, the increased rate tends to persist longer than the fever or leukocytosis. Box 12-3 lists the most common clinical implications of changes in the ESR. An ESR value exceeding 100 mm/h has a 90% predictive value for serious underlying disease—most often infection, collagen vascular disease, or metastatic tumor.[1]

Elevated Erythrocyte Sedimentation Rate

Asymptomatic Patients

The presence of an elevated ESR as the only manifestation of a disease process is quite rare. However, when present, it can be highly significant. For example, in one study of 17 patients whose increased ESR was the sole initial clue to disease, two had tuberculosis, one had colon cancer, one had systemic lupus erythematosus, three had ankylosing spondylitis (diagnoses that typically become apparent only after several years of observation), and four men had a persistently elevated ESR several years before a myocardial infarction. The remaining patients developed myeloma, prostate cancer, psoriasis, benign monoclonal gammopathy, and pancreatic cancer.[2]

Although the ESR generally makes a small contribution to disease detection in asymptomatic persons, the presence of an elevated ESR as the only clue to illness in an asymptomatic person indicates the need for a careful diagnostic workup; it may be the first sign of an occult malignancy or a chronic inflammatory disease. Laboratory evaluation for an asymptomatic patient with an elevated ESR should include complete blood cell count with differentials, blood urea nitrogen and creatinine, alkaline phosphatase measurement, serum protein electrophoresis, urinalysis, guaiac tests of stool, and chest radiograph.[2]

An ESR that exceeds 100 mm/h is definitely associated with infection, malignancy, or connective tissue disease. Rarely does disease remain undiagnosed when the ESR is greatly elevated.[1-4] If, after further clinical evaluation, an elevated ESR cannot be explained, the ESR should be repeated in 1 month.

As a Predictor of Coronary Artery Disease

An elevated ESR in white men aged 45 to 64 years was found to be an independent risk factor for coronary heart disease in the National Health and Nutrition Examination Survey-I.[5] The risk was highest when the ESR was greater than 22 mm/h. Subsequent studies and the growing awareness that atherosclerosis

BOX 12-2 Factors Interfering with the Erythrocyte Sedimentation Rate

False Increase
- Elevated levels of fibrinogen, globulins, and cholesterol
- High room temperature
- Macrocytic anemia
- Menstruation
- Pregnancy
- Running a refrigerated blood sample before it has returned to room temperature
- Tilted erythrocyte sedimentation rate tube
- Certain drugs: dextran, methyldopa, methysergide, oral contraceptive agents, penicillamine, procainamide, theophylline, trifluperidol, vitamin A

False Decrease
- Cachexia
- Clotting of blood sample
- Elevated bile salts
- Elevated phospholipids
- >2-h delay in running the test
- High doses of adrenal steroids
- Hypofibrinogenemia
- Hyperglycemia
- Hyperalbuminemia
- Leukocytosis
- Microcytic anemia
- Newborn
- Certain drugs: adrenocorticotropic hormone, cortisone, ethambutol, quinine, salicylates

Data from references 1 and 4.

BOX 12-3 Clinical Implications of Changes in the Erythrocyte Sedimentation Rate

Increased Rate
- Acute heavy metal poisoning
- All collagen diseases
- Carcinoma
- Cell or tissue destruction
- Gouty arthritis
- Infections
- Inflammatory diseases
- Leukemia
- Multiple myeloma
- Myocardial infarction
- Nephritis
- Pneumonia
- Rheumatoid arthritis
- Syphilis
- Toxemia

Decreased Rate
- Congestive heart failure
- Polycythemia
- Sickle cell disease

is associated with chronic inflammation has given support to the use of the ESR as a prognostic indicator for the risk of coronary artery disease.[6,8] It was hypothesized and later shown that an elevated ESR reflected an elevated blood fibrinogen level (see Chapter 148 for further discussion of fibrinogen). The association of an elevated ESR as a harbinger of coronary artery disease precedes an elevated CRP, and can be viewed as an easy-to-use and inexpensive method that indirectly indicates fibrinogen level and aids in the early detection of microinflammation and eventual atherosclerotic burden, even in apparently healthy people.[9,10]

Symptomatic Patients

The ESR is sometimes used to provide confirmation of a disease process when the history and physical findings point toward a specific diagnosis. Although the ESR itself does not diagnose a specific disease, when combined with information gathered in a history and physical, as well as in conjunction with other laboratory tests, it can be a great help in the formation of a specific diagnosis.

In patients with vague, unsubstantiated illness, the ESR offers limited benefit due to the lack of specificity and the presence of a normal ESR in a wide variety of illnesses. However, the ESR offers great diagnostic benefit when other signs, symptoms, and laboratory findings are present. This is particularly true in malignancies, temporal arteritis and polymyalgia rheumatica, inflammatory arthritis, and suspected infection.

Erythrocyte Sedimentation Rate in Cancer

Malignancy is quite common in symptomatic patients with an elevated ESR. In one study, 70 (8.8%) of 790 clinic patients with an elevated ESR had cancer.[1] However, of the 70 patients with malignancy and an increased ESR, 68 had local signs that led directly to the diagnosis. Thus occult malignancy was present in only 2 of the 790 patients. In addition, the ESR is often normal in patients with cancer, indicating that the ESR should not be relied on as a test to exclude occult malignancy in patients with vague symptoms.

In a prospective follow-up of 300 patients with prostate cancer, an ESR greater than 37 mm/h was associated with a higher incidence of disease progression and death. These findings paralleled other prognostic indicators such as tumor, node, and metastasis staging, grade, performance status, and age, but also indicated that ESR provided additional value in the monitoring of these patients, and presumably others with invasive cancer.[3]

Temporal Arteritis and Polymyalgia Rheumatica

Temporal arteritis and polymyalgia rheumatica are related syndromes that can occur together or alone. Both occur in older individuals and are associated with an increased ESR. Symptoms of temporal arteritis include unilateral throbbing headache, scalp sensitivity, visual symptoms, jaw claudication, and localized thickening or loss of pulsation of the temporal artery. Polymyalgia rheumatica is a fast-developing condition characterized by pain and stiffness of the pelvis and/or shoulder girdle, in association with fever, anemia, malaise, and weight loss. It is typically self-limited to 1 to 2 years.

Determination of the ESR is of critical importance in the diagnosis and management of patients with temporal arteritis, a condition that can result in blindness due to obstruction of the ophthalmic arteries. When the clinical evidence for temporal arteritis is limited, a normal ESR reduces the probability of the disease to less than 1%. When the clinical evidence is strong, it is extremely rare to have a normal ESR. Achievement of a normal ESR by using anti-inflammatory agents, such as cortisone or the natural medicines (e.g., Curcuma longa, Fish oils, Ginkgo biloba), greatly reduces the risk of developing blindness.[1,2]

Inflammatory Arthritis

The ESR is sometimes used to distinguish inflammatory arthritis from other causes of joint symptoms. This is particularly true in the differentiation of RA, which has an elevated ESR, and osteoarthritis, which typically has a normal ESR. Because ESR is not a specific indicator of RA, it is not appropriate to place much value on it as an independent diagnostic predictor of RA. An elevated ESR in patients with joint symptoms simply indicates an active inflammatory process.[1,2]

Suspected Infection

Leukocytosis and fever are better indicators than the ESR of an acute infectious process, since the ESR is typically normal during the first stages of infection. However, the ESR is of some value in the differentiation of an intact versus ruptured appendix. Researchers demonstrated that only 2 of 25 patients with nonruptured appendicitis had an ESR of greater than 20 mm/h. In contrast, 67% of patients with ruptured appendixes had an elevated ESR.[1] CRP, however, has emerged as a more accurate measure. The value of CRP for surgical indication of appendicitis is 4.95 mg/dL.[11] CRP has also been shown to correlate better with joint sepsis than ESR.[11]

Decreased Erythrocyte Sedimentation Rate

The causes of a low ESR (0 to 1 mm/h) are listed in Boxes 12-2 and 12-3. A low ESR is generally of little significance and may actually indicate a healthy state.[1-4]

Monitoring of Disease Activity

The ESR is well recognized as an aid in monitoring the activity of such inflammatory diseases as temporal arteritis, polymyalgia rheumatica, and RA.[1-3] In general, improvements in ESR levels generally reflect clinical improvement and vice versa.

Temporal Arteritis and Polymyalgia Rheumatica

The ESR is the most widely used test for assessing disease activity in patients with temporal arteritis and polymyalgia rheumatica because these conditions have few specific clinical indicators of disease activity. However, both the ESR and clinical status need to be monitored in these patients and appropriate therapy instituted if the ESR increases or if there is a worsening in the clinical picture.[1,2,12]

Rheumatoid Arthritis

Although 5% to 10% of patients with RA have a normal ESR; the ESR generally parallels disease activity. Therefore, monitoring the patient's ESR provides invaluable feedback on therapeutic effect. An isolated elevated ESR is not useful for prognosis, but sustained extreme elevation of the ESR is associated with a poor prognosis.[1-3] It is important to note that in a meta-analysis of 63 clinical trials or observational studies of RA treatment, the authors concluded that ESR was more sensitive to change than CRP and was the preferred measure of the acute phase response in RA in clinical practice.[13]

Other Inflammatory Diseases

Other inflammatory diseases, particularly autoimmune diseases such as systemic lupus erythematosus, can be monitored by the ESR in a fashion similar to that for RA.[1-3]



SUMMARY

The ESR is a simple, valuable, and useful laboratory procedure. Although it is a nonspecific indicator of inflammation, an elevated ESR (i.e., greater than 80 mm/h) indicates the presence of significant disease in more than 95% of individuals. The ESR should never be used as the sole diagnostic test. Clinical presentation, comprehensive history, laboratory investigation, and other diagnostic procedures should always be considered when interpreting ESR results. The ESR may be used as a nonspecific gauge of therapeutic efficacy and as a monitoring tool in several inflammatory conditions, including temporal arteritis, polymyalgia rheumatica, RA, certain malignancies, and atherosclerosis.

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CHAPTER 13

Fantus Test

Dirk Powell, BS, ND

CHAPTER CONTENTS

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INTRODUCTION

The Fantus test is a simple test for measuring urinary chlorides. It is used to estimate dietary sodium chloride intake. For this purpose, it has been shown to give clinically useful results if two factors are taken into consideration[1–3]:

- Concentration of urinary chloride is proportional to urinary sodium except with increased ingestion of nonsodium chloride salts (e.g., ammonium chloride or potassium chloride).
- Urinary output of sodium chloride may not be a reliable indicator of sodium intake when an individual has a salt-wasting disorder (Box 13-1).

CLINICAL APPLICATION

The Fantus test was first described by J.B. Fantus in 1936.[4] It was originally used for the diagnosis of salt and water depletion and for the differential diagnosis of edema.[5] However, this test has been found to be particularly useful for monitoring sodium intake in individuals with blood pressure disorders, including both hypotension and hypertension.

Since 1904 when Ambard and Beaujard[6] first implicated salt as a major factor in the pathogenesis of hypertension, conflicting opinions and data have confused this issue. In 1944, Kempner[7] published a classic article describing the effective treatment of essential hypertension using a salt-restricted "Rice Diet." Many studies have subsequently demonstrated the effectiveness of salt-restricted diets in treating hypertension.[8–12] Substantial evidence now exists that sodium alone does not raise blood pressure as had been previously thought, but rather that chloride also plays an important role in the elevation of blood pressure when consumed as sodium chloride, or common table salt.[13,14] Sodium bicarbonate has not been found to have the same hypertensive effect as sodium chloride.

The Fantus test is an indirect test for sodium and actually measures chloride ion concentration. Considering that sodium chloride intake, rather than sodium ion alone, is a significant factor in blood volume expansion and blood pressure elevation, the Fantus test may be more clinically useful than direct tests for urinary sodium when managing hypertension or fluid retention.[13,14]

The clinical utility of limiting salt is obvious; however, when managing hypertension with salt restriction, two difficulties arise.[15] First, effective salt restriction is difficult to maintain because of the prevalence of highly salted foods, particularly in convenience and prepared foods.

Secondly, salt must be restricted to quite low levels to be effective in the treatment of hypertension. Sodium chloride, measured in terms of sodium, must be restricted to approximately 3 g/day, compared with the 12 to 27 g of sodium per day commonly consumed in the typical Western diet.

Because the Fantus test is an inexpensive, simple in-office test, it can be effectively used to monitor salt intake where frequent sampling is useful in the management of salt-restricted diets. Salt restriction may be therapeutic in several disorders, including hypertension, congestive heart failure, premenstrual syndrome, edema, and chronic kidney disorders.

The Fantus test is also useful in monitoring salt intake in clinical conditions where restricted sodium chloride intake can be an aggravating factor, such as in Addison's disease, postural hypotension, chronic fatigue syndrome, and sodium depletion (see Box 13-1). Another use of the Fantus test is in the identification

BOX 13-1 Sodium-Wasting Conditions in Which Salt Restriction Can Be Deleterious

- Adrenocortical insufficiency
- Addison's syndrome
- Salt-wasting renal disease
- Increased sweat loss of electrolytes
- Strenuous physical exercise
- Unusual fluid losses from the gastrointestinal tract
- Chronic fatigue syndrome

of people who are ingesting excessive amounts of salt. These individuals may be without overt symptoms or signs of disease. It has been observed in animal studies that a high intake of sodium chloride decreases longevity as a factor separate from blood pressure.[16] In another study, salt-induced angiotensin elevation was found to adversely affect the myocardium in humans, even when blood pressure remained within normal limits.[17] It has been observed that the adverse effects of excess salt can persist for an extended time after excess salt ingestion has been discontinued.[18,19]

Identifying people at risk for harmful effects from excessive salt consumption is an important aspect of preventive medicine. People with risk factors for hypertension can prudently restrict salt intake. Included in this group of people at risk are individuals with chronic renal disease, those with a family history of hypertension, and individuals over the age of 50.[20]



PROCEDURE

The Fantus reagent is prepared so that the number of drops of silver nitrate ($AgNO_3$) used in the titration step can be recorded as grams of sodium per liter of urine (g Na/L urine).

Method

1. Collect a 24-hour urine sample.
2. Measure and record the 24-hour volume.
3. In a test tube add one drop of 20% potassium chromate (K_2CrO_4) solution to 10 drops of the sample of the 24-hour urine specimen.
4. Titrate (add one drop at a time) with the 2.9% silver nitrate ($AgNO_3$) solution.
5. Record the number of drops needed to turn the color from yellow to brown as g sodium/L.

(If sodium chloride is present in too low of a concentration to accurately measure, you can use 20 drops of urine. Each drop of $AgNO_3$ is then equal to 0.5 g Na/L.)

Reagents

- $AgNO_3$: 2.9% aqueous solution
- K_2CrO_4: 20% aqueous solution

Results

- Typical Western diet: 12 to 27 g Na/24 h
- Salt-restricted diet: 0.6 to 3.5 g Na/24 h



INTERPRETATION

Normally, urinary sodium varies with the sodium chloride intake, reflecting the salt content of the diet. The typical Western diet contains 12 to 27 g of sodium in a 24-hour period (80 to 180 mEq/24 hr).[21] On a salt-restricted diet, the goal is usually to reduce 24-hour urine sodium to approximately 3 g Na/24 h.[20] The minimum 24-hour sodium intake considered safe is 0.6 g Na/24 h for healthy individuals with intact adrenocortical function (see Box 13-1).

A salt intake of 3 g Na/day with an intake of 2750 mL of water from both solids and fluids corresponds to the average water turnover for a 70-kg adult. After evaporation from the lungs and other losses, the amount of water excreted by the kidneys is approximately 1500 mL/24 h.[5] This produces a urinary sodium excretion of 3 g in 24 hours and a urinary sodium concentration of 2 g/L. A 24-hour urine sample can be used to more accurately estimate 24-hour sodium intake (i.e., 24-hour urine volume x urinary sodium concentration = 24-hour sodium intake).

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CHAPTER 14

Fatty Acid Profiling

Richard S. Lord, PhD, and J. Alexander Bralley, PhD

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INTRODUCTION

The analysis of fatty acids in blood provides useful information about fatty acid deficiencies and imbalances and can also reveal a functional need for certain vitamins and minerals. Clinical interventions involve changes in food selection or supplementation with selected nut or seed extract oils and required micronutrients. Laboratory reports of fatty acid profiles typically list the fatty acids by structural type in the following order: ω-3–polyunsaturates, ω-6–polyunsaturates, monounsaturates, even-numbered saturates, odd-numbered saturates, and, finally, trans-monounsaturates. Several ratios may be calculated, and for plasma, the total fatty acid concentration may be calculated by summing the individual components and expressing the total in milligrams per deciliter, consistent with the units for serum triglycerides that are directly related to total fatty acid content.

METHODOLOGIC ISSUES

Plasma Versus Erythrocyte Fatty Acid Profiles

A plasma fatty acid profile is an amplification of the standard serum triglyceride analysis. In both cases, the fatty acids are present in lipoprotein particles. Instead of measuring only the total of all fatty acids present, the profile test reports the individual concentrations of each fatty acid. An individual with high serum triglycerides has higher levels of many individual fatty acids in plasma. Of course, any condition associated with elevated serum triglycerides is likewise revealed as elevated plasma fatty acids. Patterns of high or low concentrations in plasma depend on recent dietary intake, composition of adipose fat, and rates of metabolic conversion. Plasma is the preferred specimen for routine evaluation of essential fatty acid (EFA) status because interpretation is less complicated by metabolic issues that bear upon fatty acid levels found in erythrocytes.

In contrast, erythrocyte membrane fatty acid profiling is commonly used to investigate metabolic conversion problems and genetic diseases. The erythrocyte membrane is 45% fatty acids in the form of various phosphatides and glycolipids. The procedure used for profiling measures total concentrations of individual fatty acids per milliliter of packed cells. Erythrocyte levels reflect those present in most tissues. Both erythrocyte and plasma have been used to monitor brain fatty acid balance in Zellweger syndrome.[1] Both specimens have also revealed the need to supplement infant formulas with ω-3 fatty acids.[2]

The triglyceride-lowering drug gemfibrozil causes a profound suppression of erythrocyte unsaturated fatty acids, even in the presence of high concentrations of the same compounds in plasma. The effect is apparently due to stimulation of the peroxisomal β-oxidation system.[3] Because of the metabolic effect of the drug, a patient consuming a diet high in olive oil (largely oleic acid) may show low levels of oleic acid in erythrocyte membranes while maintaining high oleic acid in plasma. Thus, plasma profiles show the dietary changes, and erythrocyte fatty acids show the metabolic impact of the drug.

Concentration Versus Percentage

Before 1996, virtually all clinical laboratories reporting fatty acid levels expressed results as a percentage of total concentration. Individual concentrations could not

be reported due to the lack of pure standards necessary to build calibration curves. The reporting of "relative area" data has some utility but leaves important points obscured. The most abundant fatty acids are present at concentrations 50 times higher than those of the lesser components.[4] Percent area calculations cause the most abundant components to have a disproportionate impact on the minor components. If α-linolenic acid (ALA) is the same in two cases, for example, whereas palmitic acid is low in the first and high in the second, the percent ALA can appear high in the first and normal in the second because palmitic acid makes up so much of the total, and the ratios are calculated by dividing by the total.

With the availability of pure standards, it is now possible to measure the concentrations of each fatty acid. Because the molecular weights span a range of more than seventy-fold for these homologous compounds, molar units allow more meaningful comparisons. This unit also simplifies interpretation of plasma fatty acids, where the total of all fatty acids is directly proportional (and closely equivalent) to the values for total triglycerides from a standard serum chemistry assay. For erythrocytes, concentration is based on packed cell volume or on total lipid extract volume.



INTERPRETATION OF ABNORMAL FATTY ACID RESULTS

Table 14-1 summarizes common fatty acid abnormalities and interventions for correction using specific dietary oils. Table 90-4 in Chapter 90 lists the typical symptoms and diseases associated with various fatty acid abnormalities.

Omega-3 (n-3) Fatty Acids

Alpha Linolenic Acid (18:3ω-3)

Many edible plants produce this 18-carbon polyunsaturated fatty acid, but because of the small amounts of fresh vegetables consumed by many people, it is one of the least abundant of the EFAs in most diets. It is found in relatively high amounts in flax, hemp, canola seed, soybean, walnut oils, and in dark green leaves. It must be supplied by such foods because human tissues lack the necessary enzymes for its formation. Dietary insufficiencies of ALA and its ω-6 counterpart, γ-linolenic acid (GLA), play central roles in several diseases (see Tables 90-4 and 90-5 in Chapter 90). The wide range of symptoms and disease associations is due to their functions in processes of membrane integrity and cell activity regulation by eicosanoids (20-carbon fatty acids). Correction of low body pools of ALA requires dietary changes or the use of dietary supplements containing ALA. Table 14-2 lists food sources of ALA. The dietary origin of ALA deficiency disorders can be seen by inspecting the ALA content of corn, safflower, and peanut oils that are so predominant in modern diets.

Eicosapentaenoic Acid (20:5ω3)

Insufficiencies of eicosapentaenoic acid (EPA) are likely the most prevalent fatty acid abnormality affecting the health of individuals in Western societies. Low levels in plasma, erythrocytes or blood spot specimens are indicative of insufficiency. Arthritis, heart disease, and accelerated aging result from direct or indirect effects of inflammatory responses that may be modulated by

TABLE 14-1 **Summary of Common Abnormalities Found in Profiles of Fatty Acids in Plasma and Erythrocytes**

NAME	ABNORMALITY	METABOLIC ASSOCIATION	POTENTIAL RESPONSES*
		Omega-3 polyunsaturated	
Alpha linolenic	L	Essential fatty acid	Add flax or fish oils, or both
Eicosapentaenoic	L	Eicosanoid substrate	Add fish oils
Docosapentaenoic	L	Nerve membrane function	Add fish oils
Docosahexaenoic	L	Neurologic development	Add fish oils
		Omega-6 polyunsaturated	
Linoleic	L	Essential fatty acid	Add corn or borage oil
Gamma linolenic	L	Eicosanoid precursor	Add evening primrose oil
Eicosadienoic	H	Desaturase inhibition	Zinc
DGLA	L	Eicosanoid substrate	Add borage oil
Arachidonic	H	Eicosanoid substrate	Reduce red meats
Docosadienoic	H	Increase in adipose tissue	EFA and glycemic control
Docosatetraenoic	H	Increase in adipose tissue	EFA and glycemic control
Mead	H	EFA deficiency	Add balanced EFA
		Monounsaturated	
Vaccenic	H	Biotin deficiency	Biotin
Myristoleic	H	Membrane fluidity	Correct low EFA levels
Palmitoleic	H	Membrane fluidity	Correct low EFA levels
Oleic	H	Membrane fluidity	Correct low EFA levels
11-Eicosenoic	H	Membrane fluidity	Correct low EFA levels
Nervonic	L	Neurologic development	Add fish or canola oils
Erucic	L	Nerve membrane function	Add peanut oil
		Saturated	
Capric acid	H	Multiple acyl dehydrogenase deficiency	Add riboflavin
Lauric	H	Multiple acyl dehydrogenase deficiency	Add riboflavin
Myristic	H	Multiple acyl dehydrogenase deficiency	Add riboflavin

TABLE 14-1 Summary of Common Abnormalities Found in Profiles of Fatty Acids in Plasma and Erythrocytes—cont'd

NAME	ABNORMALITY	METABOLIC ASSOCIATION	POTENTIAL RESPONSES*
Palmitic	H	Cholesterogenic	Reduce saturated fats; add niacin
Stearic	H	Elevated triglycerides	Reduce saturated fats; add niacin
Arachidic	H	Elevation of these fatty acids occur in hypertriglyceridemia or perxisomal deficiency	
Behenic	H		
Lignoceric	H		
Hexacosanoic	H		
Odd-numbered			
Pentadecanoic	H	Elevation of these fatty acids can be due to deficiency of biotin or vitamin B12 or elevated intestinal propionate-producing bacteria	Assess need for additional biotin or vitamin B12
Heptadecanoic	H		
Nonadecanoic	H		
Heneicosanoic	H		
Tricosanoic	H		
Trans-fatty acids			
Palmitelaidic	H	Metabolic interference	Eliminate hydrogenated oils
Elaidic or total C18 trans	H		
Ratios and indexes			
LA/DGLA	H	Δ6 desaturase enzyme	Add zinc
DGLA/EPA	L	Eicosanoid imbalance	Add borage oil
AA/EPA	H	EFA deficiency	Add fish oils
Triene/Tetraene	H	Overall fatty acid status	Add fish oils
P/S ratio	H	Overall fatty acid status	Add balanced EFA
Stearic/oleic (RBC)	L	Rises as therapeutic efficacy marker for some cancers	

*Adult supplement doses usually range from 1 to 3 g/day in the form of extracted nut and seed oils that may contain 30%-60% of the fatty acid by weight. See appropriate chapters for supplementation levels for vitamins and minerals indicated.

AA, arachidonic acid; DGLA, dihomogammalinolenic acid; EPA, eicosapentaenoic acid; EFA, essential fatty acid; H, high; L, low; LA, linoleic acid; MAD, multiple acyl-coenzyme-A disorder; P/S, polyunsaturated/saturated (fatty acid ratio); RBC, red blood cell.

TABLE 14-2 **Distribution of α-Linolenic Acid (ALA) and Linoleic Acid (LA) in Foods with Predominantly 18-Carbon Fatty Acids**

	ALA	LA	
Food	**18:3n-3**	**18:2n-6**	**n-3/n-6**
Flaxseed oil	59.1	14	4.22
Flax seed	18.1	4.32	4.19
Walnuts	39	38.1	1.02
Butter	1.18	1.83	0.64
Canola oil	9.3	20.3	0.46
Salad dressing	3.3	24.6	0.13
Soybean oil	6.8	51	0.13
Soybean margarine	1.5	19.4	0.08
Palm oil	0.2	9.1	0.02
Corn oil	0.7	58	0.01
Sesame oil	0.3	41.3	0.01
Peanuts	0	15.6	0
Safflower margarine	0	44.5	0
Sunflower oil	0	65.7	0

raising EPA levels. Supplementation with EPA-rich fish oils (Table 14-3) aids in the prevention of cardiac arrhythmias.[5] Significant reduction in total cholesterol and triglyceride has been achieved with a combination of garlic concentrate (900 mg/day) and fish oil supplementation.[6] EPA is the precursor of the 3-series prostanoids and leukotrienes that moderate the proinflammatory effects of the 2-series derived from arachidonic acid (AA). Although EPA can be produced from the essential fatty acid ALA, dietary intake of this fatty acid is generally poor. The conversion also requires the action of the δ-6 desaturase enzyme, which may be low due to inadequate zinc, magnesium, or vitamins B_3, B_6, and C.[7] Such enzyme impairment would be indicated if EPA is low and ALA is normal or high. High levels of saturated, monounsaturated, and trans-fatty acids and cholesterol also slow the conversion of ALA to EPA (as well as GLA to dihomogammalinolenic acid [DGLA]). Dietary supplementation of EPA is an important part of nutritional support in patients with compromised immune responses, including postoperative and trauma.[8] Fish oil supplementation lowers triglycerides without effect on glycemic control in type 2 diabetes.[9]

Docosapentaenoic Acid (22:5ω3), Docosahexaenoic Acid (22:6ω3)

Growth and development of the central nervous system depend on the presence of an adequate amount of the long-chain, highly

TABLE 14-3 **Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) Content of Seafood**

	EPA	DHA		
Food	**20:5n-3**	**22:6n-3**	**EPA/DHA**	**Total n-3**
Salmon, Atlantic, farmed	0.62	1.29	0.48	2.01
Salmon, Atlantic, wild	0.32	1.12	0.29	1.73
Herring, Pacific	0.97	0.69	1.41	1.72
Anchovy, European	0.54	0.91	0.59	1.45
Salmon, Chinook	0.79	0.57	1.39	1.44
Bluefish	0.25	0.52	0.48	0.77
Shrimp, mixed species	0.26	0.22	1.18	0.49
Halibut	0.07	0.29	0.24	0.43
Tuna, yellow fin	0.04	0.18	0.22	0.23
Cod, Atlantic	0.06	0.12	0.53	0.19

unsaturated fatty acids docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA).[10,11] Attention deficit hyperactivity disorder and failures in development of the visual system in EFA deficiencies are two examples of this dependency.[12] DHA is an important member of the very long-chain fatty acids (C22-C26), which characteristically occur in glycosphingolipids, particularly those in the brain. The levels in breast milk are correlated with the mother's intake of fish oils, which are rich sources of DHA and DPA.[13] Plasma DHA levels should be checked as early as possible in pregnancy. The finding of low DHA in plasma or erythrocytes also justifies the use of supplemental DHA for depression.[14]

Omega-6 (n-6) Fatty Acids

Linoleic Acid (18:2ω6)

Linoleic acid (LA) is the most abundant polyunsaturated fatty acid (PUFA) in most human tissues. Low levels in plasma or erythrocytes indicate dietary insufficiency, which leads to various symptoms (see Table 90-4 in Chapter 90). Some of these symptoms result from a lack of LA in membranes, where it has a role in structural integrity. Most, however, are from failure to produce the 1-series and 3-series prostanoids. Neonatal LA status of this fatty acid can be insufficient.[15] Fetal LA and DHA are correlated with maternal red blood levels.[16] However, because dietary sources (especially corn oil) are abundant, LA may be above normal range in some adults. Excessive LA can contribute to an overproduction of the proinflammatory 2-series local hormones derived from AA.

Although the n-6 fatty acids, especially LA, are widely imputed as health risk factors because of their relative overabundance in modern diets, it is important to recognize that the clinical imperative is to discriminate excess from deficiency status. The only sure way to know whether a patient is in n-6 fatty acid deficit or excess is to perform a laboratory evaluation of fatty acid status.

Gamma-Linolenic Acid (18:3ω6)

GLA is the precursor of DGLA, the parent of the 1-series prostanoids. GLA is found in hemp, borage, blackcurrant, and evening primrose oils. It can be produced in human tissues by the action of desaturase enzymes on LA. Use of 1.4 g/day in the form of borage seed oil resulted in a clinically important reduction in the signs and symptoms of rheumatoid arthritis.[17] In cases of cancer, it is especially important that low levels of GLA should not be supplemented without added ω-3 fatty acids because ω-6 fatty acids can enhance tumor formation and growth, whereas ω-3 fatty acids tend to inhibit tumors.[18] GLA corrects most of the biological effects of zinc deficiency.[19]

Dihomogammalinolenic Acid (18:3ω6)

Diets low in LA are usually also low in DGLA. An insufficiency of this fatty acid impairs a wide range of cellular functions and tissue responses. DGLA is the precursor for the 1-series prostanoids that moderate the proinflammatory 2-series effects. When testing reveals low levels of DGLA, supplementation with borage or evening primrose oils should be considered.

Arachidonic Acid (18:4ω6)

Because of the prevalence of corn and corn oil products in feed for cattle and hogs, diets high in these red meats are usually rich in AA. AA is a 20-carbon or eicosanoate fatty acid that serves as a substrate for the cyclooxygenase and lipoxygenase enzymes, leading to the production of the 2-series prostanoids and leukotrienes. Several of these products have potent proinflammatory and thrombogenic activity. High AA also promotes gallstone formation by stimulating mucin production in the gallbladder mucosa.[20] Elevated AA is a frequent finding in profiles of fatty acids in plasma or erythrocytes. Such findings should trigger counseling regarding dietary AA reduction and appropriate supplementation to restore n-3/n-6 balance. However, deficiency of AA produces signs of EFA deficiency, so adding ω-6 oils is needed when low levels are found. AA levels decline rapidly when EPA levels are elevated by excessive use of flax or fish oils.

Mead Acid (20:3ω9)

Individuals with good fatty acid status have low levels of the ω-9 PUFA called Mead acid. Mead acid is produced in human tissues by repeated desaturation of stearic acid when there is chronic deficiency of n-3 and n-6 fatty acids.[15] Although Mead acid cannot participate in eicosanoid formation, it does serve to mimic the membrane fluidity contributions of PUFAs derived from essential precursors. Because the enzymes for Mead acid formation are contained in peroxisomes, conditions that cause peroxisome proliferation can produce elevated levels of Mead. Because one such condition has high levels of n-3 and n-6 fatty acids, Mead acid elevation is not indicative of EFA deficiency when such patterns are found. Mead acid is the triene mentioned in the discussion of the triene/tetraene ratio near the end of this chapter.

Monounsaturated Fatty Acids

Vaccenic Acid (14:1ω9), Palmitoleic Acid (16:1ω9), and Myristoleic Acid (18:1ω7)

The ratio of vaccenic acid to palmitoleic acid is a marker of biotin deficiency.[21] Vaccenic acid has effects on membrane fluidity, possibly due to the fact that the ω-7 double bond does not align with the much more abundant ω-9 positions of the majority of fatty acids present in the membrane. Myristoleic and palmitoleic acids are normally found in small amounts because the desaturated

enzymes have weak affinity for their saturated fatty acid precursors, myristic and palmitic acids. In long-term EFA deficiency, the low concentrations of PUFAs allow higher rates of formation of myristoleic and palmitoleic acids.

Oleic Acid (18:1ω9)

Oleic acid is present in virtually all whole foods and is easily produced by the fatty acid synthetic pathways present in normal human hepatic cells. It constitutes 15% of the fatty acids in erythrocyte membranes. Because of the presence of the double bond in the center of the molecule, it helps to govern the fluidity of the membrane matrix.

The pathogenesis of atherosclerosis involves accumulation of foam cells along the arterial wall. Lipids that transform macrophages into these foam cells are provided by oxidized low-density lipoproteins (LDLs). Oleic acid is the principal lipid of a class that makes LDLs resistant to oxidation, and thus a diet rich in this fatty acid reduces foam cell accumulation rates and thereby lowers the chances of atherosclerosis[22] (see Chapter 148 for a more complete discussion).

In tumors, the expression of genes for metabolizing fatty acids is altered so that stearic acid levels increase relative to oleic acid, causing a profound reduction in the ratio of stearic to oleic acids.[23] One likely outcome of this shift is an increased fluidity of the tumor cell membrane, resulting in more rapid movement of nutrients and waste products and allowing for a faster metabolic rate. The stearic/oleic ratio is used to monitor the effectiveness of cancer therapy.[24]

High oleic acid intake (usually as olive oil) can raise total oleic acid content of plasma above the reference range. This finding alone is not highly significant because oleic acid is a cholesterol neutral fatty acid and is produced in humans from stearic, so it is not an EFA.

Erucic Acid (22:1ω9)

This fatty acid is apparently one of the components responsible for the favorable response of individuals with adrenal leukodystrophy (ALD) to preparations containing canola and mustard seed oils.[25] Other studies using Lorenzo oil containing glycerol trierucate revealed no appreciable changes in brain lipid content.[26] In Zellweger syndrome, where peroxisomes are absent, erucic and adrenic acids accumulate. It is speculated that either the anabolic enzymes are inhibited from producing sphingolipids or the catabolic enzymes are stimulated to faster clearance of the offending products.[27]

Nervonic Acid (24:1n9)

Nervonic acid contains the longest chain of carbon atoms of all monoenoic fatty acids present at appreciable levels in plasma and erythrocytes. The unique structure of nervonic acid confers special properties to nerve membranes, where it is found in highest concentrations. The myelin sheath is especially rich in nervonic acid. Nervonic acid accumulation in red blood cells yields information on cerebrum maturation in premature infants.[28] Demyelination in ALD is associated with an accumulation of long-chain saturated fatty acids, such as 26:0, stemming from a genetic defect in the peroxisomal β-oxidation system responsible for the chain shortening of these fatty acids. Long chain monoenoic acids, such as erucic acid, 22:1(n9), can normalize elevated serum levels of 26:0 in ALD by depressing their biosynthesis from shorter chain saturated fatty acids.[29] Impairment in the provision of nervonic acid in demyelinating diseases is indicated, suggesting that dietary therapy with oils rich in very long chain, monoenoic fatty acids may be beneficial in such conditions.

Saturated Fatty Acids

Capric Acid (10:0), Lauric Acid (12:0), Myristic Acid (14:0)

These medium-chain saturated fatty acids correspond to the dicarboxylic acids that accumulate in the fatty acid catabolic disorders known as multiple acyl-coenzyme-A (CoA) dehydrogenation disorders (MADs).[30] One type of this enzyme defect is responsive to riboflavin at levels far above normal intakes.[31] A pattern of low levels of the shorter chain fatty acids and high levels of longer chain fatty acids may indicate a fatty acid restricted diet, in which case there is a stimulation of hepatic synthesis and elongation enzymes.

Palmitic Acid (16:0) and Stearic Acid (18:0)

The liver can convert fatty acids into cholesterol. Although any fatty acid can enter this pathway, palmitic acid is the most stimulatory one known and high levels lead to increased serum cholesterol levels and thus to increased risk of atherosclerosis, cardiovascular disease, and stroke. Most other fatty acids are either cholesterol neutral or have reverse effects, as in the case of EPA. Palm kernel and coconut oils are rich sources of palmitic acid. Palmitic acid is also the principal fatty acid product of human fatty acid synthesis, which is stimulated by hyperinsulinemia and by diets high in simple carbohydrates.

Stearic acid is a saturated fatty acid that is two carbon atoms longer than palmitic acid and is similarly cholesterogenic. High levels in plasma are therefore a risk factor in atherosclerotic vascular disease. Abnormal levels in erythrocyte membranes cause alteration in membrane fluidity. Low levels give increased fluidity, which is associated with active tumor proliferation.

Behenic Acid (22:0), Lignoceric Acid (24:0), Hexacosanoic Acid (26:0)

Accumulation of certain long-chain fatty acids is associated with degenerative diseases of the central nervous system, such as ALD. A large number of known genetic disorders involve accumulation of sphingolipids, usually due to the lack of enzymes necessary to maintain the turnover of membrane components. Behenic, lignoceric, and hexacosanoic acids, as well as the unsaturated members of the C22-24 classes, especially nervonic acid, are found elevated in such cases.

Odd-Numbered Fatty Acids

Pentadecanoic Acid (15:0), Heptadecanoic Acid (17:0), Nonadecanoic Acid (19:0), Heneicosanoic Acid (21:0), and Tricosanoic Acid (23:0)

Fatty acids with odd numbers of carbon atoms are produced primarily by initiating the synthetic pathway with the three carbon compound propionic acid. Vitamin B_{12} is required for the conversion of propionate into succinate for oxidation in the central energy pathways.[32] Deficiency of vitamin B_{12} results in accumulation of propionate and subsequent buildup of the odd-numbered fatty acids. The initiation of fatty acid synthesis is a biotin-dependent step. In biotin deficiency, the rate in which acetyl-CoA is converted into malonyl-CoA is reduced, allowing propionate to enter in greater amounts. Elevated levels of odd-numbered fatty acids have been shown to occur in human plasma phospholipids and in the plasma, heart, and liver of experimental animals with biotin deficiency.[33,34]

Bacteria in the gut of ruminants produce large amounts of propionate, which is absorbed and enters the metabolism. Consequently, the intake of animal and dairy products favors higher

levels of odd-numbered fatty acids. Alternatively, it is possible that the bacteria in the human gut could produce sufficient amounts of propionate to lead to an elevation in the odd-carbon fatty acids.[35] This would only occur under conditions of significant gut dysbiosis.

The association between vitamin B_{12} and abnormal fatty acid synthesis provides a rationale for the neuropathy of cobalamin deficiency. Odd-chain fatty acids build up in membrane lipids of nervous tissue, resulting in altered myelin integrity and demyelination, leading to impaired nervous system functioning.[36]

Trans-Fatty Acids

Palmitelaidic Acid (16:1ω9t), Elaidic Acid (18:1ω9t), and Other Trans-Fatty Acids

The trans-fatty acids, elaidic and palmitelaidic acids, are prevalent in most diets because of the widespread use of hydrogenated oils in food products. Because these fatty acids contain a *trans* double bond they behave like saturated fats, leading to higher cholesterol levels.[37] In contrast, they mimic unsaturated fats in binding to desaturated enzymes and interfering with the normal desaturation rates. The net effect raises plasma LDL and lowers high-density lipoprotein.

The consensus among experts in lipid nutrition is now so strong that ingestion of foods containing hydrogenated oils is a health risk that products containing them have been banned in some areas. The bacteria in the gut of ruminant animals produce small amounts of these fatty acids, which is the reason that beef and milk contain 1% to 3% of elaidic acid. If plasma or erythrocyte levels of trans-fatty acids are elevated, foods containing hydrogenated oils need to be avoided. Foods that generally contribute the greatest amounts of trans-fatty acids include stick margarine, peanut butters, and bakery products such as breads, rolls, cookies, crackers, pies, and cakes.

Two other 18-carbon isomers, petroselinic and trans-vaccenic acids, are usually present in smaller amounts than elaidic acid. Because the clinical concern is only the total accumulation of trans-fatty acids, some laboratories report the total C18 trans-fatty acid concentration rather than attempting to isolate each isomer.

Fatty Acid Ratios

These calculated values provide a quick guide to the balance between two parameters. Sometimes valuable insights into imbalances are found in ratio values, although the individual components are within normal limits.

Linoleic Acid/Dihomogammalinolenic Acid Ratio

The ratio of LA to DGLA increases when zinc deficiency or excesses of saturated, monoenoic, or trans-fatty acids inhibit the δ-6 desaturase enzyme. Under these conditions, the enzyme cannot convert the substrate (LA) to the product (DGLA) fast enough. The production of all desaturation products is affected, including EPA and AA. These longer chain polyunsaturated fatty acids then must be supplied from the diet or supplemented forms.

Dihomogammalinolenic Acid/Eicosapentaenoic Acid Ratio

The balance of 20-carbon or eicosanoic fatty acids is critical for proper supply of the prostanoid and leukotriene 1-, 2-, and 3-series local hormones that control a host of cellular functions and responses. The DGLA/EPA ratio is typically high due to DGLA being elevated relative to EPA, indicating a need for EPA sources such as fish oils. When the ratio is low, sources of DGLA (borage or evening primrose oil) are indicated.

Arachidonic Acid/Eicosapentaenoic Acid Ratio

This ratio allows a quick comparison of the relative amounts of these two eicosanoid precursors. An abundance of AA is quite common in Western diets high in meat and corn oil and can result in the elevation of the AA/EPA ratio. This is one of the indicators that extra ω-3 fatty acids, including EPA of fish oils, would be beneficial.

Triene/Tetraene Ratio (Mead/Arachidonic Acid)

The ratio of the triene Mead acid to the tetraene AA has been used as a further marker of EFA deficiency. This ratio is commonly used in studies of EFA deficiency.[38] In cases where long-term EFA supplementation has stimulated the production of Mead acid with concurrent elevation of AA, the ratio of the two is not above the normal reference limit. Only when the Mead elevation is found without high levels of PUFAs is a high triene/tetraene ratio indicative of EFA deficiency.

Red Cell Stearic/Oleic Index

The ratio of stearic to oleic acids in red cell membranes has been found to be a strong indicator of the presence of malignant tissue, since it reflects the lowered ratio found in malignant tissue cell membranes.[39] Values below 1.1 have been associated with the presence of malignancy. The ratio was found to respond to hormonal therapy for prostatic cancer and, in studies after surgical cures, individuals who maintained this ratio above 1.1 had no tumor recurrences.

The Omega-3 Index

The ω-3 index is defined as the sum of EPA and DHA expressed as a percentage of the total fatty acid content of red blood cell membranes. Because the ω-3 index half-life is 4 to 6 times longer than serum or plasma EPA and DHA, it better reflects long-term exposure to these fatty acids. It also has the advantage of not being influenced by the fasting or fed state.[40]

An analysis of related laboratory and clinical data found that the ω-3 index was inversely associated with risk for mortality because of cardiovascular disease. An ω-3 index of more than 8% was associated with the greatest protection, whereas an index of less than 4% was associated with the least protection.[41] While less precise, whole blood ω-3 content was also significantly associated with risk for sudden death. In a prospective trial using data from the Physicians' Health Study, men whose blood levels of ω-3 fatty acids were in the third and fourth quartiles had relative risks of sudden death of 0.28 and 0.19, respectively, compared to those in the lowest quartile.[42] The ω-3 index was associated with improved cardiovascular risk factors independent of body fatness in younger overweight and obese individuals, suggesting that achieving an optimal ω-3 index may negate some of the risk associated with excess weight.[43]



SUMMARY

Recent advances in laboratory methodologies now allow measurement of absolute, as well as relative, levels of essential, nonessential, and potentially damaging types of fatty acids in the blood. The research literature now provides guidance for interpretation of the clinical significance of various fatty acid patterns. Fatty acid manipulation through diet and supplementation is a powerful therapeutic resource (see Chapter 90).

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CHAPTER 15

Food Allergies

Wendy Hodsdon, ND

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INTRODUCTION

The percentage of people with food allergies or sensitivities is unknown because many people do not attribute their symptoms to the food they eat. In 2004, it was estimated that 6% of children and 4% of adults in America had immunoglobulin-E (IgE) mediated food allergies[1] and that 20% of the population altered their diet due to adverse reactions to foods.[2,3] It is clear that food reactions are common and the prevalence of food allergies specifically is rising.[1] There are a variety of reactions a person can have to food including:

1. Psychological reactions to food (via exorphins or food aversions)
2. Toxic reactions to food (food poisoning or contaminated food)
3. Immune-mediated reactions to a food (type I, II, III, or IV hypersensitivity)
4. Food intolerance reaction (enzyme deficiency or hypersensitivity to a food component or additive)

This chapter focuses on the immune-mediated reactions to food, also referred to as food allergies.

The specific nomenclature used for food allergies has been defined in position statements written by the European Academy of Allergy and Clinical Immunology (EAACI) nomenclature review committee. Allergy reactions are defined as a "hypersensitivity reaction initiated by immunologic mechanisms."[4] This includes food reactions mediated by any antibody (IgE, IgG, IgA, or IgM), as well as cell-mediated reactions (as seen in contact dermatitis).[5] Although this is the strict definition of food allergy, the same article also stated that, "Food-specific IgG antibodies in serum are not of clinical importance but merely indicate previous exposure to the food. If IgE is involved in the reaction, the term IgE-mediated food allergy is appropriate. All other reactions should be referred to as nonallergic food hypersensitivity."[5] Hypersensitivity is defined as a way to "describe objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons."[5] These definitions stated that food reactions mediated through IgG or IgA antibodies would strictly be defined as a "food sensitivity." The clinical significance of IgG and IgA antibodies is still being debated in the scientific and medical communities.[6] Most natural medicine practitioners call IgG- and IgA-mediated reactions "food allergies" because the reaction is associated with an antibody response. Food allergies will be defined here as any response to food that is immune mediated, including antibody responses (IgE, IgG, IgA, and IgM), as well as cell-mediated food reactions.

The discussion of definitions also extends into food allergy symptoms. The scientific community typically defines food allergy symptoms as IgE antibody mediated (type I or II hypersensitivity reactions). IgE associated disorders include immediate-type gastrointestinal hypersensitivity, oral allergy syndrome, acute urticaria and angioedema, allergic rhinitis, acute bronchospasm, and anaphylaxis. Symptoms include reddening of the skin; hives; pruritus of skin, mouth, or throat; swollen lips or eyelids; tightness of the throat; wheezing; difficulty breathing; coughing; vomiting; or diarrhea.[7,8] Most of these symptoms happen right after eating the offending food. Mixed IgE- and cell-mediated food reactions cited in the literature include atopic dermatitis,[9-12] asthma,[13,14] eosinophilic esophagitis,[15-17] and eosinophilic gastroenteritis.[18] Food reactions mediated by cellular (non-IgE mechanisms) include contact dermatitis,[19] food-induced pulmonary hemosiderosis,[20,21] celiac disease,[22] and food protein-induced enterocolitis syndrome.[23,24] Many natural medicine practitioners recognize a wider array of food-related disorders and symptoms that can

affect almost any system in the body. Symptoms may include diarrhea, constipation, abdominal bloating, gas, urinary irritation, rashes (including eczema and psoriasis), tinnitus, nasal congestion, chronic sinus or ear infections, joint pain, headaches, foggy thinking, fatigue, and mood disturbances.[25-28] Many of these symptoms are delayed, sometimes taking a few days to appear. Because of the variety of symptoms and the time it takes people to show a reaction to some foods, food allergy testing can be useful.

Various types of food allergy testing methods are used as tools to identify a person's reactive foods. Different tests are appropriate depending on the immunologic reaction a person is trying to discover. Food allergy or sensitivity testing can be a great motivational tool to encourage dietary changes, showing people in full color their specific reactive foods. People are often more willing to change their diet after a test provides "proof" that a particular food is reactive. Food allergy tests can also be useful when patients are unable or unwilling to do a full elimination diet, or when they are not aware of the food-related physical symptoms present in their body. Although an elimination diet is still the gold standard for food sensitivity testing, the time and diligence it takes to do a proper elimination diet is often overwhelming. An accurate and reproducible food allergy test allows nutritious foods to remain in a patient's diet while eliminating reactive foods. This chapter provides a review of the immunology of food allergies and then specifically examines the different food allergy testing methods.

IMMUNOLOGY OF FOOD ALLERGIES

Healthy individuals do not have food allergies or sensitivities. Instead they eat foods, digest them well, absorb what they need, and their immune system develops "oral tolerance" to the food. Oral tolerance describes how the body learns not to react to an antigen (food) when it is delivered through the oral route.[29-31] The factors that influence tolerance include the person's genetics, digestive function, and the nature and form of the food when it is consumed. Proteins induce tolerance more than lipids and carbohydrates,[32] and proteins given in a soluble form induce tolerance more than those that are aggregated.[29] Low doses of antigen activate regulatory/suppressor T cells, generally described as T_H3 cells (which can be both CD4 and CD8T cells).[33,34] The mucosal immune system consists of regulatory and suppressor T cells (T_H3 cells) in Peyer's patches and mesenteric lymph nodes that produce transforming growth factor-β (TGF-β). The role of TGF-β in the body is to promote B-cell class switching to IgA and to act as a general immunosuppressant for both T- and B-cell responses.[35,36] In this way, we can accept food into the body while still fighting pathogens (bacteria, viruses, parasites, or toxins).

Increased intestinal permeability is related to increased aggressive inflammation and lack of tolerance. It appears that increased permeability throughout the intestine allows food antigens to pass through the disrupted tight junctions and, in animal models, induces anaphylaxis[37-39] (see Chapter 20, Intestinal Permeability Assessment). When antigens are absorbed through the paracellular spaces, the mucosa-associated lymphoid tissue does not get the proper stimulation to induce a tolerance response. Data are conflicting regarding the integrity of the mucosal barrier in children with various gastrointestinal diseases.[40-42] The role of intestinal permeability is critical for our understanding of food allergies and may play a role in a variety of types of immune-mediated food reactions. Natural medicine practitioners often talk about healing the intestines, leaky gut, and decreasing inflammation. These types of treatments are most likely aimed at increasing the tolerance response in the intestines.

Food allergies may develop when the regulatory system falters due to defects in TGF-β or when the intestinal epithelial barrier is breached. Both of these may contribute to a reactive individual developing an antibody-mediated food reaction. When a food is taken up by Peyer's patches in a reactive individual, CD4T cells specific for the food make T_H2 cytokines, including IL-4 and IL-13. These cytokines cause B cells specific for the protein in the food to make IgE and induce mast cell activation and growth (IL-4 and IL-9).[43,44] IgG is also produced in response to food antigens, although the mechanisms leading to the production of total IgG and its subclasses are not fully elucidated at this time. Allergic sensitization to allergens was originally attributed to a dysregulation of the Th1/Th2 balance. New subsets of T cells have been shown to induce allergies or have an effect on the immune regulatory balance. These cells include Th17 cells[43] and nonclassical T cells such as natural killer T cells,[45] γδ T cells, and subsets of CD8T cells (Tc1 and Tc2 cells).[43,44]

For type I hypersensitivity reactions, antigen-specific IgE is produced by B cells. Elevated levels of antigen-specific IgE allergies are found in allergic people even with antigen avoidance for several years.[46,47] Once IgE antibodies are made to a particular food, they attach to Fc receptors on mast cells and eosinophils. When the antibody binds to its triggering food, the cells degranulate, causing traditional allergy symptoms, including hives, diarrhea, and gastric distress.[48]

Types of Hypersensitivity Reactions

Type I

Type I hypersensitivity reactions involving IgE antibodies are the most commonly recognized type of food allergy.[2] IgE antibodies are formed to soluble antigens that bind to antibodies, crosslink, and activate mast cell degranulation. Oral allergy syndrome is an IgE-mediated immune reaction; symptoms are usually limited to the oropharynx, which occurs upon ingestion of certain fresh fruits, nuts, or vegetables in pollen-sensitized individuals. The proteins in pollens and particular foods are similar in causing a reaction when particular raw fruits, nuts, or vegetables are eaten. Common symptoms include itching, tingling, erythema, and angioedema of the lips, mouth, and throat and usually occur within 5 minutes of eating the food. Cooked foods rarely induce the same response, because the protein shapes are changed when food is heated or digested.[49,50]

Type II

Type II sensitivity reactions involve IgG antibodies that are associated with cells or cell receptors. The antibodies alter signaling to the cell or affect the body through the complement system. Most often this reaction is seen in antibiotic or other drug reactions when IgG antibodies attach to red blood cells, causing destruction of red blood cells or platelets.[48]

Type III

Type III sensitivity reactions (Arthus reactions) involve IgG antibodies and soluble antigens. Normally, if an IgG antibody is produced and binds to its soluble antigen in large aggregates, the complement is fixed and the complex is readily cleared by the mononuclear phagocyte system. Small complexes are formed when there is a lot of antigen in the system; these complexes are often deposited in the blood vessels. These small complexes can bind to receptors on white blood cells, leading to white blood cell activation and tissue damage. A localized reaction is called an Arthus reaction and can be triggered in a sensitized individual

who has IgG antibodies against a particular antigen. When that antigen is injected under the skin, IgG antibodies induce a local inflammatory response in the skin, causing swelling and redness. Mast cells induce this response in the skin and in the linings of joints (synovial). This process happens in the lung epithelium induced by macrophages in the alveoli.[48] Pathologic immune-complex deposition is seen in situations where antigens persist, and when the body is not able to clear the complexes. This mechanism may be what occurs in subacute bacterial endocarditis or chronic viral hepatitis. The replicating pathogen continuously provides new antigens, and the body continues to form antibodies that result in these small complexes that deposit in blood vessels. Tissue damage can occur in a variety of tissues and organs, including skin, kidneys, and nerves.[48] Research has not been done to study antibody–antigen complexes that are formed when food is eaten continually in people with persistent IgG antibodies. This could be a possible mechanism for the food sensitivity reactions seen affecting people in a variety of tissues.

Type IV

Type IV hypersensitivity reactions are a delayed-type hypersensitivity (DTH) response that is mediated through T cells making T_H1 cytokines (interferon-γ, tumor necrosis factor-α, and tumor necrosis factor-β) rather than antibodies. Generally, soluble antigens are presented by macrophages to antigen-specific effector T cells. These T cells respond like they would to any pathogen causing a T_H1 cytokine reaction. The cytokines, chemokines, reactive oxygen species, prostaglandins, and leukotrienes formed by these T cells cause local and systemic tissue destruction. This type of reaction is being studied as a mechanism for atopic eczema.[51-54]

FOOD ALLERGY TESTING METHODS

The immune system has a variety of possible ways it can react that could induce a food allergy reaction. Different testing methods are best for specific food allergy reactions. There are variables within a testing method that may make its reliability and clinical relevance questionable. All of these factors need to be taken into consideration when selecting a food allergy testing method.

There are a variety of ways to test for food sensitivities, including elimination/challenge, skin testing, patch testing, enzyme-linked immunosorbent assay (ELISA) antibody tests for IgE, IgG, IgG4, and IgA antibodies, biochip technology, and energetic testing methods. As immunologic methods become more sophisticated, more specific and accurate tests are likely in the future. All methods look at a particular aspect of food reactions and have specific advantages and disadvantages. Clinical interpretation is required regardless of the type of testing used.

Elimination/Challenge

The most commonly used way of identifying and verifying food reactions is elimination and challenge of the specific foods. The double-blind, placebo-controlled food challenge is the gold standard for identification of food allergies and sensitivities for Western medicine.[55,56] Often the food is disguised to eliminate potential bias on behalf of the patient and is used to identify type I hypersensitivity reactions.[57] Many clinicians use food elimination and challenge as a way to confirm a food reaction. The basic design is to eliminate a suspect food for a period of time to see which symptoms subside. When the food is reintroduced to the diet, clinicians observe which symptoms reappear.[12,56]

Method: Eliminate test food or foods from the diet. This method depends on clinical presentation, ability of the person to adhere to a restricted diet, and preference of the clinician.

Eliminate:

1. A single suspect food.
2. A group of commonly allergenic foods (dairy, eggs, gluten, citrus, nuts/seeds, and shellfish, etc.) or a group of identified allergenic foods.
3. Most foods except those generally thought to be "safe." (Start eating one safe food only, add another if there is no reaction. Continue process.)
4. Water fast for a time to reduce allergenic symptom load before adding foods back to the diet.

Reintroduction: (Caution: This type of testing should not be conducted with foods that are known to induce severe or anaphylactic responses in a person.)

1. Add back one food every 3 days to diet.
2. Watch for any food sensitivity reactions to start.
3. If a reaction starts, wait until the symptoms resolve before trying a different food.

Type of reaction: This test has the potential to identify any type of food reaction causing physical symptoms, provided the person has the ability to recognize the physical symptoms when they occur. Because the test occurs in the person (in vivo) rather than with bodily fluid (in vitro), any type of immune response could show a reaction.

Advantages: This method identifies any type of reaction to foods and can be used to confirm a reaction and motivate food elimination compliance as well as identifying food sensitivities. The method is very adaptable and can accommodate a wide variety of people.

Disadvantages: This method is not appropriate for people with severe allergic reactions. People can influence the results based on their ideas rather than real reactions. The method can be time-consuming and requires the ability to be on a restricted diet. Also, some patients are not willing to stop eating favorite foods without an objective reason.

Clinical evaluation: Clinicians can consider the severity of the food allergy response, the timing and type of symptoms present, and past reactions when developing a specific, individualized protocol. The elimination/challenge diet can be used to confirm a food reaction as well as identify food allergies.

Skin Prick Testing

Skin prick testing (SPT) is the most common test performed by conventional allergists to confirm IgE-mediated allergies. This type of allergic response is typically seen in environmental allergic reactions, but can also be seen in food allergies.

Method: SPT is done by placing a drop of commercially prepared allergen on the skin and "pricking" or lightly lancing the skin. The person is allergic to the allergen when they have erythema or swelling greater than that of the control. This method identifies reactions to allergens that produce a type I, IgE-mediated allergy response.[58,59] Immunologically, the IgE antibodies that the body made from past exposure to the allergen are bound to mast cells that degranulate when the allergen is encountered during the test.

Advantages: SPT is more sensitive than radioallergosorbent testing (RAST), which is an in vitro test looking specifically for IgE antibodies. The test is very accurate for identifying environmental allergies.

Disadvantages: SPT requires that a person be exposed to the allergen before being tested, so the body can produce IgE antibodies.

A person cannot be taking antihistamines or other immune suppressants at the time of the test. Some food sensitivities are not IgE antibody mediated and therefore cannot be identified using this method. The commercial extracts used for SPT can degrade and vary by manufacturer.[60,61] Although some people react to specifically cooked or raw foods, commercial extracts may lack the ability to display the labile proteins involved.[62]

Clinical Evaluation: This test is usually performed by a board-certified allergist. People who report being tested for food allergies already have had their IgE-mediated food allergies tested through SPT. If there is no reaction with SPT, then the food reaction is almost certainly not IgE mediated (excellent negative predictive value).[24] Intradermal skin testing is a similar, more sensitive test and involves injecting the suspected allergen into the skin. This test is sometimes used by allergists when they suspect an allergy but had no response with SPT.

Atopy Patch Test

Atopy patch test (APT) is most commonly used to distinguish irritant contact dermatitis from allergic contact dermatitis. APT is used to identify allergies that take a few days to show up, also know as late-phase clinical reactions.[54] Irritant contact dermatitis does not have an immune response and is seen when a person is in contact with skin irritants such as household cleaners, paints, oils, adhesives, and cement.

Method: APT is performed by using adhesive tape to adhere particular potential allergens on the skin. The patches are left in place for 48 hours, and the skin is examined at 48 and 72 hours for a response. If the skin develops redness or blisters, the person is allergic to the substance.[63,64] This testing method identifies type IV hypersensitivity reaction, also known as DTH response. This type of immune response is mediated through T cells rather than antibodies and takes 2 to 3 days to show a response. APT is beginning to be explored in infants with atopic eczema as a way to discover food sensitivities missed by SPT and RAST testing.[65]

Advantages: APT offers a way to look at T-cell mediated reactions to foods. This type of test can be done in people taking antihistamines because it is not dependent on mast cell degranulation for a result.

Disadvantages: The research examining APT for atopic eczema is recent, yet the results appear promising.[64,66-68] Studies examining gastrointestinal diseases have had mixed results.[67,69] The patch test is performed most often with cosmetics, cleaning products, jewelry, and metals that come in contact with skin. Although most clinicians will use commercially prepared extracts, it is possible to make food extracts from fresh foods. This can be time-consuming and make interpretation more challenging. The test requires some skin that is not affected with a rash or eczema, and at least three visits to the doctor for application and interpretation.

Clinical Evaluation: APT is being used experimentally for atopic eczema, and is usually used in conjunction with other tests. A controlled, oral food challenge is still necessary to verify symptoms in reactive foods.[24]

Radioallergosorbent Testing

Radioallergosorbent Testing (RAST) was the first test reported in the literature for identification of IgE antibodies to specific allergens.[70] This test allowed the in vitro testing of allergies. Through the years, the specificity of allergens has changed and the method has developed considerably. The basic method of the RAST test is followed in different forms as the technology of antibody testing has evolved.

Method: RAST testing is performed using human serum to measure the amount of IgE antibodies present. In brief, the method involves binding a specific allergen to a solid substrate and adding human serum. Specific antibodies in the serum bind to the allergen. The serum is rinsed off, leaving the bound antibodies behind. A radioactive marker is added to bind to the IgE antibodies bound to the substrate. The radioactive signal can be measured and is proportional to the amount of allergen-specific IgE antibody in the serum. RAST identifies type I hypersensitivity reactions mediated by IgE antibodies.

Advantages: This type of testing allows for identification of allergens in the blood rather than using an SPT. RAST sets the stage for second-generation, allergen-specific antibody tests using the same basic method.[71] The newer antibody tests can measure different types of antibodies, use higher quality allergen extracts, and use different matrix substrates that improve the test accuracy and sensitivity.

Disadvantages: Antibody testing is limiting in that a person needs to be exposed to an allergen to have antibodies and a positive result. This type of testing specifically looks at only IgE antibodies and is hampered by cross-reactive proteins and low-quality test agents.[72,73]

Clinical Evaluation: RAST testing in its original form is not used currently. It has been replaced by quantitative, automated technology, bringing more accuracy and precision to this type of testing.[70]

Enzyme-Linked Immunosorbent Assay

Enzyme-Linked Immunosorbent Assay (ELISA) is a second generation, allergen-specific antibody test also known as a solid-phase immunoassay. The technology has advanced significantly since RAST was developed in 1961, allowing for a variety of changes in this type of testing. Most ELISA test results are reported qualitatively (positive or negative), or semi-qualitatively (values are assigned into different classes of reactivity).

Method: ELISA testing is similar to RAST in that an antigen (allergen) is bound to a solid substrate, and serum or whole blood is added to allow for antibodies to bind to the allergen being tested. The sample is rinsed to remove unbound antibodies and a fluorescent marker is added to bind to the desired antibody. ELISA tests can be used to identify IgE, IgG, IgA, and IgM antibodies depending on the fluorescent marker that is added. When measuring IgE antibodies, the test is looking at type I hypersensitivity responses. When measuring IgG, responses may be related to type II or type III hypersensitivity responses, although the significance of these responses to foods has not been fully elucidated. ELISA tests can be performed for whole blood (IgG, IgA, IgM), serum (IgE, IgG, IgA, IgM), saliva (IgA), and stool (IgA) samples.

Advantages: ELISA testing is versatile, relatively inexpensive, and readily available, making it a useful screening tool for food allergies. The clinical relevance of IgG antibodies to food is still being debated.[74,75] IgG testing is generally accepted in the literature for celiac disease and irritable bowel syndrome,[76] but not for other diseases.

Disadvantages: A person must be eating the food in question for it to come up positive on an antibody test. Without exposure to the food, the white blood cells do not get activated and make antibodies. More frequent exposure to specific food sensitivities induces higher antibody levels in reactive individuals. If a person stops eating the reactive food, the antibody response will initially increase, because the antibodies are still being produced, but not utilized. The amounts of antibodies will decrease over time as

long as the immune system is not reactivated by the food. Cross reactions between specific food antigens and other agents can cause a positive test reaction even when a person has never eaten the food. The significance of these types of cross reactions is generally unknown.

The quality and form of the antigen (food) being tested greatly affects the results. One research study looking at the differences between raw versus processed food allergens showed higher reactivity in processed foods.[77,78] Most commercially available antigens are made from raw foods, highlighting the importance of the type and quality of food antigen being used in testing.

Allergy shots are given specifically to induce an IgG antibody response to a food. If a person has received allergy shots as a treatment for an IgE-mediated allergy, the IgG antibody may be protecting them from a more severe anaphylactic response to that food.[70]

Clinical Evaluation: ELISA tests for IgG or IgA antibodies are often used by alternative medicine practitioners to identify food allergies that have not been identified with more conventional, but limited, methods examining IgE antibodies. People with a history of allergy shots or anaphylactic responses in the past should be monitored closely for an increase in IgE antibodies after food elimination, because IgG antibodies can increase as a protective mechanism in these people. If a person has multiple extremely high reactions to a variety of foods, it may be a nonspecific reaction to a test reagent rather than reactions to specific foods.[79] Testing total antibody levels can be instrumental in determining whether the person has a high antibody load or a nonspecific reaction to the test reagents.

Third Generation ELISA Assays

Third generation ELISA assays ImmunoCAP (Phadia, Uppsala, Sweden), Immulite (Deerfield, Ill.), and Turbo RAST (Hycor, Garden Grove, Calif.) are automated systems utilizing solid-phase immunoassay technology to identify IgE antibodies.[71,80-82] These systems are more sensitive and specific for IgE antibody tests than ELISA or RAST, although most of the research performed examined latex and other environmental allergens. Technologic advances have allowed quantification of IgE antibodies and calibration, so different tests could be compared.[70]

Method: The method is similar to RAST and ELISA testing but uses an automated machine and different solid substrates to increase sensitivity and specificity.

Advantages and Disadvantages: This technology improves on ELISA technology, but is more expensive and generally only available for IgE antibodies. These third generation of IgE ELISA tests improved on RAST by developing a dose–response curve of IgE. This allowed clinicians to study how the quantity of serum IgE antibody was related to clinical sensitivity by relating amounts of IgE antibody to the results of double-blind, placebo-controlled food challenges.[83,84] Dose–response curves have not been created for IgG, IgA, or IgM antibodies. The relationship between amount of non-IgE antibodies and clinical symptoms has not been correlated in research studies. Different systems cannot be accurately compared directly,[81] although, unlike IgG and IgA testing, there is literature comparing the different methods.[85,86]

Clinical Evaluation: For identifying specific IgE allergens, these methods are less sensitive than skin testing, but more sensitive and specific than ELISA testing. Serologic IgE antibody tests can aid in predicting the presence of clinically significant food allergies and can therefore decrease the need for food challenges.[84]

Microarray Chip Technology

Microarray chip technology (ImmunoCAP-ISAC [Phadia, Uppsala, Sweden]) is an IgE antibody technology that utilizes serum to identify IgE antibodies.[87] Recombinant proteins are used as a purified source of allergic proteins, allowing for specific identification of allergens.[88]

Method: Allergens are bound in triplicate to a microarray chip. Serum is added to the chip and antibodies specific for the allergens attach to the chip surface. IgE is detected with a fluorescently-labeled IgE and read to give a semi-quantitative estimate of amounts of IgE.[88]

Advantages and Disadvantages: This technology is being utilized to identify specific proteins in foods that a person reacts to. This may allow clinicians to correlate clinical reactivity with IgE antibodies to specific proteins in foods,[73] or identify them if cross reactivity occurs with foods carrying homologous proteins.[89-91] This type of testing could be easily adapted to identify IgE, IgG, IgA, and IgM antibodies in parallel.[88] More studies are required to fully understand the role of specific proteins in the severity and persistence of an allergy response.[92] Microarray tests are not considered as sensitive as the third generation ELISA tests (ImmunoCAP) tests when the same allergens are used.[82]

Clinical Evaluation: Identification of specific allergic proteins in foods could allow for greater correlation between antibody responses and clinical responses, and could allow for more specific immunotherapy.[92,93]

Energetic Methods

Energetic methods of food sensitivity testing (electroacupuncture according to Voll, Vega testing, Carroll testing, applied kinesiology, electrodermal screening [EDS], and bioresonance therapy) are some of the ways some alternative medicine practitioners test for food sensitivities or intolerances. They measure the energetic response to foods or other substances, such as medications, supplements, and hormones.

Methods: The methods of these types of tests vary and are generally not elucidated. Most appear to be measuring galvanic skin resistance through an electrical circuit.

Advantages and Disadvantages: Some practitioners have reported good success with these types of devices in identifying food sensitivities. Clinical trials using Vega testing and EDS have not shown them to be reliable compared with traditional allergy testing.[94,95] A review of applied kinesiology literature showed the studies to be unreliable, although many of the studies quoted in a review showed favorable results.[96]

Clinical Evaluation: Scientifically, energetic testing methods are unsupported in the literature. Some practitioners may still find these techniques to be useful tools, but they should not rely solely on this type of testing for diagnosis and treatment of food sensitivities.

Other Testing Methods

Other testing methods, including lymphocyte response testing (ELISA/ACT), cell size variability testing (ALCAT), provocation–neutralization testing, cytotoxic food allergy testing, and Nambudripad's allergy elimination techniques (NAET), have been used for food sensitivity testing and treatment. Anecdotal evidence is positive for many of these testing methods,[97,98] but systematic scientific studies have either not been done to verify the clinical relevance of these methods, or have shown the tests to be unreliable and clinically questionable.[74,99,100] Four review articles suggested

that these methods lack scientific rationale, standardization, and reproducibility.[101-104] Cell size variability testing had random results with the same sample in a study examining reproducibility and reliability of this testing method.[105]

THERAPEUTIC CONSIDERATIONS FOR FOOD ALLERGY TESTING

The list of food allergy symptoms is growing all the time. It ranges from traditionally accepted symptoms such as anaphylaxis and hives to less generally accepted symptoms such as headaches, diarrhea, fatigue, and joint pain. Food allergy tests can give clinicians good tools for developing a treatment plan for people with a wide variety of symptoms. Treatment of any type of food allergy or sensitivity is dependent on a variety of factors. A detailed medical history, physical examination, and laboratory tests must always be considered when choosing a food allergy test and interpreting the results.

When choosing which type of food allergy test to perform, consider the types of reactions the patient has had in the past. If there is any history of anaphylaxis or difficulty breathing associated with foods, then a test that evaluates a type I sensitivity response should be considered. ELISA testing for IgG antibodies (and possibly IgA and IgM) can be useful for a wide variety of symptoms. See Box 15-1 for a list of possible reactions. IgG antibody responses to foods are seen clinically,[6,106] but the relevance is still being debated in the scientific literature.[107-111] A person can have food sensitivity–related symptoms and not have any reactive foods on a test.

Many of the food allergy tests available are not standardized by the Clinical and Laboratory Standards Institute, so results between companies cannot be compared. Some tests are not internally consistent as well as not comparable to other laboratories, as shown in a small study that examined multiple samples sent to two different laboratories.[105] A clinician can test if a laboratory is internally consistent by sending to the same laboratory two samples from the same person and same blood draw, but under different names. The results should be nearly identical. This can also be done to test the accuracy of some of the energetic methods of food sensitivity testing. This can help the clinician be more confident in the reproducibility and consistency of the test results.

The relationship between non-IgE testing methods and disease is not well represented in the research literature. Clinicians are starting to recognize the importance of addressing food allergies when treating a variety of complaints. Food has a role in decreasing inflammation in the body and can be used to treat inflammatory diseases. The immune system has an extensive presence in the intestines, and by working with how the body accepts food, oral tolerance could be restored with implications in many disease processes (see Box 15-1).

CONCLUSIONS

Food allergy tests should be used in clinical practice to confirm or exclude a suspected diagnosis of food allergies and as a tool to motivate dietary changes. Selection of allergy diagnostic tests and interpretation of the results must be directed by the person's clinical history. Future research studies should address the clinical significance of IgG, IgA, and IgM antibodies to specific foods and correlate physical symptoms with food allergy elimination. Food can be medicine in chronic illnesses when food causing inflammation is eliminated from the diet. Diagnosing food-related illness will become easier as food allergy diagnostic methods continue to improve.

BOX 15-1 Food Sensitivity Reactions

- **Skin reactions:** Itching, burning, hives, red spots, sweating, eczema, psoriasis, other rashes.
- **Ear, nose, and throat:** Sneezing, runny nose, sore or dry throat, hoarseness, ringing in the ears, dizziness.
- **Eyes:** Blurring, spots before eyes, watering, pain, twitching, sensitivity to light, redness, swelling of eyelids.
- **Respiratory:** Wheezing, mucus formation, shortness of breath, tightness of chest, asthma.
- **Cardiovascular:** Pounding heart, increased heart rate, flushing, tingling, faintness.
- **Gastrointestinal:** Increased salivation, canker sores, indigestion, bloating, stomachache, heartburn, colic, constipation, abdominal pain, diarrhea, gas, itching, or burning of rectum or anus. One may also experience weight gain from food sensitivities.
- **Genitourinary:** Frequent, urgent, or painful urination; inability to control bladder; itching; discharge; pain; water retention.
- **Musculoskeletal:** Fatigue, weakness, pain, swelling, stiffness of joints, backache.
- **Nervous System:** Headache, migraine, drowsiness, inability to concentrate, depression, irritability, restlessness, hyperactivity, dizziness, numbness, tremors.

This list is just a partial list of symptoms that may respond to eliminating food allergies or sensitivities. Many of these reactions have a variety of possible causes and should be evaluated according to the clinical picture presented. Some reactions may be nonimmune mediated and not test positive on a food sensitivity test.

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CHAPTER 16

Genomics, Nutrigenomics, Nutrigenetics, and the Path of Personalized Medicine

T. Michael Culp, MA, NMD, and Patrick Hanaway, MD

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INTRODUCTION

About 3 billion years ago, the experiment known as "life" began on Earth. All living creatures from the five kingdoms are descended from a single common ancestor. We know that all creatures on this planet are related to one another because we all share the same digital "language of life," known as DNA and RNA, made from five simple nucleic acids, connected along a sugar phosphate chain. If we could meet our primordial progenitor, we might not recognize it as living at all. We suspect it was nothing more than an RNA receptor-catalyst that somehow replicated itself by consuming chemicals in its immediate environment. These simple "ribo-organisms" were inherently unstable, forming and falling apart quite easily. Only over hundreds of millions of years did these organisms gain more stability when single-stranded RNA evolved into double-stranded DNA, and even more stability when the DNA began coding for proteins that would eventually evolve into cellular structure.[1]

Inherent in this narrative is a central fact that is easy to overlook: life began and continues to evolve within specific environments. We all know the classic riddle, "Which came first, the chicken or the egg?" From the perspective of evolutionary biology, this is not much of a riddle because the chicken's ancestors and their eggs preceded the arrival of the chicken by at least 100 million years. However on closer reflection, the riddle asks a far deeper and more perplexing question, "What is the relationship between the individual and its environment, between the chicken and its egg?" A hospitable environment had to precede the development of life, and no new life can evolve unless there is an environment to support it, but environments change over time, and a species must change to accommodate the new changes in its environment or invariably become extinct, as the vast majority of species that have lived on this planet have done. The central premise of Charles Darwin's grand theory of the origin of species speaks of survival of the fittest, but over time the fittest species is the one that can adapt best to a changing environment. Adaptation is not exclusive to the development of new species, but also plays a critical role in the survival of any individual within a species as well.

The twenty-first century may well be remembered as the century in which science first truly began to understand the complex interaction between the genetic information inherent in every individual and the environment to which that individual is exposed.

GENES AND ENVIRONMENT—NATURE AND NURTURE

"Environment" is broadly understood in genetics to include everything that is not the genetic information, or genome, itself. Environment includes climate, physical surroundings, exogenous chemicals or toxins, and infectious agents, but it also includes diet, lifestyle, and behavioral factors. Scientists once believed that genes were immutable archives of digital information that simply coded for proteins, which in turn determined the structure and function of an individual's (analogue) body. However, it is now irrefutable that gene expression is substantially affected by and sensitive to environmental change. Genes quite literally respond to the environment to which they are exposed.[2] Because genes respond to the environment we subject them to, the environment itself can be proactively manipulated to alter gene expression, and therefore, to change the health state of the individual. This is the central premise of preventive or functional genomics.

In the interactive symphony between genes and environment, the balance between the two may be altered whenever either changes. Because the environment is inherently unpredictable, one effective strategy to increase the chances of survival has been promoting genetic variation within a species, because slightly altered individuals may survive environmental change, whereas others may not. It is rather like a strategy for winning a lottery: odds of winning increase linearly with the greater variety of numbers that one is able to choose. Variety may truly be the spice of life. If populations from a single species diverge into different environments, the selective pressure over time may eventually lead to the creation of separate species.

The human genome is composed of approximately 3 billion nucleotides of genetic code. If you compare your DNA with the next person you happen to meet, you would find that about 1 in every 1000 nucleotides are different. That means that there are 3 million reasons why the two of you are not the same. These subtle variations of the genetic code are known as polymorphisms (literally, "many shapes," because if the change in the genetic code results in an amino acid substitution, the resulting proteins will have different shapes and slightly altered functions as well). It is these polymorphisms that are largely responsible for our biochemical individuality. Our polymorphisms help make us unique individuals. There are many types of polymorphisms, but by far the most common is the single-nucleotide polymorphism (abbreviated SNP and pronounced "snip"), in which a single nucleotide of the DNA is altered. The sum total of all of an individual's polymorphisms significantly affects protein synthesis and physiologic function, rendering each individual biologically and biochemically unique.

WHY DO POLYMORPHISMS EXIST?

The theory of natural selection has two central tenets: (1) all organisms compete for limited resources, and (2) organisms with some advantage in acquiring those resources are more likely to survive, to thrive, and to pass on that advantage to their offspring. Polymorphic variations are the ultimate source of these advantages. All polymorphisms that are found to be common in a species must afford some adaptive advantage to survival in some specific environment. Genetic polymorphisms are preserved and become more prevalent in a species when they endow a better chance of survival or of reproduction. The cumulative weight of slight genetic variations over time is the means by which variability within a species arises and by which new species also emerge. However, what may be good for a species and its evolution may not be good for a specific individual, because the environmental pressures exerted on a species over millions of years may be very different from the environment encountered in the present.

In individuals, altered polymorphic genes (the legacy of evolution) produce altered proteins, and altered proteins exhibit altered functions. For any given individual, altered protein function may be beneficial, neutral, or harmful, depending on the environment to which he or she is exposed. Prevalent polymorphisms are likely to be beneficial in certain environments but harmful in others. Because we cannot change our genes, the goal of preventive genomics is to alter an individual's environment based on his or her specific genetic variations to optimize his or her genetic potential. Genes themselves cannot be modified, but gene expression can be. One of the common misconceptions of polymorphisms is that they reveal only limitations, but in reality, they reveal an individual's potential.

NUTRIGENETICS AND NUTRIGENOMICS

From a clinical perspective, changes in diet are one major way of altering the gene–environment balance and improving an individual's health. Two distinct but interrelated fields of inquiry and knowledge are emerging. Nutrigenetics, also referred to as personalized nutrition, is based on the understanding that our genetic polymorphisms change the way we respond physiologically to specific nutrients. By studying specific polymorphisms and their physiologic response to specific nutrients, we can determine a more optimal nutritional regimen for a specific individual based on his or her specific polymorphisms. Nutrigenomics, by contrast, focuses on the effects of specific nutrients (both macro and micro) on the genome as a whole, and subsequently on the body's resulting total pool of proteins (the proteome) and on all its subsequent metabolic activity (the metabolome) as well.[2,3]

Food is, by definition, derived from other living organisms. Inherent in any food is an information code that we read and interpret by eating that food. There is a literal exchange of information that passes between the eaten and the eater. Not surprisingly, central to life is our ability to coordinate our metabolic activities with nutrient availability. Signals from the exterior world (food, toxins, weather, stress, etc.) turn on and turn off specific metabolic processes to improve our chances of survival in an ever-changing world.[4]

The most extreme example of the interaction of food availability and metabolic change is the situation, common in nature, when no food at all is available, i.e., famine. Clive McCay at Cornell University in the 1930s found that by restricting calorie intake in rats by at least 25% from the free-feeding level, he could substantially increase their average and extreme life expectancies, delay the age of tumor onset, delay cessation of reproductive function, and preserve functional homeostasis or stress response capacity.[5] Since that time, no major investigation has failed to demonstrate significant benefits to health and longevity from calorie restriction. Calorie restriction lowers the level of insulin exposure, which in turn lowers the overall growth factor exposure, improves age-declining maintenance of mitochondrial function, and helps to maintain a long-term favorable balance of the insulin-to-growth hormone antagonism.[6] From an evolutionary perspective, this makes intuitive sense. Only when calories are abundant does an individual have the metabolic resources for growth and reproduction. Survival during times of famine necessitates metabolic shifts that conserve resources and promote repair, because growth is not an option.[7]

Reducing calorie intake not only lowers overall insulin exposure but is now known to activate the transcription of a family of genes known as sirtuins (SIRT). The SIRT enzymes appear to have first arisen in primordial eukaryotes, possibly to help them cope with adverse conditions, like famine, and today are found in all plants, yeast, and animals. In response to calorie restriction, SIRT-1 stimulates the production of new mitochondria in skeletal muscle and liver cells, thereby increasing the capacity for metabolic repair and energy production. New mitochondria produce fewer free radicals than the old mitochondria, which leads to less free-radical damage and to delayed onset of metabolic aging. SIRT-1 also has a cascading effect on multiple genes, leading to increased catalase activity, increased free fatty acid oxidation for energy, and reduced inflammation via suppression of the enzyme nuclear factor-κβ (NF-κβ).[8]

The obvious problem with calorie restriction, however, is that we like food. Recent studies on the effects of the polyphenol compound resveratrol (initially isolated from grape skins) on obese,

sedentary mice, suggested that it could mimic the beneficial health effects of calorie restriction even while the rats continued to eat a high-calorie, high-fat diet and did not exercise. Dietary supplementation with resveratrol was found to oppose the effects of the high-calorie diet in 144 of 153 altered biochemical pathways, most of which could be attributed to its activation of the transcription of the enzyme SIRT-1. Resveratrol increased insulin sensitivity, reduced insulin-like growth factor-1 production, increased adenosine monophosphate activated protein kinase, increased peroxisome proliferator-activated receptor-coactivator-1 (PPAR-1) activity, increased the number of mitochondria, and improved overall motor function.[9] Such research suggests that at some future time we just may be able to have our cake, eat it too, and suffer few of the metabolic consequences for overeating. Nevertheless, the best current nutritional advice for longevity and health remains simply, "eat less." Not only does it lower insulin load, but it activates the transcription of numerous enzymes that promote mitochondrial regeneration, health, and longevity.

Not only is nutrigenomics helping to elucidate the myriad effects of specific nutrients on our genome, but it is also helping us rethink and understand the mechanisms by which other nutrients act on our physiology. *Ginkgo biloba* is a commonly prescribed medicinal herb that is known to increase peripheral microcirculation and to contain rather potent antioxidants. The vasodilation allows delivery of these antioxidant compounds to poorly vascularized areas, like the brain. Not surprisingly, ginkgo is commonly used for impaired memory and mental function as we age. Using gene chip assays, researchers examined cellular extracts to look for altered levels of messenger RNA, an accurate measure of gene activity. In vitro studies with human bladder cancer cells that were incubated with ginkgo resulted in suppression of gene transcription by more than 50% in 16 genes and induction of 139 genes by more than 100%. The overall effect of adding ginkgo was to activate genes that code for improved mitochondrial function and antioxidant protection. Subsequent in vitro mouse studies showed activity of more than 12,000 genes and a preferential activation of genes within the brain with induction of more than 200% of 43 genes in the cortex and 13 genes in the hippocampus, including those genes that promote nerve cell growth, differentiation, regulation, and function, as well as increased mitochondrial activity and antioxidant protection.[10]

This elegant research points to a new understanding of why and how herbal medicines or other specific nutrients can act to change our physiology, but also helps to explain why specific herbs or nutrients act preferentially on specific tissues or organ systems. It is not just *Ginkgo biloba* that acts to alter gene transcription. Every medicinal herb, every nutrient, every food, and every pharmaceutical medicine is likely to act in a similar fashion. These compounds do not just have a gross chemical effect on our physiology, but they actually alter gene expression. Nutrigenomics is forcing us to rethink the ways in which our bodies respond to environmental stimuli in the form of food, herbs, or medicine.

In some areas, nutrigenomics and nutrigenetics can overlap. We propose the use of the term "preventive genomics" to include both nutrigenomics and nutrigenetics because they cannot always be easily separated. To illustrate, PPAR-γ is a nuclear hormone receptor that regulates many cellular functions, such as nutrient metabolism, cell proliferation, and cell differentiation in response to dietary macronutrients, specifically to carbohydrate and fat intake. PPAR-γ integrates the cellular control of energy, lipid, and glucose homeostasis. Its activation by increased dietary fat or sugar intake is clearly an example of nutrigenomic interaction. However, there is a common polymorphism in the gene that codes for PPAR-γ in which at the twelfth amino acid in the protein, an alanine is substituted for a proline (the polymorphism is referred to as PPAR-γ P12A). Individuals with the 12A variant display a greater metabolic tolerance to a high-fat diet, leading to a significantly reduced risk of developing insulin resistance, type 2 diabetes, coronary artery disease, and central obesity when consuming a typical Western diet.[11] Individuals with the 12P variant are more sensitive to the ill effects of excessive dietary saturated fat intake, suggesting a clear therapeutic dietary strategy in P allele carriers to prevent obesity, diabetes, and heart disease.[12]

There are many polymorphisms like the PPAR-γ proline variation that exist in a large percentage of the population and appear to increase risk of certain serious diseases. They beg the question, why do these seemingly harmful polymorphisms exist? It is important to remember that the PPAR-γ proline variation is only harmful in individuals who eat a high-calorie, high-saturated fat typical Western diet. It behooves us to remember that in most of nature and for most of human history, too much food to eat was rarely a major risk factor. Quite the opposite was true when winter and famine were common occurrences. In these environments, the ability to extract more nutrition from the same caloric intake would be a distinct advantage for survival. It is only in the last 50 to 100 years in our culture of affluence that these variations have begun to pose significant risks to our health. We call these genes, "thrifty genes," a term first coined by D.L. Coleman to explain why the Pima Indians from the desert of the American southwest were prone to develop obesity and diabetes. Thousands of years of survival in that harsh environment selected for genes that made this group incredibly efficient at retaining calories from food—a distinct adaptive advantage when food supply was scarce. However, with the 24-hour grocery only a car ride away, their genes are significantly less well adapted to survive.[13] We see similar gene variations that increase inflammation throughout the body. This seems counterproductive until we realize that infectious disease has been a major environmental risk throughout evolution, and inflammation and immune activation are essentially the same biological process. It is imperative to remember that every polymorphism that exists in humans with significant prevalence confers protection and advantages to survival in some environment. Our task as clinicians is to identify that environment and to recommend it to those patients with that particular genetic variation.

NATURE VERSUS NURTURE

The reality is that the prevention and cure of complex diseases and syndromes are not to be found exclusively in our genes or our environment, but in the interactive symphony between the two. Nature (our genes) provides a plastic template that is largely adaptable to a wide range of environments ("survival of the most adaptable"), and slight variations in those genes can cause altered responses to specific environments (nutrigenetics). In contrast, nurture (our environment) switches genes on and off, largely controlling gene expression (nutrigenomics).

To illustrate this idea of gene–environment interaction, consider the research of Caspi et al.[14] They studied variations in the promoter sequence for the gene coding for monoamine oxidase-A (MAO-A) and found that a promoter polymorphism caused some people to have high-activity MAO-A genes and others to have low-activity genes. Those with high activity MAO-A would deactivate catecholamine neurotransmitters, like dopamine and noradrenaline, more rapidly. They then examined whether these genes played a role in antisocial and violent behavior in men who had been abused as children. Remarkably, they found that men with

the high-activity MAO-A gene were virtually immune to the effects of maltreatment as children, seldom if ever becoming violent offenders, whereas men with the low-activity MAO-A gene were much more antisocial and violent, but only if they themselves were abused as children. In other words, for violent behavior to manifest in adulthood, both the low-activity gene (nature) and childhood maltreatment (nurture) needed to be present. If either was missing from the equation, the adult was very likely to be well socialized and nonviolent.

The Centers for Disease Control and Prevention (CDC) published a *Gene-Environment Interaction Fact Sheet* in August 2000[15] that outlined the basic principles of a broad understanding of the causal interaction of genes and environment in human disease. In it, the CDC makes the following four main points:

1. Virtually all human diseases result from the interaction of genetic susceptibility and modifiable environmental factors.
2. Variations in genetic makeup are associated with almost all disease.
3. Genetic variations do not cause disease but rather influence a person's susceptibility to environmental factors.
4. Genetic information can be used to target interventions.

In this brief paper, the CDC essentially outlined the chief tenets of nutrigenetics and of preventive genomics.

Ironically, these ideas are hardly new. In 1909, Archibald Garrod[16] published *Inborn Errors of Metabolism,* in which, after identifying the first human disease that behaved as a true Mendelian recessive trait (alkaptonuria), he went further to construct a sweeping hypothesis that altered heredity was "the seat of chemical individuality." "Inborn errors of metabolism," he wrote, "are due to a failure of a step in the metabolic sequence due to loss or malfunction of an enzyme." By examining the subtle end products of metabolism, he continued, we should be able to identify the differences that altered heredity produces in each individual. This is a remarkable insight, given that the words gene and genetic did not exist in 1909, and it would be roughly 50 years before the structure and true function of DNA were confirmed. Moreover, Garrod's book was published 3 years before the first vitamin was discovered, so he would have had no notion of vitamins as cofactors in enzymatic reactions. He concluded his prophetic work by envisioning the complex interaction between our unique genetic constitution and environmental factors in the exquisitely simple statement "These idiosyncrasies may be summed up in the proverbial saying that one man's meat is another man's poison."



THE CLINICAL UTILITY OF NUTRIGENOMICS AND NUTRIGENETICS

The point of using genetic and genomic information in a clinical setting is to personalize the therapeutic regimen and to develop an effective strategy towards true disease prevention. It is a common mistake, however, to think that somehow the new preventive genomic information we can access will make all previous therapies obsolete. This is evident in the mindset that thinks we can attribute disease risk to polymorphisms without reference to environment (read any genetic newspaper headline). Simply put, genetic information is no more and no less valuable than environmental information. We need them both to make an optimal difference. Furthermore, at this stage in preventive genomic research there are at best only 100 or so polymorphisms about which we have sufficient clinical information to make personalized nutritional recommendations.[17] It is useful information, to be sure, but it is insufficient for comprehensive nutritional and therapeutic recommendations.

Carl Sagan once said, "If you want to make an apple pie from scratch, you must first create the universe." Fortunately for making an apple pie, the universe has already been created, and fortunately for making comprehensive nutritional recommendations, natural selection has been active since the beginning of life on this planet. As humans, we and our ancestors have been adapting to environments for the last 3 billion years, if you want to think of all life, or for a mere 600 million years, if you want to think of eukaryotic cells with aerobic respiration. Either way, it is a lot of experimental trial and error that brought us to the present. The proper starting point of nutrigenomics and nutrigenetics is not genetics per se, but good epidemiology. Good epidemiology can tell us what is the best nutrition and lifestyle for the average person. Specific genetic polymorphisms can help us modify these recommendations to meet the specific genetic needs of an individual patient.

Discovering the optimal nutrition and lifestyle for a specific individual will depend on developing a functional matrix that is minimally composed of:

1. Good epidemiologic dietary and lifestyle data
2. Specific genomic polymorphisms that alter specific macronutrient and micronutrient requirements
3. Functional laboratory assessment of individual function, physiology, and micronutrient status

In terms of Western diets, the Mediterranean diet is one of the best studied and, which, from an epidemiologic perspective, is arguably the best for disease prevention and optimal health. It has been demonstrated to reduce cholesterol and triglycerides, to prevent atherosclerosis and high blood pressure, to reduce the risk of senility, stroke, heart disease, insulin resistance, type 2 diabetes, and numerous cancers, including those of the breast, prostate, and colon.[18] Among elderly Europeans, a Mediterranean diet combined with moderate daily activity and no smoking reduces all-cause mortality by 67%, and switching to this healthier diet and lifestyle at age 70 reduced mortality rates by 50%.[19]

Clearly, these results are impressive, but the central tenet of preventive genomics is that these risks can be reduced further with the judicious application of nutrigenetic information gathered from the analysis of individual polymorphisms. Not all polymorphisms are clinically relevant. Most of our interindividual genetic variation occurs in sections of the DNA that do not actually code for proteins. About 97% of our DNA is either of viral origin, repeats, or simply junk DNA that codes for nothing. To make genomic information clinically useful, polymorphisms must meet four essential criteria: they must be relevant, prevalent, modifiable, and measurable.

1. First, the only polymorphisms in the genome of clinical interest are those that exert an effect on some specific aspect of our biochemistry and physiology (relevant).
2. Second, given our current knowledge of the human genome, only polymorphisms that exist in a substantial portion of a population are likely to be able to be demonstrated in epidemiologic and case-controlled studies to be clinically relevant—in essence, we compare polymorphisms that occur in substantial numbers in both groups (prevalent).
3. Third, only polymorphisms whose genetic expression is modifiable via reasonable clinical intervention are clinically useful. Such an intervention may be any modification of environment, including diet, lifestyle, and targeted nutraceuticals or pharmaceuticals. Although genes themselves are not modifiable, the phenotype they generate is modifiable via environmental changes because environment turns genes on and off.

4. Finally, because our genes do not themselves change, we must be able to measure changes in our functional physiology to determine that the environmental changes implemented have been effective in modifying the phenotypic or physiologic expression of our unique genes. For this purpose, functional testing must be available and used in conjunction with genomic testing for polymorphisms (measurable).

To illustrate this model of clinical utility, let us consider the example of the detoxification and antioxidant protection afforded by the enzyme glutathione-S-transferase (GST). High levels of toxins and oxidative stress are associated with numerous degenerative diseases and with the aging process itself. So an enzyme like GST that protects against such oxidative damage is highly relevant to our health. The GST polymorphisms have been associated with numerous cancers in epidemiologic and case-control studies.[20] Although there are several isoforms of GST in the body, the μ isoform, GSTM1, is the most common in the liver. Fifty percent of the population does not have any copy of the GSTM1 gene, so clearly it is prevalent. Because other isoforms of GST and other antioxidant pathways exist, it is possible to improve antioxidant protection by maintaining a high reduction potential through exogenous avenues, including dietary antioxidants. Furthermore, men and women who lack the GSTM1 gene all together can increase their serum glutathione levels by 16% and 38%, respectively, and their other GST activity by 6% and 8%, respectively, simply by eating four or more servings of brassica vegetables weekly. Interestingly, individuals possessing a GSTM1 gene showed significantly less benefit.[21] Similar benefits were seen from regular brassica vegetable consumption in reducing colorectal cancer by 53%[22] and lung cancer in smokers by 70%,[23] but again only in individuals lacking the GSTM1 gene. Thus, the increased oxidative stress is attenuated by regular brassica vegetable consumption. Finally, we can validate the clinical efficacy of our intervention strategy by measuring functional levels of oxidative stress through any number of simple laboratory tests, such as urine lipid peroxides, 8-hydroxy-deoxyguanosine, serum glutathione, urine, or plasma cysteine/cysteine ratio, etc. The biological effects of our interventions are measurable.

Personalized Nutrition and Nutrigenetics

Currently, most of the clinically relevant nutrigenomic information available relates to the relationship between polymorphisms with increased chronic disease risk and the dietary therapies and supplements that have been demonstrated to treat the physiologic imbalance effectively. This is particularly true of SNPs. In as many as one third of genetic polymorphisms, the corresponding enzyme has a decreased binding affinity for a vitamin or mineral coenzyme, resulting in a lower rate of reaction and altered enzyme function. In a review article, Ames et al[24] provided evidence of more than 50 human diseases involving defective enzymes that could be remedied or ameliorated by the administration of higher doses of vitamins or minerals, which at least partially restore enzyme activity. Thus, the clinical validity of high-dose nutrient therapy is established, but only in genetically susceptible individuals.

CLINICAL APPLICATION OF NUTRIGENETICS

The Example of Cardiovascular Disease

Cardiovascular disease accounts for approximately 40% of all deaths in most industrialized countries and is also responsible for significant morbidity and diminished quality of life. Furthermore, using data from more than 84,000 women who were monitored for 14 years, epidemiology researchers at Harvard University estimated that about 83% of cardiovascular disease could be decreased if everyone ate a reasonably healthy diet, exercised daily, did not smoke, maintained a normal weight, and drank 1 to 2 alcoholic beverages per day.[25] Although these five diet and lifestyle changes seem fairly simple, only 3.1% of the women in the study actually adopted them. Not only is compliance an issue, but epidemiologic studies raise deeper philosophical questions, because such studies assume that all participants are essentially similar to one another. Are the same therapies equally effective for all individuals? Do all individuals need the same quantities of these diet and lifestyle modifications? Can preventive genomic testing help us individualize our therapeutic protocols?

Let us begin by asking what proportions of carbohydrate, protein, and fat in the diet are the most effective in maintaining normal serum cholesterol levels. Is it a low-fat, low-cholesterol diet as touted by Nathan Pritikin and Dean Ornish? Or perhaps a 40-30-30 (40% carbohydrate, 30% protein, 30% fat), low-calorie "Zone" diet as proposed by Barry Sears? Or a low-carbohydrate, high-protein, high-fat diet such as that made popular by Robert Atkins? Logically they cannot all be the best diet for everyone, yet some people swear by each of them as the answer for an optimal diet.

There is mounting evidence that optimal macronutrient proportions in the diet may be a function of specific polymorphisms. Apolipoprotein-E (Apo-E) is a molecule that mediates the interaction of chylomicron remnants and intermediate-density lipoprotein particles with lipoprotein receptors, including the low-density lipoprotein (LDL) receptor and the chylomicron remnant or Apo-E receptor. There are three variations of the Apo-E gene, known as Apo-E2, -E3, and -E4, and these polymorphic variants are important genetic modifiers of serum lipid responses, which consequently may significantly affect an individual's risk for development of coronary artery disease. (Technically, each of these polymorphisms is a haplotype: two individual SNPs at different points in the Apo-E gene that are linked.) The E3/E3 genotype is the most common in all populations and serves as the benchmark genotype for comparison with any other possible genotype. The E4 allele is associated with a moderately increased risk of atherosclerosis and coronary artery disease (odds ratio [OR] = 1.53 for men and 1.99 for women in one study).[26] The E2 allele is associated with lower LDL cholesterol levels. LDL cholesterol levels declined with each Apo-E2 allele by 8.8 mg/dL in Hispanics, by 25.6 mg/dL in non-Hispanic white persons, and by 18.1 mg/dL in African-Americans.[27]

Given that each person inherits two alleles, there are six possible genotypes: E2/E2, E2/E3, E3/E3, E2/E4, E3/E4, and E4/E4. In patients with elevated serum total and LDL cholesterol, the cholesterol-lowering response to a low-fat, low-cholesterol diet increased as the sum of the allele numbers increased (in other words, response improved in the order that the genotypes are listed in the first sentence in this paragraph).[28,29] Conversely, individuals carrying an E4 allele who ate a high-fat diet were much more likely to have elevated serum cholesterol.[30]

In contrast, serum triglyceride levels were found to be significantly higher in men, and to a lesser extent in women who carried an E2 allele. Moreover, the triglyceride levels of individuals with an E2 allele showed a dose-dependent relationship to table sugar consumption, an association not shared with the other genetic variations.[31] Dietary sucrose consumption also increased very low-density lipoprotein (VLDL) cholesterol and triglycerides in Apo-E2 carriers. In contrast, E3/E3 individuals were found to have the lowest triglyceride levels, and E4 carriers to have intermediate levels.[32] In another multiethnic study, plasma triglyceride levels were inversely correlated with the number of Apo-E4 alleles (175, 159,

and 143 mg/dL with 0, 1, and 2 alleles, respectively).[33] Another study found E4 carriers to have elevations in triglycerides, but only those who consumed alcohol regularly.[34] A study of Turkish men who did not consume alcohol found no elevated triglyceride values in E4 carriers.[35] The most effective dietary therapy to lower triglycerides is restricting carbohydrate, especially sugar, consumption. Because Apo-E2 men are prone to significant triglyceride elevations and their levels are less sensitive to dietary fat intake, a lower carbohydrate, higher protein, higher fat diet may be therapeutically desirable for them.

Individuals with the E3/E3 genotype are moderately affected by dietary fat intake but tend to have lower triglyceride levels than the other genotypes. In one study, individuals with high cholesterol and triglyceride values were treated with a short-term (7-day) very low-calorie juice fast (208 calories/day), and their responses were stratified by Apo-E genotype.[36] Only E3/E3 individuals experienced significant improvement in all parameters, experiencing reductions in LDL cholesterol by 10% and in triglyceride values by 18%. In these individuals, it is tempting to speculate that the low-calorie, moderate 40-30-30 carbohydrate-protein-fat ratio "Zone" diet might be more effective in treating both hypercholesterolemia and hypertriglyceridemia, although no clinical trials to validate this hypothesis have yet been published. Also, in this trial, E2 carriers experienced a 31% drop in LDL levels but a 15% increase in triglyceride levels, lending some additional support for the carbohydrate-sensitive triglyceride hypothesis. E4 carriers had an opposite response to E2 carriers: a dramatic reduction of triglyceride levels by 49% but a rise in LDL levels by 13%, while eating only 200 calories/day.

Other dietary interventions that affected cholesterol levels were fiber and alcohol. High intake of soluble fiber (5.7 g/day) reduced LDL cholesterol by 6.6% and 5.6%, respectively, in E3 and E4 allele carriers but had little effect on E2 carriers.[37] Similarly, a study of Korean patients with coronary artery disease found that replacing white rice with whole grains produced the greatest benefit in E3/E3 individuals (12% reduction in triglyceride, 8% reduction in LDL cholesterol, and 8% increase in high-density lipoprotein [HDL] cholesterol levels), as well as moderate benefit in E4 carriers (including a 15% increase in HDL cholesterol values), but there was absolutely no effect on cholesterol levels in E2 carriers.[38] Thus, a high-fiber diet may be clinically most useful for E3/E3 individuals, modestly useful for E4 carriers, but not useful for E2 carriers.

The modest consumption (1 to 2 drinks) of alcohol daily has been shown epidemiologically to be extremely protective against coronary artery disease in the general population. However, Apo-E genotyping reveals that the benefits are not the same for everyone. In a comparison of nondrinkers with drinkers of alcohol, women who were drinkers had lower cholesterol (total and LDL) than women who did not drink, regardless of Apo-E genotype. In men, however, Apo-E2 carriers who were drinkers had lower cholesterol but Apo-E4 carriers had higher cholesterol, and alcohol consumption had no significant effect for Apo-E3/E3 individuals.[39]

It is worth observing that moderate exercise, although not dietary therapy, was found to be effective in improving serum lipids in E2 and E3 genotypes but not in E4 carriers.[40] In another study, high-intensity physical exercise was most effective in E4 carriers.[41] Thus, E2 and E3 carriers may benefit from modest daily exercise, but for an individual with an E4 allele to benefit from exercise, it must be high intensity.

Similarly, knowledge of Apo-E genotype may allow for a more discriminating and more effective use of targeted pharmaceuticals for patients with lipid abnormalities. Statin drugs exhibited a greater cholesterol-lowering effect in Apo-E2 carriers, followed by Apo-E3/E3, with less effectiveness for Apo-E4 carriers. Apo-E2 carriers also showed better response to gemfibrozil and cholestyramine than the other genotypes. The greatest cholesterol-lowering effects for Apo-E4 carriers came from probucol, a potent antioxidant.[26] However, although statins had a weaker cholesterol-lowering effect in Apo-E4 carriers, statins were most protective in preventing a second heart attack in men with an E4 allele. Statin use reduced the risk of a second heart attack in E4 carriers by 64% compared with only 33% for other genotypes, despite the fact that statins reduced LDL cholesterol levels least in Apo-E4 genotypes.[42]

TABLE 16-1 **Lipid-lowering Therapies Stratified According to Apolipoprotein-E (Apo-E) Genotype**

	Genotype*		
THERAPY	**E2/2 OR E2/E3**	**E3/E3**	**E4/E3 OR E4/E4**
Diet	Lower carbohydrate	Low-calorie, moderate-fat	Low-fat, no cholesterol Soluble fiber
Alcohol intake	Daily (women and men) (little effect for men)	Daily (women) None (men)	Daily (women)
Exercise	Moderate	Moderate	High-intensity
Pharmaceutical/ nutraceutical	Bile sequestrants Statins	Statins	Probucol Statins

*The E2/E4 genotype is extremely rare and therefore lacks statistical power in both association studies and prospective trials.

More prospective clinical trials are needed to fully elucidate the optimal therapeutic dietary interventions to protect against coronary artery disease in individuals based on their Apo-E genotype status. However, distinct patterns are beginning to emerge in terms of dietary and lifestyle management for the treatment of coronary artery disease; these are summarized in Table 16-1.

Apo-E polymorphisms are the best studied in terms of their association with atherosclerosis and coronary artery disease, but other polymorphisms exert similar effects. Cholesteryl ester transfer protein (CETP) is responsible for the transfer of insoluble cholesteryl esters from HDL to other lipoproteins.[43] The Taq1B polymorphisms of the CETP gene result in increased CETP levels, with impaired ability to remove cholesterol from the cells and the blood stream. The Taq1B polymorphism occurs with lower HDL cholesterol levels and an increased risk of development of atherosclerosis and coronary artery disease.[44,45] In one study, individuals who were homozygous for the Taq1B polymorphism had larger reductions in LDL and VLDL levels through eating a low-fat diet with a high ratio of polyunsaturated to saturated dietary fat.[46] Furthermore, daily moderate alcohol consumption raised HDL levels substantially, but only in individuals with the CETP polymorphism.[47,48]

E-selectin (SELE) is a glycoprotein molecule that adheres circulating neutrophils to the endothelial lining of blood vessels. E-selectin is expressed on the surface of endothelial cells after stimulation by inflammatory mediators (mediated by NF-κβ). Several polymorphisms in the SELE gene increase adhesion activity of E-selectin, dramatically increasing the risk of atherosclerosis and premature coronary artery disease.[49,50]

The primary therapeutic aim for carriers of a SELE polymorphism is to decrease NF-κβ stimulation, in turn reducing SELE expression. Maintaining high antioxidant potential has been shown to decrease NF-κβ activation.[51,52] Thus, higher levels of dietary antioxidants and possibly supplemental antioxidants may be beneficial. The proinflammatory cytokines tumor necrosis factor-α

and interleukin-1 also increase NF-κβ activation. Antioxidants, fish oil,[53] and milk thistle (silymarin) supplementation have each been shown to suppress interleukin-1 and tumor necrosis factor-α production directly and would therefore lower NF-κβ activation.

Electrolytes and Hypertension

Hypertension is an independent risk factor for coronary artery disease and for stroke. Therapeutic response to sodium restriction in hypertensive individuals is highly variable. A SNP in the angiotensinogen gene (AGT) allows an amino acid substitution in which threonine (T) replaces methionine (M) at amino acid 235. The T allele is associated with increased production of angiotensin, with a tendency for higher blood pressure. There is a stepwise increase of serum AGT from MM to MT to TT genotypes among persons with hypertension[54] and those with normal blood pressure.[55] Although there have been some discrepancies between studies, a meta-analysis of all studies published between 1992 and 1996 showed the 235T allele had a consistent, mild association with hypertension (OR = 1.20), a positive family history of hypertension (OR = 1.42), and more severe hypertension (OR = 1.34).[56]

The 235T allele of the AGT gene is associated with greater blood pressure decreases than the 235M allele after an intervention to reduce sodium intake (>5 mg/day).[57] Persons with the TT and MT genotypes showed significant systolic blood pressure reductions when consuming mineral salt compared with control subjects (P <0.02 and P <0.001, respectively), but persons with the MM genotype did not (P <0.10). The net adjusted systolic and diastolic blood pressure reduction was –8.6 mm Hg systolic/–3.9 mm Hg diastolic for persons with the TT genotype, –9.0/–5.2 mm Hg for those with the MT genotype, and –5.3/–1.0 mm Hg for the MM genotype.

Aerobic exercise was effective in reducing blood pressure but only in the MM (–3.7 mm Hg) and MT (–3.4 mm Hg) genotypes, and not in the TT (–0.4 mm Hg) individuals, among 477 previously sedentary white Americans.[58] Finally, the use of angiotensin-converting enzyme inhibitors produced more dramatic reductions in blood pressure in 235T allele carriers (TT and MT) than in the MM genotype,[59,60] illustrating the notion that diverse modifications in "environment" (diet, exercise, targeted pharmaceuticals) may produce similar alterations in phenotype (in this case, blood pressure) among genetically susceptible individuals.

Homocysteine and Micronutrients

As mentioned previously, one common physiologic effect of SNPs is a decreased binding affinity of a vitamin or mineral coenzyme for the structurally altered enzyme. There is mounting evidence that in most cases, the diminished rate of reaction of that polymorphic enzyme can increase with high-dose cofactor micronutrient supplementation.[61] Perhaps the best studied example of this model is the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR), which is responsible for re-methylating homocysteine into methionine, allowing methylation reactions to occur efficiently in the body. When methylation reactions are impaired, plasma homocysteine levels rise. Elevated homocysteine values have been associated with increased risk of atherosclerosis,[62] risk of early coronary artery disease,[63,64] increased risk of hemostasis and venous thrombosis,[65,66] decreased bone density,[67], neural tube defects, spina bifida,[68,69] and acute leukemia in adults.[70] The risk of heart disease increases for heterozygotes as well as 677T/T homozygotes.[71] Folic acid, vitamins B_2 (as flavin adenine dinucleotide [FAD]), B_6, and B_{12} are all cofactors in the methylation cycle, and a dietary deficiency of any of these vitamins can result in elevated homocysteine levels. However, elevated homocysteine levels can also result from two common polymorphisms in MTHFR: a 677C-T nucleotide substitution and a 1298A-C nucleotide substitution. Someone with a 677T/T genotype has a 50% reduction in MTHFR enzyme activity, whereas a 1298C/C genotype has a 32% reduction. In one study, approximately 28% of patients with elevated homocysteine did not respond to supplementation with folic acid, vitamin B_{12}, and vitamin B_6 because they had the 677T/T genotype and severely impaired MTHFR activity.[72] It is worth noting that the 677C-T polymorphism occurs in the FAD site of MTHFR, suggesting that vitamin B_2 supplementation may be a critical component.[73]

Three rational therapeutic strategies may help to resolve elevated homocysteine levels. First, high-dose supplementation of the vitamin cofactors of MTHFR, which relies on the simple logic of the law of mass action in chemical reaction: higher concentrations of substrates drive the chemical reaction forward. Second, the metabolic products of the MTHFR enzyme, namely 5-methyltetrahydrofolate, may be supplemented. Third, alternate re-methylation pathways may be stimulated, namely, by supplementing trimethylglycine or betaine as alternate methyl group donors. In practice, because of the low cost and high degree of safety associated with each of these options, all three strategies may be employed simultaneously. Regardless, serial plasma homocysteine measurements allow the practitioner to determine that the therapy employed has been successful.

Although the science of nutrigenomics is still in its infancy, several principles have become clear with enormous potential impact for clinical medicine. Nutrients act as dietary signals that alter gene expression (nutrigenomics). In individuals with specific polymorphisms, their specific genetic variation may render that individual more or less sensitive to specific nutrients or environmental stimuli and, therefore, may help determine optimal diet and lifestyle (nutrigenetics). Knowing the effects of these environmental stimuli on gene expression allows us to utilize this information proactively to alter gene expression and to mitigate risk for developing various forms of chronic disease, like cardiovascular disease. These principles of nutrigenomics and nutrigenetics hold true for macronutrient balance in the diet, as well as for micronutrients, such as vitamins, minerals, and electrolytes. Although our primary focus here has been on nutrient–gene interactions, the same principles hold true for lifestyle changes and targeted pharmaceuticals. Nutritional intervention is merely a more specific application of environmental modification to alter gene expression. What should be clear is that as our knowledge of gene–gene and gene–environment interactions increases, so too will our capacity for delivery of increasingly personalized and primary prevention.

GENOMIC TESTING

From Early Detection to Prevention

We use the term susceptibility gene to refer to a polymorphism that may render us more susceptible to development of a chronic disease when we are exposed to an adverse environment. Most susceptibility genes have a low positive predictive value (the probability that a disease will develop in a person with a positive test result) and a low attributable risk (the proportion of cases of a disease that can be attributed to a susceptibility gene).[74] Therefore, some researchers have questioned the clinical utility of susceptibility genetic testing,[75] but such arguments, by applying a single-gene/single-disease model to susceptibility genes, miss the potential

clinical relevance. Susceptibility genes, much like taking a family history, must be seen as important but incomplete contributors in what is invariably a multifactorial risk assessment. In terms of health outcomes, preventive genomic polymorphisms raise risk modestly and are additive in their effects (gene–gene interactions), and their actual phenotype expression is strongly affected by diet, lifestyle, and environment (gene–environment interactions). Rather than negate their clinical utility because of a low positive predictive value and a low attributable risk, these polymorphisms begin to offer a molecular basis for understanding the pathophysiology of complex multifactorial diseases, and an understanding of the environmental factors that affect gene expression begins to evoke effective therapeutic strategies.

Because environment is broadly understood to refer to anything outside the genome itself, therapeutic regimens may be constructed to include any portion of the environment that has been shown to affect gene expression and phenotype. This is truly a holistic approach because effective therapeutic strategies may involve diet, nutritional, and targeted pharmaceutical supplementation; lifestyle and behavioral modification; and avoidance or elimination of toxins, xenobiotics, and microbes. Intervention at any level of our "environment" may prove clinically beneficial.

Functional medicine is the clinical discipline designed to promote health, to anticipate and prevent disease, or to correct an existing disease by improving physiologic function. The underlying assumption is that health and disease lie on the same continuum, and the connecting thread of the continuum is physiologic function. Before the manifestation of any frank disease, a progressive loss of homeostasis and increasing dysfunction occur. Clinical intervention in this strategy may begin at the earliest signs of imbalance.[76] The promise of preventive genomics is that the point of effective intervention may begin even earlier, before the beginnings of physiologic dysfunction.

Clinical Challenges

Preventive and nutritional genomic testing in clinical practice has its critics, who predominantly argue that there are insufficient numbers of clinical trials to demonstrate the diagnostic and therapeutic efficacy of genomic profiles.[77] However, rather than demonstrating that all pregenomic testing is "premature and scientifically unsound," as suggested recently by Dr. Muin Khoury of the CDC,[78] such objections merely underscore the perspective shared here. Namely, it is precisely because chronic disease is multifactorial with complex gene–gene and gene–environment interactions that the diagnostic and therapeutic utility of preventive genomic testing must meet the four criteria of being relevant, prevalent, modifiable, and measurable. The last criterion, measurable, is critical at this early stage of preventive genomic testing. We must be able to measure beneficial phenotypic, physiologic changes in individuals that result from the therapeutic strategy employed. There will always remain a possibility that other genetic polymorphisms or other environmental influences that we have not yet identified may also affect an individual's disease risk.

A similar cautionary argument should be made in cases in which current genomic knowledge offers conflicting therapeutic advice. A man with an Apo-E4 allele presumably should not drink alcohol, but what if he also has a CETP Taq1B polymorphism for which alcohol has been shown to boost HDL cholesterol levels dramatically? At present, we do not know the answer to this clinical conundrum. Fortunately, because fractionated lipid levels are easily measurable, the effects of moderate, daily alcohol intake on such a specific individual's lipid profile may be easily ascertained. Thus, medicine must ultimately be empirical, relying on trial and error until the desired result (e.g., lower serum cholesterol) is achieved.

Bioethical Considerations: Opportunities and Potential for Discrimination

Genetic information, because it represents an unchangeable state, has the potential at least in theory to be used in a manner by insurers, employers, and society at large. However, it should be noted that the paradigm for such discrimination views genetic information as representing an individual's immutable limitations, as typified by single-gene diseases (e.g., Tay-Sachs disease, Huntington's disease, sickle cell anemia).

A fundamental cornerstone of preventive genomics is the idea that the phenotypic outcome of any unique genotype is modifiable through environmental change. Preventive genomic testing, rather than revealing an individual's genetic limitations, more accurately reflects an individual's genetic potential, given the right environment. Genetic polymorphisms have the potential to guide an individual to adopt appropriate dietary, lifestyle, and environmental changes that can optimize health and longevity.

Now that we know there are irrefutable connections between genes and environment, and we are learning their myriad effects on health and disease, ignorance is no longer ethically neutral. Choosing not to use genomic information in treating patients, now that its health implications are being effectively documented, is ethically untenable. For the first time in the history of medicine, preventive genomic testing allows us to assess individual risk for development of chronic diseases, to develop comprehensive risk reduction strategies before imbalances in homeostasis occur, and to institute optimal therapy interventions for patients who are already sick. This new personalized medicine, made possible by the advent of preventive genomics and nutrigenomics, offers practitioners and patients new opportunities for the prevention and treatment of disease and for the promotion of optimal health.



SUMMARY

Preventive genomic testing exploring both nutrigenomics and nutrigenetics is both new and exciting. It affords practitioners both novel and effective avenues to develop personalized therapeutic regimens and to promote optimal disease prevention strategies. Although what we know is dwarfed by what we do not know, this imbalance does not negate the current therapeutic power that the last 20 years of genomic research has revealed. We agree with the following assertions made recently by Loktionov[79]:

- There are many examples of effective research on gene–environmental interactions.
- There is sufficient evidence to make clinical recommendations on the basis of individualized genomic predisposition.
- There is a need for research on traits that protect from, as well as predispose to, disease.
- Environment modification, especially dietary changes, may be the easiest and most efficient way to influence the risks of many diseases common today.

It is little wonder that Paul Berg, the pioneering researcher in recombinant DNA and genetic engineering and the winner of the Nobel Prize for Chemistry in 1980, once quipped, "All disease is genetic even when it is also something else." However, it is equally true to say that all disease is environmental even when it is also genetic. The symphony between nature and nurture is the very essence of life and health for all creatures who call this Earth their home.

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CHAPTER 17

Hair Mineral Analysis

Steve Austin, ND and Nick Soloway, LMT, DC, LAc

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INTRODUCTION

Despite many research studies since the original publication of this chapter in 1985, there has been little change in the diagnostic value of hair analysis (HA). Outside its accepted use for diagnosis of heavy metal toxicity, at this time, HA still has only limited clinical application.

In recent years, several attempts have been made to standardize HA testing techniques,[1] but laboratories still do not have an agreement on procedures for handling a hair sample.[2-4]

Many conditions and diseases have been tested for abnormal HA patterns, and a number have been shown to have patterns differing significantly from the norm, including the following:

- Learning disabilities[5-7]
- Birth defects[8,9]
- Hyperactivity[10-12]
- Down syndrome[13,14]
- Neurosis and psychosis[15]
- Senile dementia[16]
- Autism[17]
- Alopecia areata[18]
- Insulin-dependent diabetes mellitus[19,20]
- Cystic fibrosis[21]
- β-Thalassemia[22]
- Spasticity in children[23]
- Repeated exposure to radiographs[24-26]
- Nasopharyngeal cancer[27,28]
- Aplastic anemia[29]
- Metabolic syndrome[30]
- Breast cancer[31]
- Bone mineral density[32]
- Type 2 diabetes[33]

HA has been used successfully to test for drug abuse,[34-41] and studies have been performed in several locations examining the validity of using HA to test drug use before the reinstatement of driving licenses.[42,43] However, drug metabolites are not found on most commercial HAs.

HA appears to offer potential as a correlating diagnostic tool in a few of the listed conditions, although hair mineral patterns should not be used exclusively for diagnosis. For example, the high hair sodium values in infants with cystic fibrosis show very little overlap with those in controls, and one study demonstrated that children with learning disabilities can be diagnosed with 98% accuracy because of a consistent pattern of high hair values of cadmium, manganese, and chromium in conjunction with low values of lithium and cobalt.[5] The usefulness of HA as a research tool can hardly be questioned. However, significant controversy exists about using the method for the clinical diagnosis of diseases other than heavy metal toxicity and as an indicator of nutritional status. Moreover, multiple studies question the inter- and intra-laboratory accuracy of HA.[44-48] The difference between research and clinical use is significant. Although it may be of interest in a research setting in which patients with various skin conditions have lower mean levels of hair magnesium than controls, the two groups overlap so much that the procedure is diagnostically useless.[18] Moreover, even when an altered HA pattern was associated with a

disease, generally there have been few investigations as to whether mineral supplementation would affect the clinical condition or even revert the hair mineral pattern to normal.

Wide overlap of values in disease and control groups is frequently the case with HA, resulting in excessive false-positives and false-negative results. For example, mentally retarded patients have been found to have lead, sodium, and potassium hair values approximately twice those of controls,[13] but the standard deviations are extremely large for some minerals (for sodium, 1644.71 ± 1814.93 versus 744.43 ± 1987.00[18]; and for potassium, 870.15 ± 1009.19 versus 408.35 ± 689.99), and the large overlap greatly reduces the clinical use of HA. In addition, many of the altered HA patterns associated with the diseases previously listed are as yet unconfirmed.

SPECIFIC MINERALS

Calcium and Magnesium

Hair calcium and magnesium values were found to be elevated in patients with fibromyalgia.[49] High hair calcium content has been associated with a reduced risk of coronary heart disease.[50] Low hair calcium content has been found in the last trimester of pregnancy,[51] but hair calcium content increased in response to supplementation during pregnancy.[52] Low hair magnesium levels have been reported in autistic children, children with attention deficit hyperactivity disorder, patients with various skin disorders, and patients with several types of leukemia, whereas high levels have been reported in conjunction with dyslexia and Prader-Willi syndrome.[12,17,18,53-55] The meaning of these associations remains unknown for the most part.

A 2001 study concluded that analysis of hair calcium and phosphorus content was of value as a complementary detection tool in abnormalities of bone metabolism.[56] Elevations in both calcium and magnesium were correlated with a low dietary calcium/magnesium ratio in one study, suggesting that this finding may be indicative of an induced hyperparathyroidism,[57] but that hypothesis remains unproven. Hair calcium and magnesium also vary in response to the hardness and pH of the water in which the hair is usually washed.[50] Supplementation of dietary magnesium has been reported to increase hair magnesium levels in deficient children.[58] Nonetheless, in one study of congenital hypomagnesemia, researchers concluded that hair magnesium level was not a useful tool in monitoring mineral status because the values were higher in affected subjects than in subjects who were not deficient.[59]

There is limited evidence to support the use of hair calcium and magnesium measurements in clinical diagnosis at this time.

Chromium

Hair chromium content is low in insulin-dependent diabetics,[20] although there is much overlap with normal persons. Chromium levels decrease with age,[22] but the meaning of this change remains unknown. Hair and tissue chromium levels vary greatly during pregnancy, being very high during the first few months of normal pregnancy and subsequently decreasing.[60,61] Late in pregnancy, hair chromium content typically becomes low,[62] suggesting deficiency.[34] However, high hair chromium value in pregnancy is associated with low birth weight infants.[63] In patients with gestational diabetes, hair chromium content is high early in pregnancy but decreases in late pregnancy.[61] Increasing dietary intake of chromium has been linked to increasing hair chromium values,[64] but supplemental chromium does not seem to alter hair levels.[60,65]

Although normal and deficiency ranges should be more clearly defined, hair chromium content appears to have potential future use in clinical settings. However, current knowledge remains inadequate to help clinicians treat patients on the basis of abnormal hair chromium levels.

Copper

Oral contraceptive use is associated with decreased hair copper and increased serum copper.[66] High hair copper levels are associated with being female, lactation, idiopathic scoliosis, and pregnancy in some, but not all, studies.[67-70] Surprisingly, conditions that affect systemic copper status have been shown not to affect hair levels. Copper deficiency,[71] Wilson's disease,[72,73] and cirrhosis[74] do not significantly alter hair copper content. Hair copper levels also vary with geographic location.[75] However, fur and liver copper values have been found to correlate in rats,[74] and one study reported that supplemental copper raises hair copper levels.[76] Hair color also has been found to influence the levels of copper in the hair.[70,77]

At this time, hair copper measurement appears unreliable for clinical application.[67]

Manganese

Levels of hair manganese in mothers of infants with congenital malformations and their offspring were significantly lower in one study,[8] which may allow maternal hair manganese levels to be used as an indicator of the risk for malformations. Both nonsignificantly altered[78] and normal levels of manganese[79] have been reported in patients with epilepsy.[78] Hair manganese values have been reported to be elevated in people with violent behavior, with varying levels of significance.[79,80] Evidence that manganese supplementation affects behavior does not appear to exist at present.

Hair manganese may serve as a useful research tool in the study of altered behavior, but the most promising value of hair manganese may lie in the prediction of congenital malformations.

Selenium

Levels of selenium in well water and hair show good correlation.[81] High hair selenium levels are seen in toxicity,[82,83] and low levels are seen in deficiency.[84] Low hair selenium values have been reported in babies with neural tube defects and their mothers,[9] as well as in patients with phenylketonuria.[85] Tissue selenium values reflect short-term variations in intake,[40] and hair levels of the element rise significantly after supplementation. [86-88]

As with chromium, insufficient data are now available to establish reliable norms for measurement of hair selenium values, and the incidence of false-positive and false-negative results remains unknown. Hair selenium measurement shows promise for clinical use when these problems are resolved.

Sodium and Potassium

It is generally accepted, even by proponents of HA, that hair sodium and potassium do not reflect dietary status. High elevations of hair sodium may be diagnostic in cystic fibrosis,[21] but require confirmation. A relatively low sodium/potassium ratio has been reported in celiac disease.[88] Although many HA advocates cite low hair sodium and potassium as indicative of "adrenal exhaustion," the only (preliminary) study exploring this subject reported that hair sodium and potassium did not correlate with

adrenal function.[89] Except for cystic fibrosis, hair sodium and potassium appear to hold little promise for clinical use.

Zinc

Hair zinc levels have received more research attention than any other mineral. Low hair zinc has been associated with zinc deficiency, anorexia nervosa, hyperactivity, gender, age, atherosclerosis, β-thalassemia, vegetarianism, lung cancer, leukemia, celiac disease, epilepsy in males, epilepsy in general, short stature in childhood, poverty, insulin-dependent diabetes mellitus, neural tube defects, and during pregnancy.* It also has been reported in neonates if the time between pregnancies is short.[108]

Because a few of these conditions have been associated with potential zinc deficiencies and supplemental zinc has been shown to increase hair zinc levels, practitioners who use HA often rely on hair zinc as an indicator of zinc status. However, one trial reported that hair zinc levels declined after supplementation.†

Other factors that affect hair zinc levels also interfere with the clinical use of this tool. Shampooing and dying affect hair zinc levels,[111] as does the sex of the subject,[111-115] age,[70] and hair growth rate. Malnourished children have shown both low[105,116,117] and high[118] hair zinc.

Poor correlations between hair zinc and height,[119] weight, and zinc consumption also have been reported,[76,112] although one study reported a correlation among hair zinc, weight, and zinc consumption.[119] Another study found that obese people of both sexes had higher hair zinc than those of normal weight and that there was a correlation between the degree of obesity and higher hair zinc levels.[120]

Although low hair zinc levels have been reported in patients with insulin-dependent diabetes mellitus,[109] generally there is considerable overlap between cases and controls. To further complicate the picture, in a study of female children of non–insulin-dependent diabetes mellitus parents, hair zinc was found to be significantly higher compared with women with no family history of non–insulin-dependent diabetes mellitus.[121]

At this time there is no definitive understanding of the meaning of abnormal hair zinc levels. The hypothesis that high hair zinc levels reflect acute deficiency, whereas low levels indicate chronic deficiency remains unproved.

Other Minerals

Hair iron was found to correlate positively with serum ferritin,[122] although the clinical relevance of this finding is unclear.[123] Hair lithium has been reported to show a linear response to extra-dietary sources.[7] Low hair levels of lithium have also been reported in conjunction with heart disease, learning disability, and violent behavior.[7] However, research findings are far from the point at which hair lithium could be used to help clinicians diagnose or treat these conditions.

DRUG ABUSE

HA has been used to detect drugs of abuse and their metabolites when urine tests were negative.[34,36] HA has been used as evidence in a court of law concerning past drug abuse.[35] Although there are concerns about the role of HA in testing for drug abuse,[124] HA does seem to be a valuable tool in drug screening.[37,38,49,50] As mentioned, drug metabolites, not mineral levels, are measured in these trials, and drug metabolites typically are not reported on most commercially available HAs.

RATIOS

The experimental documentation for most of the "ideal" ratios that have been published by several HA companies has not been found. The zinc/copper ratio has been reported to be altered in violent patients.[80] This ratio was also elevated in survivors of myocardial infarctions.[125] Strong correlations between several mineral ratios and atherosclerosis have also been reported[126]; however, the clinical significance of these ratios is not known. The magnesium/zinc ratios helped to separate healthy (less than 1:1) from epileptic (more than 1:1) subjects in one study.[99]

DISCUSSION

Hair mineral analysis is conceptually enticing and potentially a valuable clinical tool. However, problems abound with standardization of sampling, handling, and analysis of hair samples.[44,45] Additionally, reference values can differ widely,[127,128] and many variables affect the results (see Austin for a review)[129]:

- Gender[77]
- Age[77,130,131]
- Environment[132-134]
- Hair color[70,77]
- Cold waving
- Bleaching
- Exogenous contamination[50]
- Variations in mineral content within a given sample

This is further aggravated by the reporting of different results on the same sample from different laboratories.[45,48,135] The distribution of elements within the lipid and nonlipid portions of hair and the treatment of the sample before testing may explain these variances.[4,136] As noted, dietary intakes do not consistently correlate with hair levels, and hair color, sex, age, and other variables appear to significantly affect levels of some minerals. Separate norms for age, gender, and hair color are now being established.[70,131,137] However, reviews of the literature attempting to establish reference values continue to show a large variance in mean values, standard deviations, and ranges.[75,138] Additionally, there is no basis for the nutritional advice suggested by some laboratories.

As a result of the gulf between available information on the one hand, and the clinical interest by some practitioners on the other, several articles have appeared decrying the misuses of HA.[44,45,139-141] Hambidge[140] said, "There is a wide gulf between the limited and mainly tentative justification for their use on an individual basis and the current exploitation of multi-element chemical analysis of human hair."

Klevay and associates[142] acknowledge the experimental usefulness of HA but go on to say that, "its use in clinical medicine for diagnosis, prognosis, and therapy will remain limited until validation by the standard methods of clinical investigation is achieved." Steindel and Howanitz[141] concluded:

> *Physicians and other health care professionals who are considering ordering hair analysis to assess nutritional status or who are basing nutritional counseling or therapy on hair analysis should reconsider this approach unless and until the reliability of hair analysis value is established and evidence becomes available that clinical recommendations based on hair analysis improve patient outcomes.*

*References 11, 19, 22, 53, 90-108.

†References 52, 90, 91, 102, 109, 110.

Widespread use of speculative diagnostic procedures invites condemnation, especially when the burden of these speculations falls on the pocketbook and psyche of the patient. HA is a valid and useful screening tool for toxic metal exposure (lead, mercury, cadmium, arsenic, and selenium). It has the potential of becoming a clinical tool of considerable use in other areas. Current abuse and nonstandardization of laboratory procedures are more likely to hinder this development than to help it.

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CHAPTER 18

Heidelberg pH Capsule Gastric Analysis

Michael T. Murray, ND, and Stephen Barrie, ND

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INTRODUCTION

Proper digestion is a prerequisite for optimum health, and incomplete or disordered digestion can be a major contributor in the development of many diseases. The problem is not only that ingestion of the best nutritional substances may be of little benefit when breakdown and assimilation are inadequate, but also that incompletely digested macromolecules can be inappropriately absorbed into the systemic circulation. This process can lead to various immune complex deposition diseases and is now theorized to be an integral part of the etiology of food allergies.

Adequate gastric hydrogen chloride (HCl) is also necessary for protection of the gastrointestinal tract from ingested pathogens and for the maintenance of proper bowel flora. A healthy flora is known to be important for proper immune function, vitamin absorption, and the prevention of opportunistic infections such as *Candida albicans* in the gut.

The Heidelberg gastric analysis technique was developed to measure the hydrogen ion concentration (pH) of the digestive tract and determine the acid secretory ability of the parietal cells. Its use of radiotelemetry allows the gathering of this important information in a convenient and accurate manner.

The Heidelberg pH capsule system had its origin about 50 years ago at Heidelberg University in Germany. In research sponsored by Telefunken, a West German electronics firm, the inventor H.G. Noeller studied gastric acidity in 10,000 people. Since then, about 140 studies, according to a PubMed inquiry, have used the Heidelberg system to investigate various aspects of digestion.[1-7] Physicians and researchers now use this technique for measuring the pH of the digestive system.

PHYSIOLOGY OF DIGESTION IN THE STOMACH

The epithelium of the stomach contains many gastric glands. These tubular glands consist of parietal, chief, and mucous cells. The antral portion of the stomach produces the digestive hormone gastrin, the release of which is stimulated by the following:

- Vagal nerve stimulation
- The physical bulk of the ingested food distending the stomach
- Partially digested proteins

After gastrin is absorbed into the bloodstream, it is carried to the gastric glands, where it stimulates the parietal cells to produce HCl acid and, to a lesser extent, the chief cells to produce digestive enzymes (such as pepsin and intrinsic factor). With adequate stimulation, the parietal cells increase their production of HCl by as much as eightfold.

When the pH of the stomach reaches about 2, the gastrin mechanism becomes blocked and feedback causes the parietal cells to decrease production of HCl. This concentration of hydrogen ions (by a factor of 100,000) is an energy-dependent process.

Dietary protein is composed of amino acids held together by peptide linkages. Pepsin A, the major gastric protease, cleaves these in the stomach and is most active at pH values of between 2 and 3. It is inactive at a pH of 5 and above. Consequently, to have any significant digestive effect in the stomach, the gastric juices must be acidic.

Trypsin (a protein-splitting enzyme secreted by the pancreas) completes the process, yielding amino acids and dipeptides. The biochemical messenger that

stimulates this pancreatic secretion is the acidic bolus of food moving from the stomach into the duodenum.

PROCEDURE

Equipment

The Heidelberg system consists of the following equipment:

- Radiotelemetry capsule—a hard plastic capsule (about 2 cm long × 0.8 cm in diameter) that contains a miniature radio transmitter, a pH sensing device, and a saline-activated battery.
- Waistband antenna—receives the signal from the capsule and relays it to the receiver.
- Receiver/recorder—receives and translates the signal. The pH reading is displayed on a meter and recorded by a continuous printer for a permanent record. The receiver also contains a calibration probe used to calibrate each capsule with known pH 1 and 7 solutions.
- Heater block—maintains the calibrating solutions at 37° C.

Methods

The test can be conducted in two ways: the tethered capsule repeat challenge and the flow-through method. Each gives different information and has its advantages and disadvantages. For both procedures, the test begins after the patient has fasted (food and liquid) for 8 hours.

The Tethered Capsule Repeat Challenge

In this procedure, the capsule is tethered so that it remains in the stomach while the stomach is challenged by the ingestion of a saturated sodium bicarbonate solution (i.e., baking soda).[8] The challenge solution triggers a rise in stomach pH and a subsequent attempt by the parietal cells to reestablish appropriate acidity. The majority of people have a normal initial pH of between 1 and 2.3. Abnormalities of stomach secretions are usually found only after the stomach is challenged. (A more involved protocol can be found in Wright.[8])

The procedure is as follows:

1. The waistband antenna is fastened around the patient's waist and the receiver/recorder is turned on and calibrated.
2. The patient swallows the capsule, which is attached to a 1-meter long, thin cotton thread (a small amount of distilled water is allowed). The pH reading typically starts at 7 and falls toward 1. After about 5 minutes, the capsule reaches the bottom of the stomach (which normally displays a pH of between 1 and 2) and the remaining thread is taped to the cheek to prevent movement of the capsule out of the stomach and into the intestine.
3. If the fasting pH is normal, the patient swallows the first challenge of 5 mL of the alkaline solution. Within 30 seconds, the pH normally rises to 7 and the patient is asked to lie down on his or her left side (to keep the stomach contents in as long as possible).
4. If stomach function is normal and acid is secreted sufficiently in response to the alkali challenge, the pH returns to normal (between 1 and 2) within 20 minutes.
5. The challenge is repeated up to four times, as long as the response time is within 20 minutes.

Flow-Through Capsule

In this procedure, the capsule is not tethered to a thread and is allowed to move freely from the stomach into the duodenum and the rest of the small intestine. The proponents of this method claim that this allows measurement of the gastric emptying time and intestinal pH, both of which are important parameters.

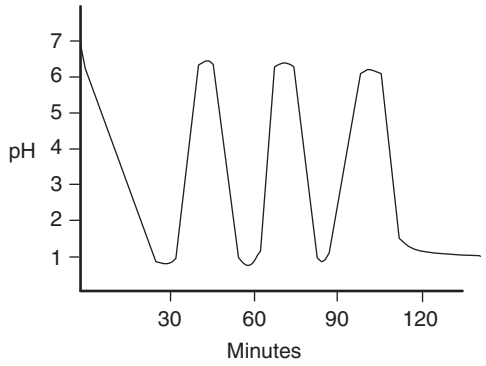


FIGURE 18-1 Normal Heidelberg gastrogram.

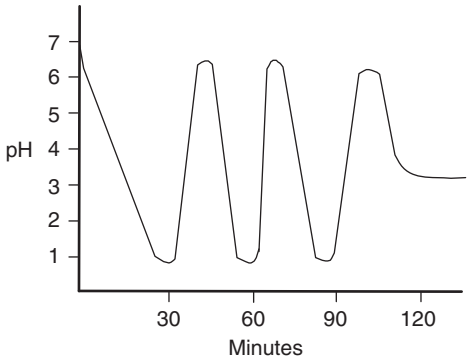


FIGURE 18-2 Hypochlorhydric gastrogram.

INTERPRETATION

Results may be classified as normal, hypochlorhydria, achlorhydria, and hyperchlorhydria.

Normal. The patient successfully reacidifies after four challenges (Figure 18-1). Curve number 1 shows the capsule entering the digestive tract; number 2 shows the capsule reaching the bottom of the stomach and alkaline challenge occurring; and number 3 shows a pH rise after swallow and subsequent reacidification within 20 minutes.

Hypochlorhydria. The patient requires more than 20 minutes to reacidify (Figure 18-2). Curve number 1 shows a pH of 1 being reached after 30 minutes. Note that on the third challenge, the pH comes back only to about 4.

Achlorhydria. The patient's stomach shows little acid secretion and is not able to secrete enough acid to bring the pH below 4, even on the first challenge (Figure 18-3). The pH remains at about 4.2 for almost 2 hours.

Hyperchlorhydria. The gastrogram shows extremely rapid reacidification (within 5 minutes) after each challenge.

Depending on specific curve components, some investigators believe that mucous quantity, fresh or chronic ulcers, and acute gastritis conditions can sometimes be identified.

CLINICAL APPLICATION

Although much is said about hyperacidity conditions, probably more significant health problems are caused by hypochlorhydria and achlorhydria. Direct measurement of gastric acid secretion

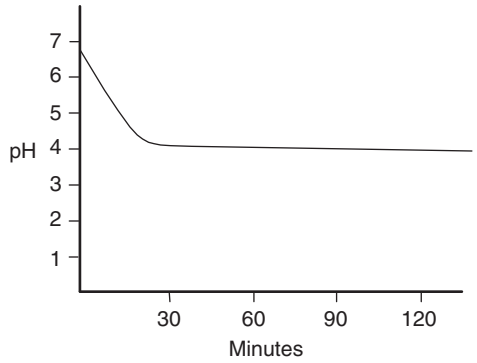


FIGURE 18-3 Achlorhydric gastrogram.

BOX 18-1 Common Symptoms of Low Gastric Acidity

- Bloating, belching, burning, and flatulence immediately after meals
- A sense of "fullness" after eating
- Indigestion, diarrhea, or constipation
- Multiple food allergies
- Nausea after taking supplements
- Itching around the rectum

Modified from Wright JV. Healing with nutrition. Emmaus, PA: Rodale Press, 1985.

through intubation and aspiration is uncomfortable and unacceptable to many patients. The Heidelberg pH capsule system offers a convenient and accurate outpatient testing system to clinicians interested in evaluating gastric function.

HCl, pepsin, and intrinsic factor are involved directly in digestion and contribute to the chemical changes in the intestines that assist in the absorption of many nutritional factors. For example, vitamin B_{12} absorption requires intrinsic factor, whereas zinc, calcium, and iron are poorly assimilated when gastric acidity is low.[9-11]

INDICATIONS

Many symptoms and signs suggest impaired acid secretory ability, and a number of specific diseases have been found to be associated with achlorhydria and hypochlorhydria (particularly human leukocyte antigen-B_8–related autoimmune diseases). These are listed in Boxes 18-1, 18-2, and 18-3.[12-23] It appears that the presence of *Helicobacter pylori* is a major factor in both achlorhydria and hypochlorhydria.[24,25]

Aging

Numerous studies have shown that acid secretory ability decreases with age. Low stomach acidity has been found in more than half of those older than age 60.[26,27] One study of the elderly found that their tissue nutrient levels could be saturated only through use of intramuscular supplementation; oral supplementation was ineffective. The authors speculated that this was due to atrophy of various digestive organs.[28]

BOX 18-2 Common Signs of Low Gastric Acidity

- Weak, peeling, and cracked fingernails
- Dilated capillaries in the cheeks and nose (in nonalcoholics)
- Postadolescent acne
- Iron deficiency
- Chronic intestinal parasites or abnormal flora
- Undigested food in stool
- Chronic candidal infections
- Upper digestive tract gassiness

Modified from Wright JV. Healing with nutrition. Emmaus, PA: Rodale Press, 1985.

BOX 18-3 Diseases Associated with Low Gastric Acidity

1. Addison disease
2. Asthma
3. Celiac disease
4. *Dermatitis herpetiformis*
5. Diabetes mellitus
6. Eczema
7. Gallbladder disease
8. Grave's disease
9. Chronic autoimmune disorders
10. Hepatitis
11. Human immunodeficiency virus/acquired immunodeficiency syndrome
12. Chronic hives
13. *Helicobacter pylori* infection
14. Lupus erythematosus
15. Myasthenia gravis
16. Osteoporosis
17. Pernicious anemia
18. Psoriasis
19. Rheumatoid arthritis
20. Rosacea
21. Sjögren's syndrome
22. Thyrotoxicosis
23. Hyperthyroidism and hypothyroidism
24. Vitiligo

Data from references 13-24.

CONCLUSION

The Heidelberg pH capsule system is an effective and convenient method to determine gastric acid secretory ability under conditions simulating ingestion of food. Results are extremely valuable in identifying the large number of people who have impaired secretion function. Ramifications of impaired acid secretion are widespread. This technology has become an accepted method of assessing gastric pH in several research settings.

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CHAPTER 19

Immune Function Assessment

Heather Zwickey, PhD

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ASSESSMENT OF THE IMMUNE SYSTEM

Background

Immune physiology involves complex interactions between cells and proteins to mediate an effective response to infectious disease. A healthy immune system eliminates pathogenic microbes while simultaneously creating a biodynamic relationship with normal microflora. Because the immune system must also effectively distinguish between dangerous foreign invaders and self-antigens, immune dysfunction can result in autoimmunity, cancer, allergies, and asthma, in addition to infection. Healthy immune function is affected by age, gender, sleep, nutrition, and exercise. Natural therapies such as herbs, meditation, hydrotherapy, and supplements can also enhance and manipulate immune reactions.

A variety of tests can be used to evaluate the immune system. To determine what type of immune assessment to use for each clinical diagnosis, it is important to understand how underlying immune physiology contributes to a clinical picture. Clinicians can assess qualitative or functional activity of immune cells. Qualitative data may include things like types, number, and activation states of cells. Cells of the immune system express different proteins on their surface. These proteins, called biomarkers, allow us to identify different cells as well as their activation state. To assess immunodeficiency and lymphoproliferative diseases, the number of T cells and B cells must be quantified. Functional activity of immune cells involves putting the cells into an in vitro assay system, adding antigen or mitogen, and measuring a function such as cytotoxicity, cytokine production, or antibody secretion. Levels of proteins that are produced by lymphocytes and monocytes, such as cytokines and antibodies, can be analyzed as well. Tests of genetic predisposition to disease can be evaluated with genetic tests. An overview of the assays used to measure cells is found in Table 19-1. A description of these tests is found in Box 19-1.

MEASUREMENT OF ANTIBODIES

Antibody (also called immunoglobulin) is a protein made by B cells in response to antigen. Each B cell has specificity for one antigen. This specificity is determined by gene rearrangement long before a B cell ever encounters antigen. The antibody is found both on the surface of B cells and is secreted. B cells are primarily found in the lymph nodes, Peyer's patches of the gut, and spleen (80%); however, antibody is readily detectable in the blood and other bodily fluids.

Antibodies look like the letter "Y". Each part of the antibody has a different function: the arms bind specifically to antigen, whereas the base (the Fc region) allows the antibody to bind to receptors. This base region is called the "isotype." Antibodies come in multiple isotypes based on the constant region of their heavy chain. These different isotypes have functional importance. Some isotypes are better than others at triggering the complement cascade. The Fc receptors of other isotypes allow them to activate specific cells, such as mast cells and eosinophils.

Antibodies are essential to measuring immune function because they can act both as an indicator of disease and as a tool to measure the levels of other proteins and cells. Monoclonal antibodies are a powerful tool (see Box 19-2).

Measuring serum antibody is essential in patients who have repeated or severe infections. Low antibody levels in these patients may indicate that they have an immunodeficiency. Patients with myelomas and lymphoproliferative disorders may

have high antibody levels. For example, patients with alcoholic liver disease often have a polyclonal expansion of immunoglobulin-A (IgA), whereas patients with systemic lupus erythematosus (SLE) and Sjögren's syndrome have polyclonal IgG expansion.[1]

The type of isotype made by B cells can provide clues as to immunologic status of the patient (see Table 19-2).

The route and duration of exposure, type of antigen, and genetic background may all affect the isotype of antibody that is produced, as well as the subclass of antibody produced. Upon immediate exposure to a novel infectious organism, the body produces IgM. After the B cell makes IgM, it class switches to another isotype, as determined by a combination of activation proteins and cytokines. If the patient has been exposed to an infectious agent, the antibody usually will class switch to IgG.

TABLE 19-1 **Overview of Assays to Measure Specific Immunity**

TYPE OF IMMUNITY	ASSAYS
Humoral immunity	Antibody production: ELISA, cytometric bead array
Cellular immunity	Cytokines: ELISA, ELISPOT, cytometric bead array, RIA, intracellular cytokine staining
	Cytotoxicity: 51 chromium release assay
	Proliferation: CFSE, lymphocyte proliferation assay
Genetics	SNPs genetic microarray

CFSE, carboxyfluorescein succinimidyl ester; ELISA, enzyme-linked immunosorbent assay; ELISPOT, enzyme-linked immunosorbent spot; RIA, radioimmunoassay; SNP, single nucleotide polymorphisms.

IgG is the major antibody found in blood, and it consists of four subclasses, originally described in the 1980s according to their abundance in serum. IgG1 and IgG2 are present in much higher concentrations than IgG3 and IgG4. All subclasses of IgG are low in pediatric populations. Deficiency in some IgG subclasses results in increased susceptibility to bacterial infections.[2] IgG subtypes vary in their ability to activate complement and Fc receptor binding. IgG3 has a strong affinity for Fc receptors and has the greatest ability to activate complement. The type of antigen can influence the subclass of antibody response. For example, IgG2 antibodies appear to influence polysaccharide antigens, whereas protein antigens and whole bacteria preferentially elicit IgG1.[3-5]

IgG4 antibodies, found at lowest concentration in the serum, are generated to repeatedly presented antigens. IgG4 deficient individuals may be more susceptible to pyogenic infections of the respiratory tract. Antibodies against dietary antigens are frequently IgG4. In a community survey of 40 individuals, anti-food antibodies to milk, egg, and fish of the IgG4 subclass were found in a significant proportion of a healthy population, indicating that IgG4 antibodies against food antigens cannot serve as markers of atopic disease. Because IgG4 cannot activate complement, it has been hypothesized that it may serve for protective clearance mechanisms and may be a desirable response to dietary antigens.[6] IgG1 and IgG2 have also been found for dietary antigens, but the immunologic outcome of these subclasses may be food intolerance that is not caused by IgE mediated hypersensitivity.[7] A larger discussion of the immune response to food can be found in Chapter 15.

Antibodies of each of the IgG subclasses can be detected by a variety of techniques, including radioactive iodine labeling, antigen

BOX 19-1 **Testing Methods**

ELISA

Enzyme-linked immunosorbent assay (ELISA) is an assay used to measure proteins of the immune system. In ELISA, an antigen is fixed to the surface of a 96-well plate, then a specific antibody is incubated with the antigen so that it forms an immunocomplex. This antibody is linked to an enzyme that allows the antigen to be converted into a detectable signal, most often a change in color. The more antigen that is present, the darker the color.

ELISPOT

A variation of the ELISA is the enzyme-linked immunosorbent assay (ELISPOT). Peripheral blood mononuclear cells (PBMCs) are plated on a filter-bottom 96-well plate coated with anticytokine antibody. The plate is cultured 24 to 48 hours to allow cytokine secretion and capture on the plate. Cells are washed off and detector antibody is added, followed by enzyme substrate. Cytokine-secreting cells are identified as spots of secreted cytokine.

Cytometric Bead Array

A cytometric bead array uses multiplexed beads labeled with capture antibodies for specific analytes, such as cytokines or other serum proteins. Serum is added together with Phycoerythrin (PE) PE-labeled detector antibody. The antibody–antigen complex is run through the flow cytometer, and software calculates the level of each analyte based on PE fluorescence of each bead population relative to a standard curve.

Intracelluar Cytokine Staining

This technique uses the flow cytometer to ensure production of cytokines in short-term stimulated whole blood or PBMCs before the cytokines are secreted from the cells. One advantage of this assay is that multiple cell surface and intracellular markers can be analyzed in combination using multiparameter flow cytometry.

Chromium-51 Release Assay

To test the ability of CD8 T cells or natural killers (NKs) to kill, target cells are incubated with radioactive isotope of chromium-51, which can be released when the cell dies. The CD8 T cells or NKs are then placed in serial dilution with the antigen presenting cells. Antigen is added in the case of the CD8 T cells. When the target cells are killed by the CD8s, the amount of radioactivity or enzyme can be analyzed.

Lymphocyte Proliferation Assay

Proliferation capability of T cells can be measured by isolating PBMCs, separating the T cells, and incubating with tritiated thymidine (^{3}H). A mitogen such as lipopolysaccharide is added to the cell culture. This mitogen may induce cell proliferation. As the cells divide, they incorporate the ^{3}H into the DNA, and analysis of radioactivity can determine how many cell divisions occurred. An ELISA may also be performed to measure cytokine production by the CD4 T cell.

Carboxyfluorescein succinimidyl ester

Carboxyfluorescein succinimidyl ester (CFSE) can be used to measure cell division. In this assay, the parent cell is incubated with CFSE, which is incorporated into DNA during cell division. As the cell divides, each of the daughter cells contains half of the CFSE stain. Every subsequent cell division halves the amount of CFSE in the daughter cells. When these cells are run through a flow cytometer, a characteristic pattern is seen (see Figure 19-2).

coated red cells, immunofluorescence with antigen coated sepharose, radioimmunoassay (RIA), and enzyme-linked immunosorbent assay (ELISA) with monoclonal antibodies (Figure 19-1).[8]

IgA can also be made to infectious agents and occurs in two forms, IgA1 and IgA2. IgA in serum predominantly exists in the monomeric form, IgA1. The ratio of IgA1:IgA2 in serum is about 9:1. IgA found in secretions, termed secretory IgA, occurs as dimers. The ratio of IgA1:IgA2 in secretions varies, but is approximately 6:4 in saliva.[9] Because IgA is found at mucosal surfaces and lines the mucosal surface of the gut, it is not uncommon to find IgA antibody specific for food antigens. Because IgA is at high levels in secretions, it can be found in saliva in addition to serum, and salivary IgA tests are readily available.[10,11]

An immune response to parasites, specifically worms, triggers an IgE response.[12] IgE elicits an immune response by binding to Fc receptors on mast cells, eosinophils, and basophils, causing degranulation and cytokine release. In atopic individuals, IgE is also made to allergens. IgE is at low levels in the blood. Measurement of total serum IgE is useful in patients in whom parasitic infection is suspected, but is not valuable for measuring allergies. Thus, the most common method for allergy testing is the skin prick test.[13] In this test, a small amount of the suspected allergen is placed on the skin. Then the skin is pricked so that the allergen goes under the skin's surface. If the patient is allergic to the allergen, swelling and redness will appear within 15 to 20 minutes.

Measuring total antibody in blood involves protein electrophoresis or ELISA, and is valuable. However, quantifying the total amount of antibody specific for an antigen is even more desirable. Antibody titers for common antigens, such as those found in vaccines, can be ordered. Each laboratory has its own reference levels for titers, because the sensitivity of the test is related to the specificity and affinity of the reagents they are using.

Specific antibodies, rather than total levels, are also measured for circulating autoantibodies. These antibodies can be detected with immunofluorescence, RIA, and ELISA.[14] Immunofluorescence involves examining the tissue directly with microscopy and is the least sensitive of these tests. The patient's tissue is frozen and sections cut on a cryostat. This tissue is incubated with patient serum, such that autoantibodies in the serum can bind. A fluorescently tagged secondary antibody specific for human immunoglobulin is then used to detect the autoantibodies. Immunofluorescence examination of biopsy specimens of damaged or normal tissue may reveal deposits of immunoglobulins caused by antibodies reacting with an organ or tissue specific antigens. This approach is especially important in the diagnosis of antiglomerular basement antibody disease and bullous skin disorders, but may show false positives when used for SLE. (See Table 19-3 for a listing of common autoantibodies.)

RIA is a far more sensitive test used for measuring antibodies that are in low concentrations. In RIA, an antibody specific for human antibody is tagged with a radioactive isotope. When this antibody is incubated with an autoantibody, the contact detects even low levels of autoantibody. ELISA is very similar to RIA; however, the enzymatic substrate is linked to the detection antibody.

BOX 19-2 Monoclonal Antibodies

One of the primary tools used in many of the assays for immune function is the monoclonal antibody. Monoclonal antibodies are the product of a single B cell. To generate a monoclonal antibody, an antigen is injected into an animal, and the resultant B cells are isolated. These B cells are diluted, and a single B cell is fused with a nonsecreting myeloma cell line to form hybrids. These hybrids then produce the monoclonal antibodies highly specific for the injected antigen. In contrast, when any animal is injected with an antigen, polyclonal antibodies are generated. Many different B cells specific for that antigen release antibody, which is harvested and purified. This collection of antibodies is called polyclonal because, unlike monoclonal antibodies, it has many specificities to the same antigen. Polyclonal and monoclonal antibodies can be tagged with enzymes for fluorescence to detect the original protein antigens for which they are specific.[1]

Many proteins have monoclonal antibodies specific for them, including cell surface markers, cytokines, and even other antibodies. The quality of the monoclonal antibody can determine the sensitivity and specificity of the test used.

TABLE 19-2 Antibody Function

ISOTYPE	SERUM LEVELS*	SUBCLASSES	FUNCTION/DESCRIPTION
IgM	0.5-2.0		Secreted during initial infection; Makes large antibody-antigen complexes.
IgD	Trace		Function unknown.
IgG			Coats microorganisms, making them more likely to be phagocytosed by macrophages, dendritic cells, and neutrophils; neutralizes toxins.
	5.0-12	IgG1	Responds to protein antigens.
	2.0-6.0	IgG2	Primarily responds to polysaccharide antigens; binds poorly to Fc receptors.
	0.5-1.0	IgG3	Responds to protein antigens.
	0.1-1.0	IgG4	Response to repeated antigenic exposure; binds poorly to Fc receptors.
IgE	Trace		Binds to Fc receptors on mast cells/eosinophils and basophils to elicit allergic response; also involved in response to parasites and worms.
IgA			Provides protection at mucosal surfaces
	0.5-3.0	IgA1	Monomeric form found in blood; can trigger inflammation through FcαR1.
	0-0.2	IgA2	Dimeric form found in secretions like tears, saliva, and breast milk.

Ig, immunoglobulin.
*Serum levels presented in grams per liter.

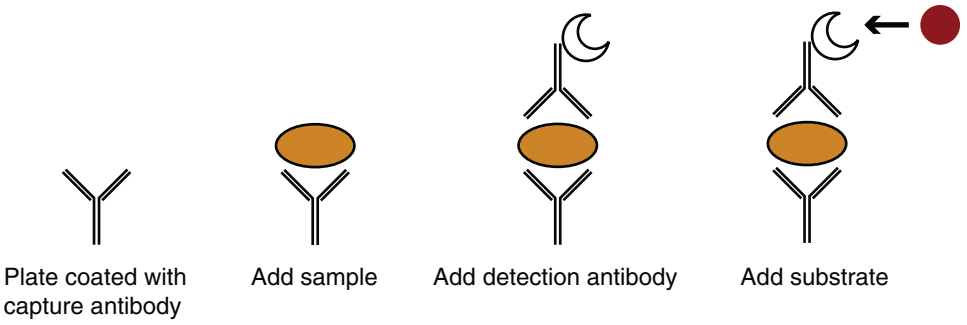


FIGURE 19-1 ELISA. A capture antibody specific for an antigen in a sample is attached to the bottom of a plate. The sample (blood, saliva, etc.) is added and excess sample is washed from the plate. A secondary antibody also specific for the antigen is added to the plate. This secondary antibody is labeled with an enzyme. When the substrate for the enzyme is added to the plate, it elicits a color change. The intensity of the color, as measured by spectrophotometry, indicates the amount of antigen that is present. Courtesy Heather Schiffke.

TABLE 19-3 **Common Autoantibodies**

AUTOANTIBODY	CLINICAL RELEVANCE
Antinuclear antibody	Systemic rheumatic diseases
Smooth-muscle antibody	Nonspecific liver damage; chronic hepatitis
Antimitochondrial antibody	Primary biliary cirrhosis
Endomysial antibody	Celiac disease; dermatitis; psoriasis
Antineutrophil cytoplasmic antibody	Vasculitis
Gastric parietal cell antibody	Pernicious anemia
Adrenal antibody	Idiopathic Addison's disease
Pancreatic islet cell antibody	Insulin-dependent diabetes mellitus
Skin antibodies	Pemphigus vulgaris; Bullous pemphigoid
Antiacetylcholine receptor	Myasthenia gravis
Antimyelin basic protein	Multiple sclerosis
Double-stranded DNA autoantibody	Systemic lupus erythmatosus
Thyroid stimulating hormone antibody	Graves' disease

Urine

When an antibody is made, the antibody light chains, κ and λ, are made in excess. These are present as free forms in serum and urine. Although small amounts of light chains are found in everyone, people with renal damage excrete higher levels of light chains in their urine. Free light chains are associated with malignant plasma dyscrasia and other lymphocyte-related immunoproliferative disorders. Intact immunoglobulin can also be found in urine.[15]

Cerebrospinal Fluid

IgG can be measured in the cerebrospinal fluid (CSF), which is important in autoimmune diseases such as multiple sclerosis.[16] Albumin can also be measured in CSF; however, albumin is not synthesized in the brain. Therefore, a comparison of IgG to albumin levels in CSF provides an indirect indication of how much IgG has been synthesized within the brain.[1]

MEASUREMENT OF COMPLEMENT AND HIGH-SENSITIVITY C-REACTIVE PROTEIN

Complement is a series of proteins that result in the destruction of microbes. Assays for complement can either be those that recognize individual complement components (such as ELISA for C3 or C4) or functional activity of complement, such as lysis. Measurement of C3 and C4 levels is sufficient, except for rare patients with genetic deficiencies, such as hereditary angioedema. Low levels of complement are more significant than high levels. For example, complement levels may be low in patients with glomerulonephritis or SLE.[17,18] However, the complement levels return to normal when patients are in remission.

High-Sensitivity C-Reactive Protein

C-reactive protein (CRP) is involved in the complement pathway. CRP functions by opsonizing bacteria, marking them for destruction by the complement cascade. Because it is readily detectable in the blood, CRP has become an important marker of inflammation. CRP is released early in infection (the first 4 to 24 hours) during the same window that many other components of inflammation are being activated. However, because it is far easier to measure than cytokines or other proteins, high levels of CRP are a more consistent marker of a recent infection.[19] Laboratories consistently offer a high-sensitivity test for CRP, called hs-CRP. This test is more sensitive than the original test for CRP, allowing detection of lower levels of CRP. Consistently high levels of hs-CRP may be diagnostic of chronic inflammation.

MEASUREMENT OF CELLS

Lymphocyte Subpopulations

T Cells

CD4T cells make cytokines that direct various arms of the immune system. CD8T cells kill infected cells. The proteins on the surface of T cells that allow them to be identified are listed in Table 19-4. To qualitatively identify T cells and separate them from other cell types, two proteins are used: CD3 and CD4 or CD8. CD3 is a signaling molecule associated with the T cell receptor and is on all T cells. CD4 and CD8 function to increase the interaction between the T cell and the antigen presenting cell. A sample of how T cells appear on a flow cytometry dot plot is in

TABLE 19-4 **Regulatory T Cells**

TYPE OF REGULATORY CELL	CYTOKINES MADE	ACTION	DEVELOPMENT OF
Treg cells (CD4+CD25+CD152+)*	TGF-β	Control overall autoimmune state?	Thymus
Type I NKT (cells) (NK cells that express a semi-invariant TCR)	Immunoregulatory Proinflammatory		Thymus
Tr1 cells (CD4+CD152+)	High IL-10 Moderate TGF-β and IFN-γ No IL-2 or IL-4	Suppress MS; suppress intestinal inflammation	Periphery systemic differentiate from Th0
Th3 cells (CD4+)	High TGFβ Low IL-4 and IL-10 No IFN-γ and IL-2	Oral tolerance	Periphery differentiate in intestinal mucosa
T suppressor cells (CD8+CD28-)	High IL-10	Suppress DC activation	Periphery

Adapted from Venken 2010.[21]
DC, dendritic cell; IFN, interferon; IL, interleukin; MS, multiple sclerosis; NK, natural killer; NKT, natural killer T cells; TCR, T cell receptor; TGF, tumor growth factor; Treg, regulatory T cells.
*Note: nTreg (natural Treg) and iTreg (inducible Treg)

BOX 19-3 **Sample Flow Cytometry Dot Plot**

Flow Cytometry

Flow cytometry is a technique for counting cells and other microscopic particles such as cytokines and proteins. Similar to microscopy, flow cytometry allows identification of cells based on their morphology and cell surface proteins; however, flow cytometry evaluates cell populations, rather than individual cells. Cells are incubated with monoclonal antibodies specific for certain proteins on their surface. Each antibody is tagged with a different color fluorochrome. The cells are then suspended in fluid and passed through the flow cytometer. Light from lasers in the flow cytometer passes through the cells, allowing detectors on the other side to read the light scatter from the cells based on their granularity and size. The detectors also evaluate the colors of the fluorescence associated with each individual cell. The resulting data are plotted using specialized software.

Box 19-3. In healthy individuals, the CD4/CD8 ratio should be approximately 2:1. This ratio may differ in some ethnic groups.[20] CD4/CD8 ratios can be used to evaluate disease progression patients with human immunodeficiency virus infection.

When a clinician approaches a patient with suspected immunodeficiency, he or she may decide to recommend a functional test. Immunodeficiency could be caused by a cell's inability to proliferate. In this case, a lymphocyte proliferation assay or a carboxyfluorescein succinimidyl ester (CFSE) assay would be completed.

CD4 T Helper Subsets

CD4 T cells secrete discrete patterns of cytokines. Each pattern is good for different types of immune responses. A single CD4 T cell specific for a single antigen can secrete any pattern of cytokines, but will be skewed toward secreting one pattern or another depending on the initial triggering infection. CD4 T helper subsets cannot be identified by surface markers. However, because CD4 T helper subsets secrete different patterns of cytokines, intracellular cytokine staining can discriminate between subsets.

The Th0 pattern is secreted by a naïve T cell, i.e., one that has not yet seen antigen. It is the cytokine pattern that is designed to simply keep T cells alive. Th0 cells secrete interleukin (IL-2).

The Th1 pattern is secreted by T cells exposed to bacterial or viral antigens. Overactivity of Th1 T cells has been linked to many autoimmune diseases. Th1 T cells secrete interferon-γ, as well as some other cytokines.

The Th2 pattern is secreted by T cells exposed to worms and parasites, but is also involved in allergy and asthma. Th2 T cells secrete IL-4, IL-5, and IL-13.

The Th3 pattern is secreted in response to food. Because the immune response to food should be relatively inert, Th3 cells are considered a type of regulatory T cell (Treg), and are involved in immunologic tolerance. Th3 T cells secrete tumor growth factor-β.

The Th17 pattern is secreted in response to molds and extracellular bacteria. This population of T cells has recently been linked to many autoimmune diseases. Th17 T cells secrete IL-17.

Regulatory T Cells

Tregs play a key role in maintaining tolerance. The loss of Tregs is associated with disease, especially autoimmune disease. Studies of Tregs have been limited largely because of their considerable diversity and lack of unique surface markers; the current state of the science is found in Table 19-4.[21] Much of the knowledge about Tregs is from mouse models. Human Tregs have been phenotypically identified as CD4+CD25+, CD4+CD25^{high}, or CD4+CD25+FoxP3+ cells, based upon how they stain and present in flow cytometry. CD39 is another protein on the surface of Tregs that may allow reliable identification.[22] Although most CD4 T cells express CD127, Tregs display lower surface expression of this marker.[23] Tregs behave similarly to other regulatory cells, such as Th3 cells found in the gut and Tr1 cells found in the periphery, but Tregs originate in the thymus and produce different cytokines upon stimulation than these other types of regulatory cells. Activation of Th1, Th2, and Tregs can be measured with expression of CD69.[24]

B Cells

B cells are identified by the surface markers CD19 and CD20 (see Table 19-5). In addition to being markers for B cells, CD20 is a marker of non-Hodgkin lymphoma and is a current drug target.[25] Monoclonal antibodies directed at CD19 are therapeutic targets in rheumatoid arthritis.[26] The products of B cells are antibodies and can be measured as described earlier in "Measurement of Antibodies".

Monocytes and Neutrophils

Neutrophils and monocytes act early in disease. Tethered to the blood muscle walls, neutrophils are some of the first cells to reach infectious agents. Monocytes can quickly extravasate into tissues, differentiating into macrophages and joining tissue macrophages already present at the site of infection. If monocytes and neutrophils are not functioning properly, severe infections can result. It

TABLE 19-5 **Cell Markers**

ANTIGEN	IDENTITY/FUNCTION
CD3	Present on all T cells
CD4	Present on T helper cells and some dendritic cells
CD8	Present on cytotoxic T lymphocytes
CD16/CD56	Combination identifies NK cells
CD19/CD20	B cell markers
Markers of T cell activation	
CD25	IL-2 receptor; serves as a marker for Treg cells
CD28	Activation marker on CD4 and CD8 T cells
CD38	Expressed on T cells after activation; function unknown
CD39	Acts on the nucleotide base responsible for enzymatic cleavage of ATP to AMP; marker for Tregs
CD45RA	Marker of a naïve/resting T cell
CD45RO	Marker of a recently activated T cell
CD69	Early activation marker for T cells, as well as B, NK, monocytes, and neutrophils[24]
CD71	Early activation marker for T cells
CD127	α-Chain of the IL-7 receptor; absence identifies Tregs

AMP, adenosine monophosphate; ATP, adenosine triphosphate; IL, interleukin; NK, natural killer; Treg, regulatory T cells.

TABLE 19-6 **Cytokine Patterns**

IMMUNOLOGICAL EVENT	NAME OF PATTERN	CYTOKINES
Inflammation	Proinflammatory	IL-1
		IL-6
		IL-8*
		TNF-α
T activation	Th1	IFN-γ
		IL-2
		TNF-α
		GM-CSF
	Th2	IL-4
		IL-5
		IL-10
		IL-13
	Th17	IL-17
T regulation	Th3	TGF-β
		IL-4
		IL-10
	Treg	TGF-β
	Tr1	IL-10
		TGF-β
		IFN-γ

GM-CSF, granulocyte macrophage colony stimulating factor; IFN, interferon; IL, interleukin; TGF, tumor growth factor; TNF, tumor necrosis factor; Treg, regulatory T cell.
*IL-8 is a chemokine.

is rare to find patients with low functioning monocytes, because the consequences can be extreme.

When patients have severe staphylococcal or fungal infections, neutrophil numbers should be evaluated, and function should be tested. Neutropenia is more common in neutrophil dysfunction. CD18 is a consistent and reliable marker for neutrophils and can be used as a marker for flow cytometry.[27] In healthy individuals, the neutrophil count normally exceeds 1.5×10^9/L. Mild neutropenia is usually asymptomatic, whereas moderate to severe reductions in numbers are associated with a progressive increase in the risk and severity of infections. Episodes of infection are likely to be life threatening when the neutrophil count falls below 0.5×10^9/L. Neutropenia is a frequent side effect of chemotherapy.[28]

Neutrophil function consists of adhesion, migration, chemotaxis, phagocytosis, and a respiratory burst. Defects in the respiratory burst can cause chronic granulomatosis disease. One simple method to evaluate neutrophil function involves a nitro blue tetrazolium test. In this test, neutrophils ingest and reduce a soluble yellow dye to an intracellular blue crystal. Neutrophils are separated and then stimulated with endotoxin (lipopolysaccharide) and the cells are viewed microscopically.

Neutrophils and monocytes can kill microbes with a respiratory burst. Another test of neutrophil function takes advantage of this activity. Neutrophils or monocytes are incubated with live microbes, such as *Staphylococcus aureus*. After the cells have phagocytosed the organisms, they are washed to remove extracellular organisms. The cells are then lysed, and the lysate is cultured on nutrient agar. Live bacteria will grow on the agar. The number of viable organisms inversely reflects the degree of intracellular killing.

Natural Killer Cells

When cells are infected with a virus or become cancerous, they often express less major histocompatibility complex on their surface. This makes them a target for natural killer (NK) cells. NKs express surface receptors that allow them to recognize the absence of major histocompatibility complex on a target cell and kill it. In addition to this mechanism, NK cells can be identified with CD56.[29] Like CD8 activity, NK function can be measured with a 51-chromium release assay (see Box 19-3).

CYTOKINES

Cytokines are immunomodulatory molecules that play an essential role in cell–cell communication and immune reactions. They are produced by most immune cell types, and many physical symptoms of immune dysfunction are triggered by cytokines. Cytokine expression has been studied extensively in autoimmune disorders, chronic inflammation, and other diseases. Cytokine expression is most accurate when measured locally at the tissue site; however, systemic cytokine levels can be detected in serum and saliva. Cytokines may contribute to disease progression and are thus potential targets for therapeutic intervention.[30,31]

Cytokine levels can be tested with ELISA or cytometric bead array. Because clinical testing for cytokines is relatively new, clinical cytokine testing is not as validated as other forms of testing. Furthermore, cytokine levels are affected by exercise, diet, sleep, age, and gender. Cytokines tend to be secreted in patterns (see Table 19-6). Because many natural therapies can modify cytokine expression, skilled clinicians can switch people from one pattern of cytokines to another.

GENETICS

The genetic control of immunity has long been recognized. Many autoimmune diseases map to specific genetic loci. Polymorphisms in the human leukocyte antigen have been linked to insulin-dependent diabetes mellitus, multiple sclerosis, and rheumatoid arthritis. Single nucleotide polymorphisms (SNPs) in cytokine

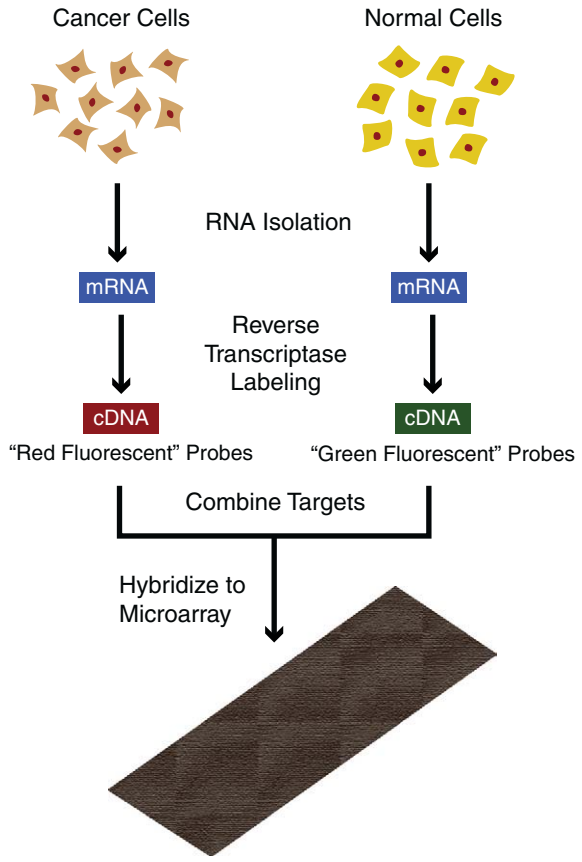


FIGURE 19-2 DNA Microarray. RNA is prepared from a collection of cells, normal and/or diseased. The RNA is translated into cDNA in vitro. The cDNA from each cell type is labeled with a different color of fluorescent dye. These cDNAs are then added to a chip or bead that has been previously hybridized with DNA probes. A computer analyzes the color of the DNA spots on the chip or bead. Relative difference in color indicates difference in gene expression between the two cell types. Courtesy Heather Schiffke.

and cytokine receptor genes are associated with the variability of immune response between individuals to infectious disease.[32] Some clinical laboratories now offer testing for SNPs. SNPs are detected using polymerase chain reaction (PCR).[33] Gene primer pairs for the candidate gene are used to amplify the DNA sequence of the patient's gene. The patient's gene is then sequenced and compared with a standard sequence.

Genetic microarray provides a second test for genetic variability and may allow clinicians to pinpoint genes that are key players in different diseases (see Figure 19-2). In addition to determining patterns of gene expression that contribute to complex disorders, microarray could elucidate gene interactions that lead to clinical symptoms or tell a physician whether a patient is responding to a therapy. Microarray involves isolating RNA from tissue, labeling it with fluorescent probe, and then comparing it with a standardized or control tissue by combining the RNA samples and hybridizing them to a chip. The color patterns are read by a computer. The expression of some genes (housekeeping genes) tends to be more stable and can act as a control. There are still several obstacles to overcome with genetic microarray technology, but clinical utility is likely.[34]

CLINICAL SYMPTOMS

It would be an oversight to exclude clinical symptoms as one of the primary ways that the immune system is evaluated. Clinical symptoms usually occur after an immune response is underway, but are often the first sign to the patient and physician that something may be amiss. Physicians recognized an immune response long before the first immune cells and proteins were discovered. The classic symptoms of inflammation: calor (heat), dolor (pain), rubor (redness), and tumor (swelling) were originally described and recorded by Aulus (Aurelius) Cornelius, a Roman physician and medical writer who lived from about 30 BC to 45 AD. These hallmarks of inflammation are caused by many complex interactions between cells and cytokines of the immune and nervous system and allow a clinician to make some assumption about immune processes without even drawing blood. For example, calor (heat) refers to fever. If a patient has a fever, a physician may assume that IL-1β is elevated. Table 19-7 illustrates which immune processes underlie the hallmarks of inflammation.

TABLE 19-7 **Hallmarks of Inflammation**

LATIN	ENGLISH	CYTOKINES AND CELLS INVOLVED
Calor	Heat	IL-1β, IL-6 act at the hippocampus, causing the body to increase blood flow, resulting in heat.
Dolor	Pain	TNF-α and IL-1β lead to localized edema that nerve endings sense as pain.
Rubor	Redness	TNF-α and IL-1β cause vasodilation and increased blood flow.
Tumor	Swelling	TNF-α and IL-1β cause increased permeability of the capillaries.

IL, interleukin; TNF, tumor necrosis factor.

Sickness Behavior

Proinflammatory cytokines act in the brain to induce nonspecific symptoms of infection. In addition to triggering fever, cytokines elicit profound psychological and behavioral changes. Sick individuals experience several symptoms, including malaise, fatigue, weakness, an inability to concentrate, and listlessness. They become sleepy (hypersomnia) and experience depressed activity and a desire to be isolated. These infection-induced changes are referred to as "sickness behavior."[35] Sickness behaviors have a variety of advantages to both the sick individual and the population at large. Malaise, fatigue, and listlessness cause a person to rest, and thus conserve energy. Rest further aids the body by decreasing heat loss, whereas shivering increases heat production. Social isolation may help prevent spread of the infection to others.[36]

Most sickness behaviors are caused by cytokines, and may help an observant clinician make a diagnosis. For example, fatigue and malaise are most commonly triggered by IL-1β. Interestingly, in some people, tumor necrosis factor-α and IL-6 may cause anger or hostility, and this emotional response leads to the social isolation.[37]

SUMMARY

Choosing appropriate immunologic tests requires physiologic, economical, and ethical considerations. To choose the right test for the patient, the reliability of the tests as well as their specificity and sensitivity must be considered. Assessing the immune system is further complicated by its sensitivity to the environment. Thus, running tests in duplicate or triplicate may be necessary to validate results.

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CHAPTER 20

Intestinal Permeability Assessment

Corene Humphreys, BHSc, ND, DipMedHerb, DipHom

INTRODUCTION

The small intestine is a multifaceted organ, playing a major role in digestive and absorptive processes as well as acting as a barrier against harmful macromolecules. However, when this absorptive capacity or barrier function is compromised, the health of an individual may be adversely affected. Pathologic changes in permeability of the intestinal mucosa have been identified in a number of local and systemic disease conditions. This chapter focuses on clinical consequences that may result from a breach of gut mucosal integrity and how they relate to specific disease states. It also outlines the use of noninvasive testing to identify intestinal permeability and summarizes therapeutic options to restore mucosal integrity.

GUT MUCOSAL INTEGRITY: MECHANISMS OF DISRUPTION

A key function of healthy gut mucosa is to prevent bacteria and their endotoxins from reaching portal circulation. For this purpose, a natural physiologic barrier is formed by the mucous layer, the epithelial cells and apical junctional complex, and the lamina propria (Figure 20-1, *A*). When one or more of these components is impaired, damage to the intestinal barrier may result, allowing luminal toxins to translocate from the gut into the systemic circulation.[1,2]

The small intestine consists of specific intrinsic factors that help protect the host from environmental pathogens. These are the enterocytes as well as the paracellular spaces composed of structures called tight junctions, adherens junctions, and desmosomes (Figure 20-1, *B*). The tight junctions surround the upper portion of the lateral surfaces and the adjacent epithelial cells to create fusion points. This creates distinct fluid compartments that maintain cellular polarity and regulate the passive transepithelial movement of molecules.[3]

The tight junction zonula occludins (ZO1) is located just below the base of the microvilli and acts as the primary permeability barrier between the external and internal milieus of the body.[2] Transmembrane proteins that form part of the tight junction include the claudins and occludin families. Claudins proteins act as sealing proteins, forming ion-selective pores within the tight junction strands, whereas occludin proteins are thought to have adhesive and transducing properties. Both claudins and occludin interact with cytosolic complexes such as actin and myosin, which serve as contractile elements to open and close the paracellular junctions.[4] Transmembrane proteins can be affected by cytokines, and minor defects in the paracellular pathway can set up a vicious cycle, whereby antigen presenting cells (e.g., dendritic cells) stimulate the production of Th-1 cells that increase the production of tumor necrosis factor-γ (TNF-γ) and interferon-γ (IFN-γ) and further increase tight junction permeability.[3]

The immune system of the gastrointestinal tract also helps prevent the translocation of harmful molecules across the gut mucosa. Gut associated lymphoid tissue comprises approximately 25% of the mucosal mass of the intestine. It is considered the body's largest immune organ, containing 40% of its immune effector cells.

Gut immunity consists of two distinct mucosal defense mechanisms: the specific system and the nonspecific system. The specific system is composed of secretory immunoglobulin-A (sIgA). The nonspecific system comprises gastric acidity, motility, mucus, digestive enzymes, normal bacterial flora, and bacterial antagonism.

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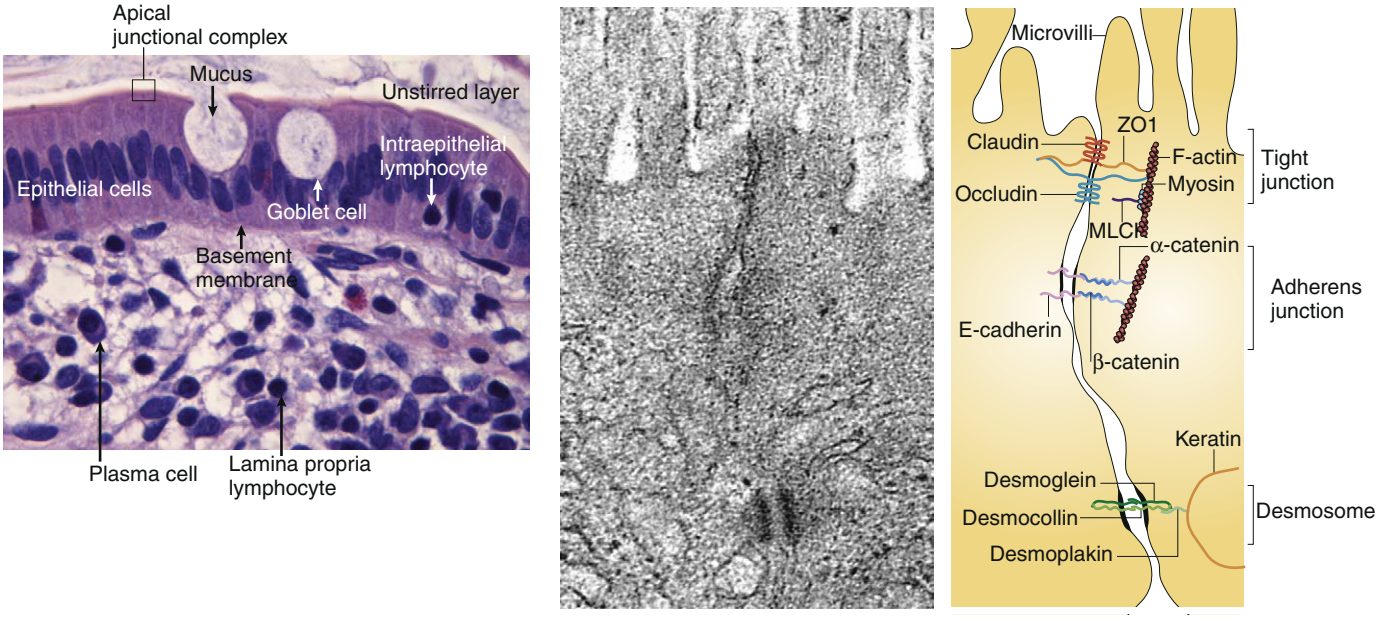


FIGURE 20-1 Anatomy of mucosal barriers. (Reprinted by permission from Macmillan Publishers Ltd. From Turner J. Intestinal mucosal barrier function in health and disease. Nature Rev Immunol 2009:9:799-809. http://www.nature.com/nri.)

Disruptions in gut barrier function may result from impaired host immunity, alterations in gut flora, or direct mucosal injury.[5]

Ordinarily, normal gut microflora provides "resistance to colonization," preventing the adherence of pathogenic organisms to the intestinal wall and their subsequent translocation.[6] Changes in gut ecology, however, can reduce this natural resistance and encourage the colonization of potentially harmful bacterial species.

Bacteria and the toxins they produce can alter membrane integrity through various mechanisms. Bacteria can secrete enzymes, such as elastase and protease, which hydrolyze the epithelial membrane and cause cells to detach from the epithelial sheet. Bacterial toxins may act on or within membranes and compromise tight junction integrity by binding to membrane receptors. Some toxins can traverse the cell membrane and inhibit cellular growth by altering protein synthesis. They may also alter membrane lipid composition, act as detergents, or form transmembrane pores. The net effect is cellular swelling, lysis, loss of intracellular constituents, and uncontrolled influx of toxic substances.[7]

Bacterial endotoxins and cytokines have been shown to impair barrier function by activating inducible nitric oxide synthase. Upregulation of this enzyme increases the amount of nitric oxide. Prolonged exposure of the cells to nitric oxide is thought to inhibit cellular respiration, decrease mesenteric blood flow, and alter intestinal permeability.[8]

Clinical Applications

Because the intestinal mucosa plays a pivotal role in immune defense and nutrient absorption, a wide variety of diseases and conditions are associated with abnormal bowel permeability (Box 20-1). Abnormal permeability is often identified through assessment of the relative rate at which two nondigestible sugars, lactulose and mannitol, permeate the intestinal mucosa. A higher lactulose-to-mannitol (L/M) ratio indicates increased gut permeability (see section on "Measuring Intestinal Permeability" on page x).

BOX 20-1 Conditions Associated with Abnormal Bowel Permeability

- Inflammatory bowel disease
- Celiac disease
- Type 1 diabetes
- Inflammatory joint disease
- Rheumatoid arthritis
- Ankylosing spondylitis
- Reiter syndrome
- Food allergies
- Alcoholism

Inflammatory Bowel Disease

To date, it is not certain if the altered intestinal permeability seen in patients with Crohn's disease is a consequence or a cause of the disease.[9] Recent research by Takeuchi et al[10] favored the notion that increased gut permeability is secondary to intestinal inflammation. In assessing healthy, first-degree relatives of patients with Crohn's disease, they found a 50% prevalence of subclinical inflammation as evidenced by an increase in fecal calprotectin (a protein marker that reflects white blood cell infiltration into the gut lumen). Expanding this data, Meddings[11] proposed a model for the development of inflammatory bowel disease (IBD) that necessitates the presence of at least three conditions: (1) an abnormal immune system that interacts inappropriately with environmental antigens, (2) the presence of an antigenic agent, and (3) a breach in gut barrier function that allows the antigen to reach the immune system.[11]

Measuring intestinal permeability in asymptomatic patients with Crohn's disease can help monitor progress and predict disease relapse. A normal lactulose recovery and L/M ratio is associated with good short-term (6 to 12 months) prognosis, whereas

increased intestinal permeability is indicative of a relapse within 6 months.[10]

Celiac Disease

Gut barrier function is altered in nearly all patients with untreated celiac disease. Intestinal permeability testing is therefore an ideal noninvasive screening test, offering a sensitivity of 89%, a specificity of 54%, and negative predictive value of 95% compared with jejunal biopsy.[12] Although jejunal biopsy is considered the gold standard for identifying celiac disease, this test is time-consuming, unpleasant, and costly, making it unsuitable as a screening tool for the general population.[13] An elevated L/M ratio helps identify which patients should undergo jejunal biopsy when clinical features are compatible with celiac disease. It can also help determine the timing of follow-up biopsy and monitor the recovery of the mucosa.[14] Impaired permeability tends to normalize within 5 months when patients strictly adhere to a gluten-free diet. Serial intestinal permeability testing can also be used to monitor dietary compliance in these patients.[12]

Diabetes

An emerging body of evidence suggests altered gut barrier function may be an etiologic factor in the pathogenesis of type 1 diabetes.[4,15-17] Bosi et al[18] assessed intestinal permeability in 81 subjects with islet cell autoimmunity, 18 of whom were in the preclinical phase, 28 with newly diagnosed type 1 diabetes, and 35 with a long-term history of the disease. The researchers found an elevation in lactulose and the L/M ratio across all groups, with the highest levels reported in the preclinical group. These results suggest that increased permeability tracks the course of the autoimmune process and precedes the clinical onset of type 1 diabetes.

Alterations in gut permeability in type 1 diabetics are thought to arise from luminal antigens, such as bovine insulin from cow's milk, gliadin from wheat, enteral viruses (e.g., enteroviruses and rotavirus), and/or disturbed microbiota. The increased antigenic load appears to activate T cells in both the small intestine and the pancreatic lymph nodes, causing β-cell damage through autoimmunity and Th-1 cytokine upregulation.[19] Type 2 diabetes does not appear to be associated with primary changes in the intestinal mucosal epithelium.[20]

Inflammatory Joint Diseases

Numerous studies have shown a correlation between different types of arthritides and increased intestinal permeability.[21,22] It is estimated that between 30% and 60% of such patients have occult intestinal inflammation.[23] To date, however, it has not been fully determined whether this correlation results from the disease process itself or is due to mucosal damage caused by treatment with nonsteroidal anti-inflammatory drugs (NSAIDs).[24-27]

Evidence for a primary cause of intestinal barrier dysfunction may be related to gut microbial infections. Specific pathogenic organisms (*Campylobacter*, *Klebsiella*, *Proteus*, *Shigella*, *Salmonella,* and *Yersinia*) have been found in patients with various arthritides who have altered intestinal permeability.[28-31] It has been postulated that gut bacterial antigens, when absorbed by the intestinal mucosa, elicit an immune response, with tissue damage occurring from molecular mimicry.[32] Measuring intestinal permeability before and after NSAID therapy in patients with inflammatory joint disease helps establish whether mucosal disruption is solely an iatrogenic response.

Food Allergies

The mucosal surface of the small intestine is the largest surface area in the body that comes into direct contact with the external environment and is estimated to be more than 200 m^2.[33] The advantage of such a vast internal surface area is that dietary nutrients can be rapidly absorbed.[34] When there is a breach of gut barrier function, dietary antigens and other luminal toxins can also be translocated across the intestinal wall. Recent research suggests that environmental factors, such as infection or stress, increase gut permeability, which in susceptible individuals can contribute to food allergies.[17]

For food allergies to manifest, intraluminal antigens must first penetrate the intestinal epithelial barrier before gaining access to mast cells in the subepithelial compartment and triggering hypersensitivity reactions. This pattern has been observed in children with atopic eczema associated with cow's milk allergy.[33] Under normal conditions, most dietary proteins are digested by gastric and pancreatic proteases and brush-border enzymes and transformed into peptides and amino acids before being absorbed by the enterocytes.[17,35] In healthy individuals, a small amount of intact proteins in the gut are taken up by enterocytes and broken down inside lysosomal compartments, which prevents undigested proteins from entering the subepithelial compartment.[35,36] In atopic individuals, CD23 (the low affinity receptor located on the apical membrane of the epithelial cell) is overexpressed, which leads to the protected transfer of IgE/allergen complexes and transepithelial passage of intact allergens.

Repeated exposure to IgE-mediated antigens places significant demands on the gut mucosa and further increases intestinal permeability, setting up a self-perpetuating cycle that maintains the allergenic state.[33,36] In addition to IgE production, the sensitization phase of allergy involves the upregulation of Th-2 cytokines (interleukin-4 [IL-4], IL-5, and IL-13).[35] In the animal model, increased production of IL-4 was found to upregulate CD23 expression. This finding may in part explain the role of IL-4 in enhancing intestinal permeability.[36]

Given the recent scientific findings, a multifactorial approach to food allergy management has been proposed; it includes allergen elimination as well as reducing inflammatory reactions and stabilizing the gut mucosal barrier.[33]

Alcoholism

Alcohol consumption can lead to pronounced changes in the ultrastructure of the epithelial layer in the small intestine. In a recent paper by Cariello et al,[37] intestinal permeability was increased in 15% to 35% of patients without cirrhosis, suggesting that altered gut permeability may be a pathogenic cofactor in the progression of chronic liver disease. A breach in gut barrier function allows gram-negative bacterial endotoxins to enter systemic circulation, contributing to the onset of portal hypertension and proinflammatory cytokine production with resultant liver damage.[38]

Factors Affecting Intestinal Permeability

A variety of treatments and conditions may impair mucosal integrity and trigger changes in intestinal permeability (Box 20-2). More recently, it was also proposed that genetic alterations in tight junction proteins might also be a precipitating factor in altered gut barrier function.[15]

BOX 20-2 Causes of Changes in Permeability

Intestinal infection
Nonsteroidal anti-inflammatory drugs
Nutritional depletion
Trauma
Chemotherapy

BOX 20-3 Gastrointestinal Infections Associated with Increased Gut Permeability

Bacterial Infections
Clostridium perfringens
Clostridium difficile
Escherichia coli
Helicobacter pylori
Vibrio cholerae

Viral Infections
Enteroviruses
Rotavirus

Parasitic Infections
Blastocystis hominis
Entamoeba histolytica
Giardia lamblia

Intestinal Infections

A number of bacterial organisms are known to interfere with the integrity of the tight junctions (Box 20-3). Exposure of the intestinal epithelia to these organisms is associated with a reduction in transepithelial resistance and disarray in the patterns of the transmembranous junctional proteins (claudins and occludin) and intracellular ZO1.[39]

Rotavirus is the most common cause of diarrhea in children and is associated with an increase in gut permeability. Repeated rotaviral infections during infancy may also increase the risk of allergy and atopy later on in life.[36]

Changes in intestinal permeability have been observed in patients with protozoan infections, specifically those caused by *Entamoeba histolytica*,[39] *Giardia lamblia,*[40] and *Blastocystis hominis*.[41] Protozoa conventionally classified as nonpathogens (e.g., *Entamoeba coli*) do not appear to alter intestinal permeability.[41]

A shift in the L/M ratio was also observed in patients with small intestinal bacterial overgrowth. Riordan et al[42] found an increase in intestinal permeability associated with an overgrowth of colonic-type bacteria, specifically *Enterobacteriaceae*, within the small intestine.

Nonsteroidal Antiinflammatory Drugs

NSAIDs are the most commonly prescribed antirheumatic drugs, and NSAID enteropathy is estimated to occur in 65% of long-term users. Even short-term NSAID therapy has been shown to cause changes in intestinal permeability similar to those seen in patients with active IBD.[43]

Ingestion of NSAIDs initially damages the enterocytes and increases intestinal permeability. The damaged mucosa is then exposed to endogenous substances, such as bile acids, bacterial products, and hydrolytic and proteolytic enzymes, which generate a chemotactic neutrophilic response. Secondary damage with subsequent bleeding and protein loss associated with NSAID enteropathy only occurs when a neutrophil chemoattractant gains access to the mucosa.[44]

Initially it was thought that cyclooxygenase-1 (COX-1) selective agents were mainly implicated in NSAID enteropathy; however, recent research suggested that long-term use of COX-2 inhibitors could lead to severe small bowel damage. It is thought that COX-2 inhibition may set up a proinflammatory immune reaction in the small intestine with subsequent mucosal damage.[44]

Nutritional Depletion

Parenteral nutrition and enteral starvation in humans have been shown to raise intestinal permeability and reduce villous height. These effects may be associated with reduced concentrations of the amino acid glutamine in the intestinal mucosa.[1]

Trauma

Patients undergoing major surgery or experiencing sustained severe trauma are more likely to have an intense systemic inflammatory response that may be followed by organ dysfunction and multiple organ failure.[45] However, patients that experience such complications often show no evidence of uncontrolled sepsis. For this reason, it has been postulated that altered paracellular permeability secondary to mucosal damage in the gut may be the etiologic factor.[46] In this theory, greater permeability results in bacterial translocation and penetration of the gut wall by intraluminal toxins, thereby initiating the secondary systemic inflammatory response.

Chemotherapy

Like hemopoietic cells, enterocytes are rapidly dividing cells that are sensitive to the effects of chemotherapeutic agents. Pledger et al[47] demonstrated a significant reduction in the absorption of mannitol and an increased L/M ratio in children treated for solid tumors. A study by Fazeny-Dorner et al[48] found an acute, transient elevation in intestinal permeability after initiation of drug therapy, with permeability returning to normal in all patients 2 weeks after chemotherapy treatment.

This toxicity to the gastrointestinal tract is an important factor that generally limits the dose of antineoplastic medication a person can receive. For this reason, monitoring intestinal permeability in patients with cancer can be a valuable means of determining the optimal timing and dosage of their medication.[49]

MEASURING INTESTINAL PERMEABILITY

Altered intestinal permeability or "leaky gut" can be assessed with a challenge test that measures the recovery of two nonmetabolized sugars: lactulose and mannitol. The different molecular weights of these sugars enable assessment of both transcellular and paracellular absorption.

Mannitol is a small molecule (molecular weight [MW] 182) that is thought to traverse the epithelium via water-filled pores in the lipid membrane of the enterocyte. Lactulose is a larger molecule (MW 342) that passes through the intestinal epithelium via the paracellular route. Diseases and treatments that alter the membrane composition and affect the tight junctions between the cells increase transport via the paracellular route.[12]

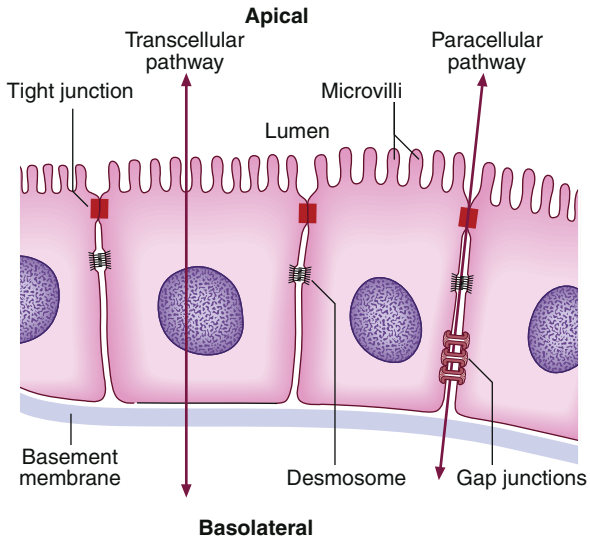


FIGURE 20-2 A sheet of epithelial cells. (From Naish J, Revest P, Court DS. Medical sciences. Edinburgh: Saunders Ltd., 2009.)

Although a number of challenge substances have been used to assess intestinal permeability, all have certain limitations. Ideally, a challenge substance should be nontoxic, completely absorbable via passive diffusion, and easily measured in urine. It should not be a substance produced endogenously, degraded enzymatically, or consumed in the diet.[15,16] Other commonly used saccharide probes to assess paracellular and transcellular pathways are cellobiose/mannitol, lactulose/rhamnose, and cellobiose/rhamnose.[50] The drawback of using cellobiose (an alternative for lactulose) is that it can be hydrolyzed by the brush-border enzyme, lactase.[13] Rhamnose (an alternative for mannitol) is incompletely excreted after an oral load.[12] Hence, lactulose and mannitol are the best documented substances for assessing intestinal permeability and most closely meet the preceding criteria for an ideal challenge substance.[17,51,52]

Because all saccharide probes are degraded by colonic bacteria, they can only provide information about the small intestine. Probes such as sucralose and chromium-ethylenediaminetetraacetic acid (Cr-EDTA) are stable throughout the entire intestinal tract and, as such, are suitable markers to assess colonic permeability (Figure 20-2).[15]

Test Procedure

The patient collects a first morning prechallenge urine sample after an overnight fast (8 hours). A premeasured lactulose/mannitol drink is then ingested, and urine is collected for the next 6 hours. The total urine volume is recorded and both samples are returned to the laboratory for assessment of the individual recovery of the two sugars and their ratio (L/M).

Interpretation

In healthy individuals, there is a 20% to 30% recovery of mannitol and less than a 1% recovery of lactulose over a 6-hour period.[12] Under pathologic conditions, the amount of lactulose permeating the intestinal barrier increases and the amount of mannitol does not change or decrease. This results in a rise is the L/M ratio, which reflects disturbances in the integrity of the small bowel.[15]

Factors That Affect the Excretion of Lactulose and Mannitol

The excretion of lactulose and mannitol depends on many factors, which can be categorized as follows:

- Premucosal factors: proper digestion, gastric dilution and emptying, intestinal dilution, transit time, and bacterial degradation
- Mucosal factors: brush-border hydrolysis, permeation pathways, and blood flow
- Post-mucosal factors: endogenous sugar production, metabolism, tissue distribution, renal excretion, and proper urine test collection

The sensitivity and specificity of the test are markedly increased if two challenge substances are used and a pretest sample is collected.[53] When both challenge substances are administered simultaneously and their ratio determined, extraneous factors such as gastric and bladder emptying, renal and hepatic disease, and intestinal motility are eliminated.[13] A pretest urine sample identifies a small percentage of patients who produce mannitol endogenously.[13]

THERAPEUTIC CONSIDERATIONS

Natural agents with the greatest evidence for their use in protecting the intestinal epithelium include the amino acid glutamine and certain probiotics. The pharmacologic agent sodium cromoglycate has good research to support its use in allergy-mediated gut permeability (see Table 20-1 for condition specific indications).

Glutamine is a preferential fuel for the small intestine and considered vital for the maintenance of mucosal growth, structure, and function.[54] It helps prevent the deterioration of gut permeability in catabolic conditions (e.g., burns, sepsis, trauma, and after major surgery).[55] Glutamine also protects against chemotherapy-induced gut permeability.[56,57] Given its role in intestinal metabolism and immunity, glutamine initially held promise as a nutraceutical for patients with IBD. However, research in this cohort is conflicting, and it is now thought that glutamine may exacerbate IBD symptoms.[55,58] Supplementation with glutamine may enhance T-cell function, which can lead to the upregulation of proinflammatory cytokines and aggravate Crohn's disease. Glutamine may also indirectly increase nitric oxide synthesis via its metabolism from citrulline to arginine, with resultant inflammation and tissue injury in patients with ulcerative colitis and Crohn's disease.[59]

Probiotics (live microbial foods beneficial to health) have been found to protect the intestinal mucosa by several proposed mechanisms (Figure 20-3).

1. They exert direct effects on the epithelium by increasing mucin and β-defensin expression and secretion, which prevents the proliferation of commensal and pathogenic organisms and restricts the movement of bacteria across the mucous layer.
2. Probiotics enhance mucosal immunity by increasing the production and secretion of sIgA, which binds to bacteria and bacterial antigens and protects against epithelial colonization.
3. Probiotics exhibit effects on neighboring bacteria by altering gene expression and/or microbiota composition and increasing commensal bacteria.

Certain probiotic strains may also produce antimicrobial factors (e.g., bacteriocins) that inhibit or kill pathogenic bacteria.[60] In addition, numerous studies have shown that probiotics can protect against epithelial tight junction alterations associated with infection, stress, and proinflammatory cytokines.[60] (See Chapters 115 and 116 for a complete discussion of prebiotics and probiotics, respectively.)

TABLE 20-1 **Therapeutic Agents for Enhancing Intestinal Barrier Function**

THERAPEUTIC CONSIDERATIONS	DOSE	STUDY DESIGN	INDICATION(S)	OUTCOMES/ MECHANISM OF ACTION
Bovine colostrum[63]	125 mL 3 times a day.	Randomized, double-blind, placebo-controlled trial.	NSAID-induced alterations in small intestinal permeability.	Prevented a 3-fold rise in intestinal permeability after short-term NSAID use. Did not influence small bowel integrity in long-term NSAID users.
Glutamine[56]	IV alanyl-glutamine dipeptide 0.3 g/kg/day for 5 days commencing on day 1 of chemotherapy.	Randomized, double-blind, crossover trial.	Chemotherapy-induced intestinal epithelial damage in patients with gastric or colorectal cancer aged 46–68 y.	Increased glutamine stores and reduced plasma endotoxin levels. (*P:* 19549287) Deficiency of glutamine is associated with a reduction in claudin-1, occludin, and ZO1.
Glutamine[57]	30 g/day for 12 days commencing on the day of chemotherapy.	Randomized controlled trial.	Chemotherapy-induced intestinal permeability in breast cancer patients aged 45–58 y.	Ameliorated chemotherapy-induced increases in intestinal permeability. Did not interfere with the antitumor effect of chemotherapy.
Glutamine[65]	30 g/day for 7 days postsurgery (taken orally or via nasogastric tube).	Randomized, double-blind, controlled trial.	Postoperative patients (abdominal surgery) aged 16–85 y.	Decreased intestinal permeability (reduced L/M ratio). Reduced serum endotoxin levels.
Glutamine[66]	30.5 g/day for 10 days (via nasogastric or jejunal tube).	Randomized, single-blind, multicenter trial.	Hospitalized critically ill patients with systemic inflammatory response syndrome aged 18–85 y.	Reduced nosocomial infection rate.
Glutamine[67]	20 g/day of alanyl-glutamine (8.18 g of alanine and 13.42 g of glutamine) administered parenterally.	Randomized, double-blind, controlled, parallel multicenter trial.	Postoperative patients (abdominal surgery) aged 44–66 y.	Decreased intestinal permeability (reduced L/M ratio), reduced hospital stay (4 days less than controls), increased glutamine stores, increased nitrogen balance.
Glutamine[68]	30 g/day for 28 days.	Randomized controlled trial.	Patients with advanced esophageal cancer who underwent radiochemotherapy, aged 56–66 y.	Decreased intestinal permeability and maintained lymphocyte counts after radiochemotherapy. Increased salivary sIgA.
Multistrain fermented milk beverage containing: *Streptococcus thermophilus*, *Lactobacillus acidophilus*, *Lactobacillus bulgaricus,* and *Bifidobacterium longum*[69]	*S. thermophilus* (20 billion CFU), *L. acidophilus* (2 billion CFU), *L. bulgaricus* (2 billion CFU), *B. longum* (2 billion CFU) administered twice a day for 4 wks.	Randomized, single-blind, placebo-controlled trial.	Diarrhea predominant IBS in adults aged 32–57 y.	Decreased small bowel permeability and improved mean global IBS scores.[69] May improve intestinal permeability by increasing the expression of tight junction proteins ZO1 and occludin (*Bifidobacterium*).[70]
Lactobacillus plantarum 299[71]	10 billion CFU/day (via nasojejunal tube) for 7 days.	Randomized, single-blind parallel trial.	Acute pancreatitis in adults aged 25–75 y.	Reduced the incidence of septic complications by maintaining the integrity of the intestinal mucosal barrier.[71] *L. plantarum* (WCFS1 strain) increases the localization of occludin and ZO1 in the tight junctions of the intestinal epithelium.[72]

TABLE 20-1 **Therapeutic Agents for Enhancing Intestinal Barrier Function—cont'd**

THERAPEUTIC CONSIDERATIONS	DOSE	STUDY DESIGN	INDICATION(S)	OUTCOMES/ MECHANISM OF ACTION
Lactobacillus rhamnosus 19070-2 and *Lactobacillus reuteri* DSM 12246[73]	100 billion CFU of each strain, administered twice a day for 6 wks.	Randomized, double-blind, placebo-controlled crossover trial.	Moderate to severe atopic dermatitis in children aged 1 –13 y.	Improved gut barrier (reduced L/M ratio).[73] Thought to work by suppressing T-helper cell proliferation, reducing proinflammatory cytokine secretion and controlling IgE-mediated responses. Increased systemic and mucosal IgA responses.[33]
Lactobacillus rhamnosus GG[74]	2.4 billion CFU/day for 5 days.	Randomized, double-blind, placebo-controlled trial.	NSAID-induced alterations in gastric permeability.	LGG protected the integrity of the gastric mucosal barrier.
Lactobacillus rhamnosus GG[75]	500 million CFU/g infant formula. 20 billion CFU twice a day (mothers).	Randomized, double-blind, placebo-controlled trial.	Atopic dermatitis and food allergies in infants. Eczema in nursing mothers.	Alleviated intestinal inflammation and promoted endogenous barrier mechanisms by reducing TNF-α and IL-4.
Saccharomyces boulardii[76]	200 mg capsules administered 3 times a day for 3 mo (400 million CFU per capsule).	Randomized, single-blind, placebo-controlled trial.	Crohn's disease in adults aged 19–54 y.	Improved intestinal permeability (reduced L/M ratio). Prevented the activation of NF-κβ and downstream proinflammatory cytokines. Inhibited the migration of CD4 + T cells and stimulated apoptosis of infiltrating cells.
Sodium cromoglycate[77]	300 mg 15 min before a food challenge.	Controlled trial.	Adults with food allergies, aged 16–65 y.	Prevented allergy-mediated changes (normal L/M ratio) after a provocation test. Reduced the allergic response by binding to mast cells and blocking the release of histamine, which prevented the synthesis of arachidonic acid mediators, such as leukotrienes and prostaglandins. Binds to other cell types, such as macrophages, monocytes, eosinophils, neutrophils, and platelets, all of which have receptors with a low affinity for IgE.
Sodium cromoglycate[78]	100 mg 4 times a day before meals.	Controlled trial.	Children with food allergies aged between 8 y and 1 mo and 9 y and 5 mo.	Reduced mast cell degranulation and prevented the appearance of IgE-IgG antigen complexes.

CFU, colony forming units; IBS, irritable bowel syndrome; Ig, immunoglobulin; IL, interleukin; LGG, *Lactobacillus rhamnosus* GG; L/M, lactulose/mannitol; NF-κβ, nuclear factor-κβ; NSAID, nonsteroidal anti-inflammatory drug; sIg, secretory immunoglobulin; TNF, tumor necrosis factor; ZO1, zonula occludins.

Other nutrients with preliminary evidence for supporting endothelial barrier integrity include: *N*-acetylcysteine, polyunsaturated fatty acids, zinc, and the polyphenols quercetin and green tea. These natural substances are thought to exert their beneficial effects by enhancing the expression of tight junction proteins.[61,62] Bovine colostrum may hold promise as a natural agent to protect against NSAID-induced alterations in mucosal integrity by downregulating proinflammatory cytokines.[63,64]



CONCLUSION

Intestinal barrier function has important implications for the etiology and pathogenesis of numerous intestinal and systemic diseases. Using lactulose and mannitol as markers to measure intestinal permeability is a safe, well tolerated, and noninvasive way to assess the integrity of the small bowel. Intestinal permeability testing can be used as a screening tool to identify patients who require further, more aggressive investigation or to assess clinical progress and response to therapy.

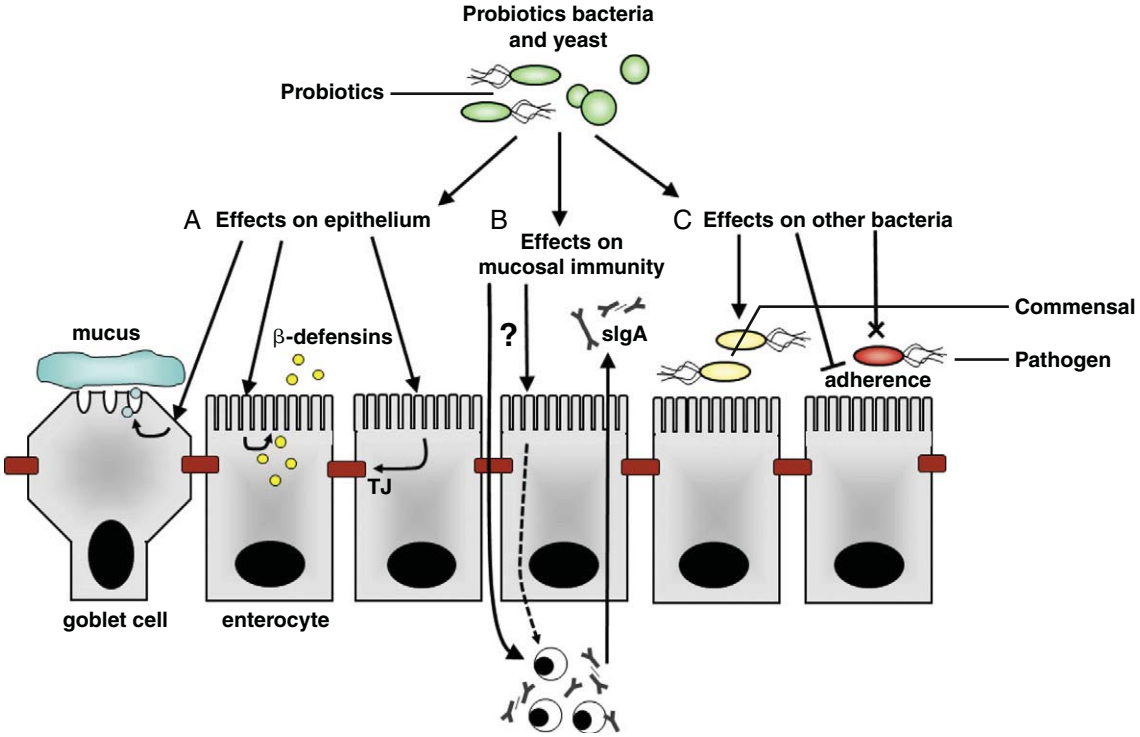


FIGURE 20-3 Effects of probiotic bacteria and yeast on epithelial barrier function. (From Ohland C, MacNaughton W. Probiotic bacteria and intestinal epithelial barrier function. Am J Physiol, Gastrointest Liver Physiol 2010:298; G807-G819. Used with permission.)

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CHAPTER 21

Laboratory Tests for the Determination of Vitamin Status

Joseph E. Pizzorno, ND

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INTRODUCTION

Laboratory assessment of vitamin status is a significant challenge for the clinician. Although measurement of blood and serum levels is easily available, their clinical value is limited to the detection of severe deficiencies. Detection of functional deficiencies requires far more sophistication.

ASSESSMENT OF VITAMIN STATUS

See Table 21-1 for laboratory tests and optimal ranges for common vitamins.[1–5]

Water-Soluble Vitamins

Ascorbic Acid (Vitamin C)

Assessment of vitamin C is particularly difficult because ascorbate readily oxidizes in assay samples. In addition, serum levels reflect recent dietary uptake rather than actual tissue levels. Recent research in an animal model of vitamin C deficiency (the *Gulo* mouse) clearly demonstrated that a dietary intake that does not lead to serum saturation of vitamin C results in tissue deficits.[6] Serum saturation of vitamin C was required to achieve tissue concentrations similar to wild-type animals, which can synthesize ascorbate. In humans, maximum serum saturation from oral dosing was predicted to be roughly 1/60th of that achieved with intravenous administration, highlighting the inability of serum levels to predict optimal physiologic function.[7,8] Leukocyte levels are not as susceptible to dietary intake but are also readily affected by infection, hypoglycemia, and many common prescription and over-the-counter drugs. The popular lingual ascorbate test does not appear to be reliable because it does not correlate well with leukocyte or serum levels. The loading test, if carefully controlled, is probably most accurate, although good standard ranges have yet to be determined. Finally, discovery of ascorbate-dependent enzymes involved in cell signaling pathways and epigenetic modulation offer the possibility for more functional analysis in the future, although unfortunately no definitive analysis is currently available.[9]

Biotin

Biotin is a vitamin B complex especially affected by oral antibiotics. Food is a poor source of this vitamin, making humans more dependent on gut flora sources. Elevation of 3-hydroxyisovalerate (3-HIA) due to deficiency of the biotin-dependent enzyme appears a useful measure. Additionally, two recent studies in which healthy volunteers were intentionally made biotin deficient suggested that elevated urinary levels of 3-HIA-carnitine might be a sensitive indicator, even for a marginal deficiency. This offers greater accuracy and is less prone to laboratory error than the traditional urinary 3-HIA.[10,11] Plasma levels of 3-HIA-carnitine may also prove to be a sensitive marker and reduce the dependency on renal function for an accurate determination, an important consideration during pregnancy.[12]

Folate

Serum folate is too greatly affected by recent consumption to be clinically useful. Homocysteine levels may be elevated because of deficiency of vitamins B_6 and/or B_{12} as well as folate. Erythrocyte folate is more accurate and considered a more reliable indicator of tissue status. Evaluation of other B vitamin status, particularly B_{12},

TABLE 21-1 **Laboratory Tests and Optimal Ranges for Common Vitamins**

NUTRIENT	TEST	ACCEPTABLE LEVEL
Water-Soluble		
Ascorbic acid	Serum	>0.3 mg/dL
	Leukocyte	30 mcg/10^8 WBCs
	Load test	0.3-2.0 mg/h in control 24-49 mg/h after 500 mg
Biotin	3-hydroxyisovalerate	<20 mcg/mg creatinine (overnight urine)
Folate	Erythrocyte folate	>160-650 ng/mL (~350 nmol/L)
	Serum homocysteine	<10 mcmol/L
Niacin	Urinary *N*-methylnicotinamide	>1.6 mg/g creatinine
	2-pyridone 5-carboxamide (2-PYR)	>1.6 mg/g creatinine
	RBC NAD/NADP	>1.0
Pantothenic acid	Urinary pantothenic acid	>1 mg/day
Pyridoxine	Serum level	>50 ng/mL
	Tryptophan load	<35 mg/24 h xanthurenic acid
	AST	<1.5 (ratio)
	ALT	<1.25
	Plasma pyridoxal 5-phosphate	>30 nmol/L
	Urinary 4-PA	>3.0 mol/d
	Serum homocysteine	<10 µmol/L
Riboflavin	EGRAC	<1.3
Thiamine	RBC transketolase	<15% increase
	Whole blood thiamine (HPLC)	>16ng/mL
Vitamin B_{12}	Serum B_{12}	>150 pg/mL
	Urinary methylmalonic acid Serum merhylmalonic acid	<5 mcg/mg creatinine
	Serum homocysteine	<0.45 mcmol/L
	Holotranscobalamin	<0.10 mcmol/L >30 pmol/L
Fat-Soluble		
Vitamin A	Plasma retinol:	15-60 mcg/dL:
	0-5 mo	>20
	6 mo-17 yr	>30
	Adult	>20
Vitamin D	25 (OH) vitamin D	40-80 ng/mL
Vitamin E	Plasma α-tocopherol	>16.2 mcmol/L
	α-tocopherol:cholestrol	>5.2 mcmol/L
Vitamin K	% serum uncarboxylated osteocalcin	<20 ? (optimal not yet determined)

Data from references 1-5.

ALT, alanine aminotranferase; AST, aspartate aminotransferase; EGOT, erythrocyte glutamic oxaloacetic transaminase; EGPT, erythrocyte glutamic pyruvic transaminase: FAD, flavin adenine dinucleotide; H_2O_2, hydrogen perioxide; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; RBC, red blood cell; WBC white blood cell.

may be necessary to rule out a folate deficiency. Although the presence of neutrophil hypersegmentation has been used to identify folate deficiency, this also occurs with B_{12} and iron deficiency, making it a very nonspecific marker.[13]

Niacin

Although measurement of nicotinic acid in the blood is not very reliable, measurement of its metabolites provides a clinically useful function assessment. Several metabolite tests are now available, including urinary levels of 2-pyridone 5-carboxymide and *n*-methylnicotinamide.[14,15]

Pantothenic Acid

Serum pantothenic acid does not correspond well with dietary intake, although erythrocyte levels are more closely correlated.[16] Measurement of urinary excretion of pantothenic acid appears reliable.

Pyridoxine

Several procedures are available for assessing vitamin B_6 status. Unfortunately, substantial agreement on the best methodology has not been established, because variations in phenotypes significantly alter the results of functional and loading tests. The active form of pyridoxine (pyridoxal 5′-phosphate [P5P]) is involved in some 60 enzymes, so deficient activity of these enzymes can be measured as a functional assessment of pyridoxine. Plasma levels of P5P appear to be a better functional indicator than erythrocyte levels, at least in patients with rheumatoid arthritis.[17] Plasma levels below 30 nmol/L (considered borderline deficient) have independently been associated with an increased risk for coronary artery disease, with a particularly high risk when combined with high-sensitivity C-reactive protein.[18,19] Although suitable for most circumstances, plasma P5P does not appear to be reliable during pregnancy or the acute phase of myocardial infarction, and alternatives should be used. Urinary 4-pyridoxic acid is a useful marker of recent intake only, whereas erythrocyte aminotransferase (EAST) and erythrocyte alanine aminotransferase (EALT) activation by pyridoxal phosphate may be a better indicator of long-term status.[20] Elevated homocysteine may also be a sign of deficiency, at least in some populations.[21]

Riboflavin

The most common measure of riboflavin is red blood cell (RBC) glutathione reductase activity. The enzyme is stimulated in vitro by the addition of flavin adenine dinucleotide, and expressed as erythrocyte glutathione reductase activation coefficient (EGRAC). An EGRAC greater than 1.30 is typically used as a cutoff (with higher values indicative of suboptimal status), although one recent study suggested this threshold for deficiency might need to be raised. This same study also demonstrated that riboflavin supplementation caused an increase in hemoglobin status among women with the lowest riboflavin intakes, despite no change in iron intake or absorption.[22] EGRAC is not reliable

in individuals with glucose-6-phosphate dehydrogenase deficiency. In this population, pyridoxamine phosphate oxidase may be more appropriate.[23] Blood riboflavin levels are not reliable because of technical difficulties in measurement. Lastly, homocysteine levels may be relevant for those with genetic variation in the ethylenetetrahydrofolate reductase gene. Individuals with the TT genotype of the C677 T polymorphism may have increased riboflavin needs.[24]

Thiamine

The most common measure of thiamin is erythrocyte transketolase activity. The enzyme is stimulated in vitro by the addition of thiamine pyrophosphate. Elevation in activity greater than 15% indicates a functional deficiency. The test is not reliable in patients with diabetes mellitus, pernicious anemia, or a significant negative nitrogen balance. For example, growing evidence has indicated that a tissue deficiency of thiamine exists in patients with diabetes, and may increase the risk for vascular and neurologic complications. Despite markedly reduced plasma levels of thiamine among individuals with type 1 and type 2 diabetes, erythrocyte transketolase activity remained normal, largely because of an upregulation of RBC thiamine transporter levels.[25,26] Advances in high-performance liquid chromatography technology now allow for direct measurement of either whole blood or erythrocyte thiamine, which may be a valuable alternative.[27,28]

Additionally, measurement of amino acids and their ketoacid analogues that are excreted in thiamine deficiency is being used. (See Brally and Lord[4] for a more complete discussion.)

Vitamin B_{12}

Serum levels of vitamin B_{12} are of some value, although they do not track cerebrospinal fluid levels very well, and only a small portion (20% to 30%) of total cobalamin levels are bound to transcobalamin and taken up via receptor-mediated cellular uptake. Erythrocyte cell size is also not reliable, since neurologic signs and symptoms can precede macrocytosis by 6 to 12 months.

A recent analysis found that serum levels of holotranscobalamin may be the optimal first line diagnostic procedure, at least among elderly patients. It has been suggested to be one of the earliest markers of negative B_{12} balance, and its diagnostic accuracy is not affected by renal insufficiency, a problem with total cobalamin levels and methylmalonic acid.[29,30]

Measurement of either urinary or serum methylmalonic acid is considered fairly sensitive and specific in those with healthy renal function, especially when expressed as a ratio with the urinary creatinine measurement.[31,32] Elevated homocysteine concentrations may indicate deficiency, but it is not specific to B_{12}.

Fat-Soluble Vitamins

Vitamin A

Although liver biopsy is the most accurate method of vitamin A assessment, other less invasive and less expensive methodologies are more appropriate. As with most other nutrients, serum levels of vitamin A fall significantly only after tissue reserves have been depleted, and are subject to numerous laboratory challenges as well as other factors, (e.g., infection, protein status). Serum retinol binding protein is sometimes used as an alternative to serum retinol, because it avoids many of these complications, although it is also susceptible to artificial decreases due to inflammation or protein malnutrition.[33] Optimal cutoffs have not been clearly established for retinol binding protein, although levels greater than 0.825 μmol/L have been suggested for children and greater than 1.05 μmol/L for adults.[34,35] The dark adaptation test detects early deficiency of this nutrient, and provides a useful alternative (see Chapter 26). Lastly, given the variation in the ability to convert β-carotene to retinol, the use of plasma carotene levels is probably not a useful marker of vitamin A status.[36]

Vitamin D

The widespread deficiency of vitamin D has gained a much greater degree of recognition, with most recommendations based upon 25(OH) vitamin D levels. Most functional indicators, such as levels of parathyroid hormone, point to a level of 25(OH) vitamin D greater than or equal to 80 nmol/L as being sufficient, although some evidence has suggested higher levels might be optimal, particularly for cancer prevention.[37–39]

Vitamin E

Despite dietary intake of γ-tocopherol being ten fold greater than α-tocopherol, the preference of the α-tocopherol transfer protein for α-tocopherol results in much higher serum levels, which is why the latter is often used as a biomarker. Emerging evidence suggests that despite the ease in measurement, and the widespread supplementation with α-tocopherol, mixed tocopherols (such as the γ form) is likely of greater physiologic importance.[40,41] Unfortunately, optimal levels of other biomarkers have not yet been established, although one review reported a γ-tocopherol levels range between 2 and 5 μmol/L.[42] It is also important to adjust vitamin E levels to lipid levels, such as triglycerides or cholesterol, with the latter more commonly used.

Adipose and platelet levels have been suggested to be better biomarkers, as have cells with low-density lipoprotein receptors, such as mononuclear leukocytes and buccal mucosal cells.[43]

Vitamin K

In recent years the importance of vitamin K for physiologic functions other than blood coagulation has been recognized, including functions related to both bone and vascular disease. For this reason, the traditional methods of assessment, such as prothrombin and clotting assays, may not be sufficient markers of vitamin K status, at least in regard to these other functions.[44] Better functional markers may be serum uncarboxylated osteocalcin (ucOC) levels, or perhaps a serum carboxylated OC to serum total OC ratio. One review suggested that a percent of ucOC greater than 20 is probably optimal, although genetic variations may modify this to some degree.[45–47]

CONCLUSION

As described here, many procedures are now available for the assessment of functional vitamin status. Although research continues in this important area, the reader is advised to carefully study the discussion of urinary organic acids profiling (see Chapter 28). Utilizing metabolic products excreted in the urine now allows the clinician far greater specificity in recognizing dysfunctional enzyme systems, whether they are due to genetic deviations or nutritional deficiencies.

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CHAPTER 22

Lactose Malabsorption Testing

Tina Kaczor, ND, FABNO, and Jeff Baker, ND, DHANP, CCH

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INTRODUCTION

Lactose malabsorption results from the inability to properly digest lactose, the disaccharide found in mammalian milk. Lactase is an enzyme in the brush border (microvilli) of the small intestine responsible for cleaving lactose into absorbable monosaccharides. Lactase enzyme deficiency leads to lactose malabsorption as the gut is unable to absorb the larger diasaccharide. When symptoms such as diarrhea, bloating, flatulence, or abdominal discomfort result from this malabsorption, a diagnosis of lactose intolerance is given. Lactose intolerance affects an estimated 25% of Americans and 75% of adults worldwide.[1] As shown in Table 22-1, the condition occurs in people of all ethnic backgrounds, with a near 100% prevalence observed in Asians. Within the United States, prevalence parallels country of origin, with the highest rates in African Americans, Hispanic Americans, Asian Americans, and Native Americans.[2]

The generalized nature of abdominal symptoms of lactose intolerance can obscure proper diagnosis,[3] resulting in symptom management through medical intervention. However, when properly diagnosed, lactose intolerance may be treated with patient education, lactase supplementation, and dietary modifications,[4] eliminating the need for medical interventions. In patients experiencing symptoms, a nutritional history and objective measures of lactose malabsorption can lead to the diagnosis of lactose intolerance. Objective measures for lactose malaborption include stool pH testing, lactose tolerance testing, and hydrogen/methane breath testing. In addition, genomic tests are also available to assess the presence or absence of polymorphisms linked to lactase enzyme deficiency.

Controversy surrounds the subject of lactose intolerance stemming from the dramatic decrease in dairy consumption that can result from its diagnosis. Numerous studies showed a correlation between decreased dairy consumption and a rise in calcium-dependent conditions, such as osteoporosis, heart disease, and colon cancer.[5-10] Studies also indicated that food-based calcium was a better source of this nutrient than supplements. Because dairy foods are the richest and best-absorbed dietary sources of calcium, careful diagnosis should be made before these foods are eliminated from the patient's diet. Dietary limitation of calcium rich foods should only be done in the context of objectively proven lactose intolerance. Many patients with lactose malabsorption are able to consume moderate amounts of lactose without

TABLE 22-1 **Prevalence of Lactose Intolerance by Ethnic Group**

GROUP	PREVALENCE (%)
African blacks	97-100
Asians	90-100
North American blacks	70-75
Mexicans	70-80
Persons of Mediterranean descent	60-90
Persons of Jewish descent	60-80
North American whites	7-15
Northern Europeans	1-5

symptoms, so both the diagnosis and treatment should be pursued under professional guidance.[11]

PATHOPHYSIOLOGY

Lactose is a disaccharide that can be hydrolyzed by the lactase enzyme lactase-phlorizin hydrolase (LPH) into glucose and galactose, which are actively absorbed in the small intestine (Figure 22-1). When LPH activity is decreased in the brush border (microvilli) of the distal duodenum and proximal jejunum, then lactose malabsorption results. The presence of lactose malabsorption does not always result in lactose intolerance. Only when the amount of lactose ingested exceeds digestive capacity does lactose persist in the lumen, ultimately reaching the colon, where it may lead to osmotic retention of fluid and bacterial fermentation, thus causing the symptoms characteristic of lactose intolerance (see Figure 22-1).[12] Therefore, symptoms of lactose intolerance often require several contributing factors in addition to LPH deficiency, including (1) relatively high lactose load, (2) gut dysmotility[13] (3) rapid small bowel transit, (4) heightened visceral sensitivity,[14] and/or (5) altered bowel flora.[15]

ADULT-TYPE (PRIMARY) LACTOSE DEFICIENCY

The majority of the world's population has a normal decrease in LPH synthesis after weaning. This common autosomal recessive genotype confers the phenotype of primary lactase deficiency (lactase nonpersistence). Genetically, nucleotide sequences in the distal enhancer region of the *LCT* gene (chromosome 2), which encodes LPH, appear responsible for this developmentally programmed loss of transcription.[16]

It is theorized that maintaining the ability to digest lactose into adulthood (lactase persistence) is the result of a relatively new evolutionary genetic mutation that occurred after the domestication of farm animals.[17] Preservation of lactase synthesis has been associated with several distinct single nucleotide polymorphisms (SNPs) on the distal enhancer region of the *LCT* gene (*–13910C>T*, *–13915T>G*, *–14010G>C*). Although the presence of any these SNPs suggests lactase persistence, their absence does not equate to lactase nonpersistence, because there appear to be other SNPs that have not yet been determined.[18]

ACQUIRED (SECONDARY) LACTASE DEFICIENCY

Because LPH is located in the brush border (microvilli) of gut mucosal cells, LPH deficiency may be secondary to diseases that damage these cells. Lactose intolerance has been observed as a secondary feature in celiac disease,[19] tropical sprue, acute gastroenteritis, chemotherapy-induced mucositis,[20] cystic fibrosis, alcoholism,[21] pelvic radiation therapy,[22] and Crohn's disease.[23] In secondary lactase deficiency, treating the underlying condition and resultant restoration of mucosal integrity often restores lactase activity.[24]

CONGENITAL LACTASE DEFICIENCY

Congenital lactase deficiency is a rare inborn error of metabolism characterized by very low or absent lactase activity in the intestinal

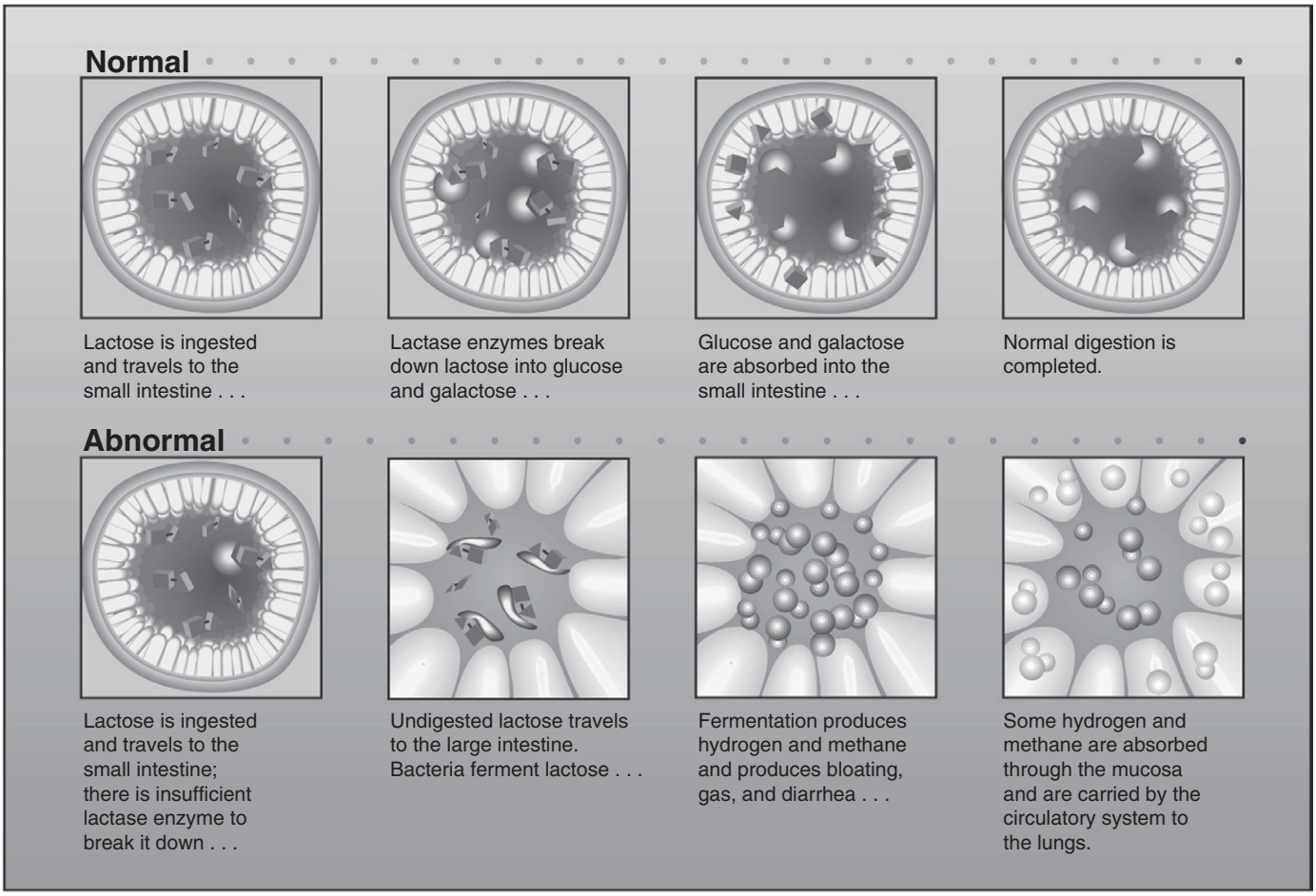


FIGURE 22-1 Lactose digestion.

microvilli at birth. Unlike lactase nonpersistence mutations, which affect upstream enhancer regions of *LCT*, mutations in the *LCT* gene itself appear to be responsible for congenital lactase deficiency.[25] Clinical symptoms include severe diarrhea, dehydration, and malnutrition, and often appear during the first week with the consumption of lactose. Separately, preterm infants may exhibit symptoms of lactase deficiency if born before 34 weeks' gestation, a condition called developmental lactase deficiency.[26] As expected, preterm infants can gain function of the lactase enzyme with time.

LACTOSE INTOLERANCE VERSUS DAIRY ALLERGY

Lactose intolerance and dairy allergy are separate pathologies. Lactose intolerance results from the maldigestion of dairy carbohydrate (lactose), whereas dairy allergy is an immune response to dairy proteins (e.g., casein, lactalbumin, whey). Dairy allergy may involve reactions (e.g., systemic anaphylaxis) that affect the gastrointestinal tract, skin, respiratory tract, or multiple systems. These immediate reactions are often mediated by immunoglobulin-E (IgE) and can cause severe morbidity and even death; however, in such cases, dietary elimination of dairy products is associated with good prognosis.[27] The prevalence of IgE-mediated allergic reaction to dairy protein in the general population is estimated at 1% to 3%, being highest in infants and lowest in adults. However, the prevalence of IgG-mediated allergic reactions may be higher.

DIAGNOSIS OF LACTOSE INTOLERANCE

Clinical suspicion of lactose intolerance should be raised when foods containing milk or milk products produce symptoms of gas, bloating, cramping, or diarrhea (Box 22-1). A short course of dietary manipulation, with careful removal of milk containing products, can strengthen the case for lactose intolerance as a diagnosis. Testing stool acidity, oral lactose tolerance testing, breath tests for hydrogen and methane, and/or genomic evaluation for *LCT* haplotypes should be used to confirm the diagnosis. Because the presence of lactase deficiency does not always result in lactose intolerance, genomic testing should never be used as a sole determinant in diagnosis. Breath testing provides the most reliable noninvasive means of determining lactose malabsorption, but must be used in the context of symptomology to make the diagnosis of lactose intolerance. In contrast, a positive breath test coupled with the absence of *LCT* haplotyping indicating primary lactase deficiency suggests a secondary causation, the diagnosis of which should be pursued.

There have been conflicting results regarding the presence of lactose intolerance in patients with irritable bowel syndrome (IBS). By definition, the diagnosis of IBS is a functional diagnosis that is made when all organic causes of symptoms have been ruled out. However, studies have shown that IBS patients have a high rate of lactose intolerance, with resolution of IBS symptoms upon lactose limitation or removal.[28-30] Rana et al[31] found that patients with diarrhea-predominant IBS had a higher incidence of lactose intolerance (82%) than patients who had either spastic-type IBS or features of both IBS types. For this reason, lactose intolerance should always be investigated in cases of IBS, a condition that affects up to 20% of Americans.[32]

A number of studies have suggested that transient lactose intolerance is also associated with infantile colic.[33,34] For susceptible children with lactose maldigestion, only 12 grams of lactose (~1 cup of milk) daily has been shown to be associated with increased abdominal pain.[35]

BOX 22-1 Symptoms of Lactose Intolerance

- Indigestion
- Bloating
- Flatulence
- Nausea
- Diarrhea
- Failure to thrive
- Abdominal cramps

Nutritional History

A detailed history of the patient's average consumption of lactose-containing food should be obtained. Often, patients do not consider yogurt, ice cream, chocolate milk, and milk ingested with cereal as important sources of lactose. They also may not be aware that lactose is added to many nondairy products to provide texture, flavor, and browning, and to absorb flavors, aromas, and food colors (Box 22-2). In addition, because of its excellent binding ability, lactose is contained in many drugs and over-the-counter products (Box 22-3). Identifying all sources of lactose is necessary to (1) identify the potential relationship between gastrointestinal symptoms and lactose consumption and (2) develop an effective lactose-free diet, if necessary.

Empirical Testing (Trial Elimination of Milk Products from the Diet)

If the patient experiences symptoms after consuming food products containing lactose, a temporary exclusion of all lactose-containing products from the diet as a preliminary diagnostic procedure may be helpful. However, diagnosis of lactose intolerance should not be based solely on elimination of milk products. This subjective test may be misleading if hidden sources of lactose (see Box 22-3) are not removed or if unrelated symptoms coincidently abate during this period.[36]

BOX 22-2 Sources of Lactose

Obvious Sources
- Milk (whole, skim, dry powdered, evaporated)
- Cheeses
- Butter, many margarines
- Goat's milk
- Half-and-half cream
- Ice cream and many sherbets
- Yogurt

Hidden Sources
- Artificial sweeteners containing lactose
- Breads, biscuits and crackers, doughnuts made with milk
- Breading on fried foods
- Breakfast and baby cereals containing milk solids
- Buttered or creamed foods (soups and vegetables)
- Cake and pudding mixes, many frostings
- Candies with milk chocolate
- Cookies made with milk
- Hot dogs, luncheon meats, sausage, hash, processed and canned meats
- Mayonnaise and salad dressings made with milk
- Nondairy creamers (except for Coffee Rich)

BOX 22-3 Prescription and Over-the-Counter Drugs Containing Lactose

Prescription Drugs	Over-the-Counter Drugs
Ativan	Actifed tablets
Bumex	Allbee C-800 Plus iron tablets
Calan	Benadryl tablets
Coumadin tablets	Chlor-Trimeton Allergy tablets
ERYC	Ferro-Sequels
Glucotrol	Imodium A-D caplets
Lasix	Marezine tablets
Lotronex	Pepcid AC chewable
Mevacor	Slow FE iron tablets
Premarin	Sudafed Plus tablets
Prilosec	Unifed Chewable tablets
Propecia	
Reglan	
Synthroid	
Vasotec	
Xanax	

Stool Testing

The fermentation of undigested disaccharides of any kind within the colon results in the overproduction of fatty acids by colonic bacteria, which lowers the pH of the stool. Normal stool pH is between 6.0 and 7.0 in young children and adults. Although infants may normally have a lower pH due to a high lactose diet, pH of less than 5.3 suggests maldigestion. Although pH testing can be used to raise clinical suspicion of malabsorption, further workup is warranted to make a diagnosis of lactose intolerance.

Breath Testing

Breath testing is the method of choice for diagnosing lactose maldigestion.[37] It is sensitive and specific,[38] simple to perform, noninvasive, and inexpensive.[36] Breath testing is based on the ability of intestinal microbes to ferment carbohydrates, in this case lactose, producing hydrogen or methane in the process. A fraction of these gases naturally diffuses from the bowel to the circulation and is eliminated via the lungs. Because there is no other metabolic production of hydrogen and methane, pulmonary excretion of these gases may be used as an indirect measure of lactose maldigestion, indicating lactase deficiency.[39]

The benefits of breath testing are as follows:

- Its results correlate strongly with the symptoms of lactose intolerance.[40]
- It can be done at home by the patient or in the physician's office.[41]
- The lower challenge dose of lactose causes significantly fewer side effects than the large doses used in blood and urine galactose tests.[42]
- The breath hydrogen/methane test is the standard in pediatric cases in which other tests would be difficult to perform.[43-45]

Historically, breath testing measured hydrogen only. However, Tormo et al[46] showed that methane is produced instead of hydrogen in some patients with lactose malabsorption. They concluded that measuring both gases was necessary for accurate diagnosis of lactose maldigestion. Other researchers suggested that although methane was produced predominantly in some cases, hydrogen production correlated more strongly with symptoms; therefore, hydrogen testing alone might be sufficient for the diagnosis of lactose intolerance.[47,48] Breath testing using a radiolabeled carbon molecule (^{13}C) in the lactose structure, showed poor correlation with lactose intolerance, as evidenced by poor $^{13}CO_2$ output by the lungs.[40]

Procedure

After an overnight fast, a baseline breath sample is collected 30 minutes after rising. The patient then ingests a challenge dose of lactose (up to a maximum of 25 grams), and breath samples are collected 1, 2, and 3 hours after ingestion of the challenge dose.[49,50]

Interpretation

If lactose maldigestion is present, breath levels of hydrogen or methane will rise within 1 to 2 hours after ingesting the lactose challenge. As little as 2 grams of carbohydrate reaching the colon produces a detectable increase in breath hydrogen.[51]

Hydrogen and Methane Responses

The normal breath hydrogen level in a healthy, fasting patient is less than 10 ppm. Patients with lactose malabsorption show an increase in breath hydrogen concentration of 20 ppm or more during the test.[52,53]

The normal breath methane level in a fasting patient is 0 to 7 ppm. An increase of at least 12 ppm of methane alone during the test is considered positive for lactose malabsorption, regardless of the hydrogen response.[54-56]

If both breath hydrogen and methane rise after a lactose challenge, the two responses are added to estimate the degree of malabsorption. The rises in breath hydrogen and methane levels together must be 20 ppm or more to suggest lactose malabsorption.[56] The extent of elevation relates to the degree of malabsorption.

False-Positive Results

False-positive results occur rarely and are usually a consequence of the following interfering factors:

- *Fiber intake.* Fiber should be avoided 24 hours before the test. Ingesting fiber in food or in supplements increases fermentation and hydrogen production.[57-59]
- *Exposure to tobacco smoke.* Tobacco smoke increases hydrogen levels and should be avoided immediately before and during testing.[60]
- *Sleeping.* Sleeping between breath sample collections may increase both hydrogen and methane levels.[61]

False-Negative Results

Breath hydrogen/methane testing has a false-negative rate of approximately 5%; the false-negative rate is 10% if only hydrogen is measured. False-negative results can occur because of the following factors:

- Use of lactase supplements.[42]
- Use of antibiotics before the test. Antibiotics decrease the bacteria that ferment lactose.[62]
- Use of laxatives or enemas before the test. These decrease hydrogen and methane responses in patients with lactose malabsorption and reduce fermentation in the colon.[63]
- Severe diarrhea or hyperacidic colon contents. Hyperacidity inhibits the production of hydrogen and promotes the production of methane by colonic bacteria.[64,65]

High Baseline Levels

An elevated baseline level of breath hydrogen indicates that one or more interfering factors are present. Testing must be repeated to obtain reliable results. A baseline breath hydrogen level greater than 10 ppm can be due to:

- Improper fasting.
- Consumption of high-fiber foods the day before testing.

- Performance of test immediately after awakening.[54]

A baseline breath hydrogen level more than 20 ppm can be due to:

- Possible small intestine bacterial overgrowth.[66] Elevated fasting levels of hydrogen occur in up to one third of patients with small intestinal bacterial overgrowth[67] and may be caused by the fermentation of endogenous brush-border glycoproteins.[68]
- Small intestine bacterial overgrowth may elevate baseline methane readings as well.[54,66,68,69]

Genomic Testing

Genomic testing requires a single blood sample and avoids the diet restrictions, lengthy collection regimen, and potential for abdominal symptoms that are associated with using an oral lactose challenge. The *LCT* gene on chromosome 2 encodes for the enzyme LPH, and wild type is associated with lactase nonpersistence. Lactase persistence is associated with two polymorphisms on the enhancer region upstream from *LCT*, C/T_{13910} and G/A_{22018}. Heterozygotes are considered to have lactase persistence but with intermediate lactase activity. Homozygotes T/T_{13910} and G/G_{22018} have lactase persistence genotype, whereas C/C and G/G homozygotes carry the wild type nonpersistence genotype. Genomic testing, although useful, only establishes a lactase enzyme deficiency, the presence of which does not always lead to lactose intolerance symptoms. Heterozygotes, although considered carriers of lactase persistence genotyping, can have bouts of impaired lactase activity due to stress or infection, rendering intermittent bouts of lactose intolerance.[70] Therefore, testing for lactose malabsorption through an objective measure of lactose malabsorption, such as hydrogen breath testing, is still warranted.[71]

Tissue Sampling

An endoscopic biopsy of the jejunum can assess the presence of lactase as well as other disaccharidases, although this test is rarely used due to the expense and discomfort involved. Morphologically, enterocytes would not show abnormality in cases of primary lactase deficiency, but may show blunting of microvilli or inflammatory changes associated with secondary causes of lactose intolerance.

Blood Testing

Lactose tolerance testing (LTT) was formerly used, but has been replaced by more sensitive breath testing as previously described. LTT required a large dose of glucose challenge, up to 50 grams, which often led to abdominal symptoms that are avoided with the lower doses used in breath testing. If the rise in serum glucose after challenge was less than 26 mg/dL during the ensuing 2 hours, then lactose maldigestion was presumed. Another similar test uses radiolabeled lactose,[13] C-lactose. Although it has been shown to have the ability to differentiate between those who can digest lactose and those with maldigestion, this method has not been evaluated for its ability to identify symptoms directly related to lactose intolerance,[66] and it is not available clinically.

OTHER TYPES OF SUGAR INTOLERANCES

Inability to properly digest other types of saccharides can produce symptoms similar to those caused by lactose intolerance. For this reason, it may be necessary to investigate other types of sugar intolerances, especially in patients whose clinical test results do not support a diagnosis of lactose intolerance. Commonly ingested sugars such as fructose, sucrose, and maltose should be considered if sugar intolerance is suspected in the presence of normal breath and genetic testing.

SUMMARY

The majority of the world's population is lactase deficient. However, lactose intolerance may not develop in all of these individuals. A comprehensive evaluation that incorporates diagnostic testing, the patient's nutritional history, and the relationship between diet and gastrointestinal symptoms is necessary for an accurate diagnosis. Proper diagnosis of lactose intolerance allows for dietary modifications that may allow a limited amount of dairy products in some lactose intolerant individuals. Exclusion of lactose containing foods altogether should be done only for those requiring strict avoidance, with careful attention to replacement of lost nutrients such as calcium. Breath testing of hydrogen/methane production after a lactose challenge is the diagnostic method of choice.

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CHAPTER 23

Metal Toxicity: Assessment of Exposure and Retention

David Quig, PhD

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INTRODUCTION

The incidence of high-level exposure to toxic metals and acute "poisoning" is rare and is most commonly associated with occupational exposure. Associated symptoms are well defined and accepted. A plethora of published research has clearly defined many of the precise biochemical mechanisms by which specific metals elicit a vast array of adverse effects that can culminate in neurotoxicity, nephrotoxicity, cardiovascular and pulmonary disease, cancer, teratogenicity, and dysregulation of immune function. Despite knowledge of the effects of metals on the most basic biochemical processes that affect human health, the concept that "subthreshold" levels of metals in the body can negatively affect health and daily functioning is not generally accepted by the dominant medical community. However, with respect to lead, mercury, and cadmium, a consultant to the National Institute of Environmental Health Sciences stated that the margin between the levels of exposure for people in industrialized nations and the levels of exposure that are currently recognized as producing the lowest adverse effect levels is small.[1,2]

The methods for assessing metal toxicity established as standards for medical practice are best suited for detection of acute metal poisoning or recent or ongoing exposure, but do not provide an accurate estimate of the actual levels of metals that have accumulated in the body. The purpose of this chapter is to provide an overview of the various laboratory tests for the assessment of (1) exposure to toxic metals and (2) the net retention of toxic metals. It is beyond the scope of this chapter to discuss the sources and symptoms associated with long-term exposure to the most commonly encountered metals. Thorough reviews of these topics have been published elsewhere.[3-7]

The most commonly encountered toxic metals (mercury, lead, cadmium, and arsenic) are natural constituents of the earth's crust, but their increasing abundance in air, water, and surface soil results primarily from industrial demand and energy production (pollution). Consequently, the environment today has become contaminated to the point that we are all, regardless of occupation, at higher risk for at least long-term, low-level exposure to toxic metals. However, consistent with the basic principles of toxicology, confirmation of exposure is by no means valid documentation of clinically significant retention and toxicity. For a given individual, toxicity is exhibited when the level of retention exceeds physiologic tolerance, and net retention (body burden) is determined by the relative rates of toxic metal assimilation and excretion.

Two important concepts that have been largely overlooked with respect to metal toxicity may explain the discrepancies of opinion expressed by practitioners of traditional medicine and preventive medicine. The first is the potential for the combined effects of multiple toxic metals, which can have not only additive, but also synergistic, adverse physiologic effects.[8,9]

This concept should be further extended to include consideration of the potential combined effects of toxic chemicals and toxic metals, the total toxic load. The broad heading of toxic chemical entities includes not only naturally occurring and synthetic exogenous compounds but also noxious endogenous compounds derived from a severely dysbiotic or poorly functioning gastrointestinal (GI) system. The second is the remarkable individual variability in susceptibility or tolerance to toxic metals. Established precedence for the phenomena has been provided by such observations as the rapid contact allergic response that is elicited by mercury in a small percentage of a population.[10] Individual variability in susceptibility is determined in part by genetic polymorphisms, nutritional status, and the total toxic load.[7,9]

The factors of multiple toxins and individual variability impede simple interpretation of any test result for an individual patient.

No single perfect test is available for the diagnosis of chronic metal toxicity; any test result must be interpreted in conjunction with a thorough review of a patient's physical findings, exposure history, and symptoms. However, the symptoms associated with a chronic toxic metal retention appear to be diverse and rather nondescript, and they may not be fully expressed until later in life. Clear examples of such latency of symptom expression have been provided for lead and hypertension[11] and cardiovascular mortality.[12] Therefore, to address the needs of clinicians who focus on preventive medicine as opposed to crisis management, the following review of laboratory tests emphasizes testing that has greater sensitivity with respect to detection of the bioaccumulation of the most commonly encountered toxic metals. Emphasis has been placed on the distinction between testing that is most appropriate for assessment of exposure versus net retention.

ASSESSMENT OF TOXIC METAL EXPOSURE

Hair Elemental Analysis

When performed properly, hair elemental analysis can serve as a qualitative screening test for exposure to toxic metals, but it is not a reliable method for the diagnosis of metal toxicity. Hair is an excretory tissue that can provide a chronologic record of bioavailable trace elements in the body, and the hair content of mercury, arsenic, lead, and thallium has been used as evidence for the cause of death.[13] Once metals are incorporated into growing hair, there is no back exchange into the body; therefore, the concentration of metals in hair is usually far greater than that in blood or urine. The length of the hair specimen analyzed dictates the duration of time during which exposure occurred, and segmental analysis of hair can be used forensically to estimate the chronologic course of exposure. A study of the lead and mercury content of hair from a long-deceased president of the United States was performed at the Armed Forces Institute of Pathology in Washington, DC, exemplifying the potential utility of hair analysis for exposure to toxic metals.[14] Detection of toxic metals in hair actually predates that in blood and urine.[15]

A growing number of peer-reviewed publications support the value of elemental analysis of hair specimens for the detection of exposure to toxic metals. For example, elevations of arsenic in both hair and urine confirmed arsenic exposure from a pesticide in an individual with peripheral neuropathy and macrocytosis.[16] Hair levels of lead, manganese, cadmium, and other toxic metals have been correlated with psychological conditions and deviant or violent behaviors.[17] Lead, cadmium, and mercury levels in children's hair have been correlated with childhood intelligence. Hair analysis has been used to identify historical as opposed to current exposure to lead.[18] School children with relatively high levels of lead in their hair had slower reaction times and less flexibility in changing their focus of attention than children with relatively low concentrations of lead in hair.[19]

The Agency for Toxic Substances and Disease Registry (ATSDR), the U.S. Environmental Protection Agency, and the National Academy of Sciences recognize the scientific validity of hair mercury levels as an indicator of maternal and fetal exposure to methylmercury. In a cognitive performance study of children in the Faroe Islands, there were detectable effects on brain function in the children whose mothers had elevated levels of hair mercury.[20] History of fish consumption and mercury in hair samples are considered the best indicators of human exposure to methylmercury.[21] Fish consumption among Scandinavian[22] and Tyrrhenian men,[23] Amazonian children,[24] and people from the Minamata Bay area[24] was positively correlated with hair and blood mercury levels. Note that hair elemental analysis definitely provides useful information about exposure to methylmercury (fish consumption); however, it is not nearly as useful for disclosing information about exposure to inorganic mercury as derived from dental amalgams.[24] The concentration of methylmercury in hair is about 300 times higher than that in blood.[25] In sharp contrast, about 75% of total hair arsenic is present in the inorganic form.[26]

Although an increasing number of peer-reviewed reports support the clinical utility of elemental analysis of hair for the assessment of exposure to specific toxic metals, some considerations prevent its acceptance by governmental agencies in the United States. In June 2001, the ATSDR convened a panel of scientists with some expertise in hair analysis or risk assessment to explore "the state of the science of hair analysis."[27] Overall, the discussion was objective and focused on the existing scientific data. A summary statement from the meeting concluded, "In general, hair analysis results can provide limited qualitative insights into environmental exposures and rarely can answer questions about potential health effects."[28] Primary concerns raised by the group pertained to uncertainties about the quantitative relationship among the actual "internal dose," the rate of incorporation into hair, and the current lack of well-established data to enable one to predict potential health effects for a given concentration of a specific metal in hair. Over interpretation of the results of elemental analysis of hair is a serious concern shared by science-based laboratories and astute clinicians as well as the ATSDR. It should be kept in mind that the ATSDR has been interested in the use of hair analysis as an initial screening tool for inexpensive exposure biomonitoring of groups of people who are exposed to toxins at suspected sites of contamination. The goal of the ATSDR to be able to use hair elemental analysis as confirmation of toxicity is quite different from the use of the procedure in preventive or comprehensive medicine simply to provide an initial indication of exposure.

The consensus report by the ATSDR is consistent with the aforementioned statement that hair analysis can provide some qualitative information about exposure to toxic metals but does not provide a basis for diagnosis of metal toxicity. As such, hair analysis may be helpful to clinicians as a step toward identifying potential health problems that may be associated with toxic metal exposures before significant symptoms are expressed. Further testing should be performed before treatment options are considered. The clinician should be wary of laboratories that perform hair analysis as a vehicle to sell nutritional supplements and should be aware of interlaboratory variation.[29] Clinicians are recommended to use only laboratories that can validate their certification or accreditation and incorporate state-of-the-art methodologies for washing, digesting, and analyzing hair specimens.[30] Appropriate quality control characteristics and the validation of the establishment of reference ranges, accuracy, precision, and reliability of state-of-the-art hair analysis have been described.[31-33]

Blood Analysis: Toxic Metal Exposure

For the most commonly encountered toxic metals, the current standard for diagnosis of metal toxicity is abnormally high concentrations in whole blood or urine. However, blood analysis for toxic metals is a better indicator of exposure than toxicity in most cases. Distribution of metals, such as lead, in the body has been long recognized as initially dependent on the rate of delivery via the blood to various tissues and organs.[34] Subsequent redistribution then depends on the relative affinities of tissues for the metals

and toxicodynamics, which can vary markedly among individuals. Tissue affinities for metals are determined in large part by the high relative intracellular concentrations of reduced glutathione and metallothionein.[35] Further, blood levels can fluctuate considerably with intermittent exposure and assimilation. Thus, as stated by the ATSDR/Centers for Disease Control, the concentration of lead in blood reflects mainly the exposure history of the previous few months and does not necessarily reflect the larger burden and much slower elimination kinetics of lead in bone.[9]

Examining kinetic models of metal metabolism shows that the blood metal compartment has the shortest biological half-life. Metals leave the blood by excretion (urine, bile, and sweat) and transfer to tissues. The retention by tissues, such as bone, kidneys, and brain, accounts for the much longer biological half-lives of most toxic metals in the body. This simple concept has been obviated in studies presented in the *Physician's Desk Reference*.[36] Adult and pediatric patients who were diagnosed with lead toxicity on the basis of elevated blood lead values exhibited marked reductions in blood lead levels after chelation therapy with succimer. However, 2 weeks after cessation of chelation, blood lead levels rebounded between 60% to 85% of pretreatment levels (the rebound effect was associated to some degree with all pharmacologic chelators). The relationship between blood lead levels and the quantity of lead excreted in urine after calcium ethylenediaminetetraacetic acid (Ca-EDT) or succimer chelation was nonlinear, in that arithmetic increases in blood lead were associated with exponential increases in lead excretion.[1,37]

The correlation between blood lead and chelatable lead is poor in adults with previous exposure.[1]

Under extreme conditions of massive accumulation of metals (long-term occupational exposure), the equilibrium between tissue stores and blood can result in blood metal levels that are at or above the established threshold values for the diagnosis of metal toxicity but still do not indicate the extent of total body retention. The current gold standard of blood lead measurement for assessment of lead toxicity in children is disturbing: no minimum response levels have been established for lead because a threshold has yet to be defined for the most sensitive effect of lead neurotoxicity.[38]

Interestingly, fractionization of blood into the plasma versus red blood cell compartments can provide valuable information to the clinician about the primary sources of exposure to mercury. Approximately 95% of methylmercury, most commonly derived from contaminated fish, is associated with red blood cells,[39,40] whereas about 90% of inorganic mercury (amalgams, occupational exposure) is found in the plasma compartment bound to albumin, cysteine, and nonspecific proteins.[40] Because the first step in successful detoxification is to remove the source of exposure, documentation of the primary source of exposure to mercury can be instrumental for efficient detoxification. Blood arsenic levels, albeit with a very short half-life (approximately 6 hours), reflect exposure to inorganic arsenic and methylated metabolites of arsenic, but not dietary arsenic (shellfish), which is rapidly excreted in the urine.[41,42]

The analysis of whole blood, plasma, and red blood cells can provide valuable information about exposure to specific forms of some metals without the need for expensive determination of subspeciation.

Urinalysis of Toxic Metals: Unprovoked

In general, and despite the current standards for medical care, urinalysis for toxic metals does not provide a scientifically valid basis for diagnosis of metal toxicity. However, in some cases it provides an indication of recent or ongoing exposure to certain metals.

Such is not the case for lead, because urinary lead is generally not a useful biomarker to estimate low-level exposure to lead. However, elevated urinary lead–chelate complexes resulting from the Ca-EDTA mobilization test provide a good means to assess increased lead retention.[9]

A different scenario exists for organic arsenic as well as inorganic and organic mercury. The most commonly accepted biomarker for exposure to inorganic mercury is the urinary level of inorganic mercury.[43] However, the World Health Organization (WHO) standard for occupational exposure is very high (50 mcg/g creatinine).[44] This high standard has been challenged because neurologic impairment has been reported for occupationally exposed subjects[45,46] whose urinary mercury levels were well below the WHO standard. Evidence that urinary mercury levels are indicative of exposure to implanted mercury amalgams has also been published.[47] In a study of 1127 Vietnam-era veterans reported by the National Institute of Dental Research, a highly statistically significant correlation was detected between the level of amalgam exposure and urinary mercury levels, although mean urinary mercury levels were only about 2 mcg/g creatinine. Several other studies have reported an association between amalgam exposure and urinary mercury levels.[48-51] Elevations of urinary arsenic have been detected in workers during periods of occupational exposure, including copper smelting, spraying of insecticides or herbicides, and application of wood treatments.[52]

Arsenic can be markedly and transiently elevated in individuals within 48 hours after consumption of shellfish that contain high levels of relatively nontoxic species of organic arsenic.[53] Urinary mercury is frequently elevated in people who consume high levels of fish.[22,54] Therefore, analysis of an unprovoked urine specimen is highly recommended to avoid alarmism and confounding the interpretation of the results of a urinary metals provocation test, and patients should be instructed to abstain from the consumption of fish and shellfish for about a week before a chelation challenge is performed. Elevated urinary values of arsenic and mercury associated with the specific dietary and occupational conditions reflect recent or ongoing high-level exposure, but are not necessarily reflective of the body burden of the specific metals. Although blood metal levels reflect transient transport in the body, urinary levels qualitatively reflect excretion of an unknown fraction of the total body pools of assimilated metals.

Urinalysis: Biomarkers of Renal Toxicity

Toxic metals such as cadmium, mercury, and lead are known to be nephrotoxic at high levels of assimilation. Cadmium is of particular concern because of its exceedingly long residence time in the kidneys.[55] Therefore, in addition to urine levels of cadmium, urinary biomarkers of renal damage should be assessed for documentation of cadmium toxicity. Early markers of cadmium-induced renal damage include proteinuria, glucosuria, aminoaciduria, hypercalciuria, and polyuria.[56] Sensitive urinary biomarkers for more advanced cadmium-induced tubular damage include elevated levels of the low-molecular-weight protein β_2-microglobulin, retinal-binding protein, and *N*-acetyl-β-D-glucosaminidase (NAG).[57] Abnormal urinary levels of NAG have also been reported in association with markedly high urinary mercury levels (35 mcg/g creatinine) in chloralkali workers with long-term exposure to inorganic mercury.[58] It is noteworthy that the urinary NAG levels were correlated with urinary mercury and integrated dose of exposure but not with concurrently measured blood mercury levels.[57] Thus, it appears that assessment of urinary biomarkers of renal damage may be useful in the diagnosis of toxicity in cases of very high exposure

to cadmium and perhaps mercury. However, negative findings for the renal biomarkers do not exclude the possibility of chronic low-level metal toxicity that is most commonly encountered in general clinical practice.



ASSESSMENT OF RETENTION: URINALYSIS, PROVOCATION TESTS

The best currently available method to estimate the level of retention of toxic metals in the body is urinalysis for toxic metals after the administration of a chelating agent. In the 1970s, the value of a standardized calcium-disodium EDTA (Ca-Na_2-EDTA) provocative test was recognized as sensitive to determine the mobile and potentially toxic body lead stores, and to assess response to chelation therapy in pediatric patients with high blood lead levels.[59–61] Subsequently, Markowitz and Rosen[62] described the results of a comparable, yet more convenient test that would permit use in a greater number of qualifying patients.

The concept and value of using metal complexing agents to estimate the body burden of readily available tissue depots of other toxic metals have gained increasing acceptance in the United States, and currently, several other pharmaceutical agents are widely used for this purpose. The most commonly used pharmaceutical agents are Ca-Na_2-EDTA, Dimaval,-(R,S)-2,3-dimercapto-propropane-1 sulfonate (DMPS), and meso-2,3-dimercaptosuccinic acid (DMSA). Nonpharmaceutical compounds that have also been utilized as possible provocation agents include *N*-acetyl-cysteine (*N*-AC) and potassium-citrate (K-citrate). The latter compounds are not chelators by definition and have not been studied extensively.[63]

EDTA

Ca-EDTA has been approved by the U.S. Food and Drug Administration (FDA) and used intravenously for many years as the provocation agent and therapeutic agent of choice for patients with high blood lead levels. The compound is also well known to be effective for increasing the urinary excretion of iron, copper, nickel, cadmium, and manganese.[64] Ca-EDTA also has a high affinity for zinc and, if not used properly, can cause zinc deficiency. The maximum recommended Ca-EDTA (50 mg/ kg, ≤ 3 g) infusion rate is 1 g/h, and clinicians are strongly encouraged to assess glomerular function before use (Ca-EDTA mobilized metals are excreted in the urine). Before attempting to embark on the safe and effective use of Ca-EDTA, clinicians should attend specific training courses. Although the "slow-push" Ca-Na_2-EDTA protocol introduced in the United States appears to be effective for increasing the urinary excretion of lead,[65] it has not been formally evaluated for safety. Ca-EDTA is not nearly as effective a chelator of mercury as are the dithiol chelators. Therefore, this chapter focuses on the metal complexing agents that are newer to the United States, the dithiol agents DMPS and DMSA.

DMPS

DMPS appears to be the most productive agent for the mobilization of mercury, as determined in vitro[66] and in a comparative study during the Iraqi mercury crisis, in which people were acutely poisoned after consumption of grains contaminated with a methylmercury-containing fungicide.[67] More relevant to the typically encountered clinical situation, a DMPS provocation study was conducted with volunteer college students.[68] Subjects with and without amalgam fillings were given 300 mg DMPS (orally), and all urine was collected over the subsequent 9 hours. DMPS raised mean urinary mercury for the nonamalgam group from 0.27 to 5.1 mcg and that of the amalgam group from 0.7 to 17.2 mcg over the 9-hour period. A highly significant positive correlation was detected between the amount of mercury excreted after the DMPS challenge and amalgam surface area.

An additional study supports the value of provocation testing for people occupationally exposed to mercury vapors. A comparison of urinary mercury levels was made before and after oral administration of a 300-mg dose of DMPS to dental technicians, dentists, and nonoccupationally exposed controls.[49] Unprovoked urine mercury levels were comparable for dental technicians and dentists and were about five times higher than those in controls. Compared with prechallenge values, DMPS-induced urinary mercury (micrograms per 6 hours) increased by a factor of 87, 49, and 34 for the technicians, dentists, and controls, respectively. Post-DMPS urinary mercury levels were 16 and 6 times higher than in controls for the technicians and dentists, respectively. The group mean urinary mercury for the technicians after DMPS was 424 ± 85 mcg/6 h. Baseline urinary coproporphyrin levels, which are biomarkers of aberrant heme biosynthesis, were significantly correlated with urinary mercury levels after DMPS but were not correlated with baseline urinary mercury levels. The researchers concluded that post-DMPS urinary mercury levels were better indicators of exposure and retention than unprovoked urinary mercury levels.

The pharmacokinetics of DMPS have been well defined,[69,70] and the efficacy of DMPS for detoxification of mercury,[71] arsenic,[72] and lead (pediatric)[73] have been documented. Although DMPS is not approved by the FDA, it is registered in Germany with the German Drug Regulatory Authorities and is available in the oral form without prescription.[69] In the United States, DMPS is available by prescription only from compounding pharmacies for oral and IV or intramuscular injection. Slow infusion (approximately 10 minutes) is recommended when giving DMPS IV (3 to 5 mg/kg, not to exceed 250 mg) to avoid hypotension. Because DMPS is not an FDA-approved drug but is permitted to be compounded for use by physicians, the clinician is advised to obtain a signed informed consent form from each patient before administering DMPS. DMPS is associated with a very low incidence of serious side effects,[69] and its safety in general was evident from the observations made during the course of extensive IV administration (250 mg every 4 hours for 12 consecutive days) in a young woman who had severe arsenic toxicity.[72] The most commonly reported side effects associated with DMPS are nausea, weakness, vertigo, chills, fever, cutaneous reactions/itching, erythema multiforme, and elevations of transaminases.[70,72,73] An extensive review of the German literature about the pharmacokinetics, affinities for various metals, and side effects of DMPS is available.[73]

A detailed description of an extensively used oral DMPS provocation protocol has been presented,[69] as well as an intravenous DMPS provocation protocol.[5] To establish the basal urinary rate of metal excretion, the patient is instructed to fast overnight and to collect a urine specimen. In the morning, with an empty stomach and after the bladder is emptied, the patient is given 300 mg (or 10 mg/kg) DMPS orally, and all urine is collected for the subsequent 6 hours.[69] A light meal (no seafood or fish) may be consumed after about 2 hours, and fluid consumption is encouraged. The specific laboratory instructions should be followed for preserving and shipping the specimen. Metals mobilized by DMPS are excreted primarily by the kidney and to a much lesser extent by the liver (biliary/fecal).[69] A thorough discussion of mercury detoxification protocols based on clinical experience has been presented.[5]

Equilibrium and stability constants (in vitro) for various DMPS-metal complexes have been presented.[74] In the clinical setting, DMPS is effective for the mobilization and excretion of bismuth, mercury (organic and inorganic), copper, lead, arsenic, antimony, nickel, tin, tungsten, and gold but does not affect aluminum or uranium excretion. In the majority of adult patients, mercury is the predominant metal excreted after DMPS, and elevation of copper is normal. As mercury levels decline during detoxification therapy, it is common to see increased urinary levels of other metals, such as lead and tin, with subsequent challenges. The shifting pattern of metal species excreted is based on a combination of affinities of DMPS for the different metals as well as on mass competition for metal binding sites. There are no well-established guidelines for the interpretation of the results of the DMPS challenge test. Therefore, conclusions about toxicity cannot be made from the DMPS test results alone. Consideration has to be given to the overall medical examination, medical and exposure history, and presenting symptoms. If a decision is made to proceed with some form of detoxification therapy, the initial challenge result can serve as a reference point against which subsequent challenge results can be compared to evaluate the efficacy of treatment. The levels of other toxic metals excreted should always be considered, and one should note that DMPS does not provide direct information as to the level of mercury present in the central nervous system. It is beyond the scope of this chapter to discuss protocols for metal detoxification, but it is emphasized that if a pharmaceutic metal complexing agent is to be used, glomerular filtration rate must be assessed before initiation of chelation therapy.

DMSA

Another dithiol metal complexing agent, DMSA, is also widely used for provocation testing, as well as detoxification therapy for lead, mercury species, and other sulfhydryl reactive metals (e.g., arsenic, antimony). Several studies demonstrated the effectiveness of DMSA to increase the urinary excretion of lead[75-77] and mercury and decrease the blood levels of these metals.[37,78-80]

DMSA was approved by the FDA for lead detoxification and is an agent of choice for lead detoxification in children and adults. DMSA is available only for oral administration, and only about 20% of orally administered DMSA is systemically available after a single dose.[36] DMSA, when used in conjunction with Ca-Na_2-EDTA, increases cumulative urinary lead excretion and ameliorates redistribution of lead and mercury to soft tissues.[81,82] DMSA is restricted to the extracellular compartment[69] and does not appear to cross a healthy blood–brain barrier. In rodent models, however, DMSA has been demonstrated to be effective in decreasing the levels of lead and mercury in the brain.[78,83-85] Animal studies also indicated greater efficacy of DMSA for lead detoxification when the compound was concomitantly administered with antioxidants.[79,80] This is the case for all bona fide metal complexing agents. However, the antioxidants lipoic acid and *N*-AC alone had no effect on lead excretion. To date, no reliable studies have been published to indicate that lipoic acid is an effective metal-binding agent that has a net effect on metal excretion in humans, and the potential for lipoic acid-induced mercury redistribution, particularly to the brain, is a significant consideration.[86]

DMSA is generally well tolerated with common but mild side effects, including GI bloating and/or gas, occasional loose stools, and skin rash. Assessment of liver enzyme levels is recommended before and periodically during extended administration. Compared with DMPS and Ca-EDTA, DMSA has minimal effects on essential elements such as copper and zinc, but DMSA is excreted primarily as a mixed disulfide with two molecules of cysteine.[87] Thorough reviews of the pharmacokinetics and clinical use of DMSA have been presented.[5,69,70,88] It should be noted that there is a tremendous difference between the DMSA protocol described for acute lead poisoning[77] and that commonly used for chronic lead retention.

Various protocols for DMSA provocation testing have been suggested.[5,89] However, a convenient and productive provocation protocol has been described that entails giving a single dose of DMSA orally (30 mg/kg, not more than 2 g) on an empty stomach and collection of all urine for the subsequent 6 hours.[63] The peak rate of excretion of metals occurs after about 3 hours. The protocol is well tolerated, enhances compliance, and significantly reduces exposure to the compound. However, the potential for a single large dose of DMSA to leave behind some metals that have been mobilized but not excreted should be considered. It may be beneficial to continue to give DMSA at the standard treatment dose of 5 to 10 mg/kg three times daily for the next day or two to "clean up" metals that may have been left behind. Patients should be advised in advance that their urine will transiently have a foul, sulfurous odor and transient GI inconvenience may occur.

Nonpharmaceutical Agents

Nonpharmaceutical compounds, such as *N*-acetyl-L-cysteine (*N*-AC) and potassium citrate (K-citrate) have been tested for efficacy as provocation agents for mercury in one published study.[63] Urinary mercury levels, expressed as micrograms per liter, were compared before and after a single oral dose of *N*-AC (30 mg/kg), K-citrate (5 g in 200 ml water), DMSA (30 mg/kg), or DMPS (Unithiol, 250 mg in 5 ml water). Basal urinary mercury levels (about 5 mcg/L) were comparable for all of the treatment groups, each of which contained 16 to 65 polysymptomatic subjects. All subjects either had dental amalgams or had recently undergone removal of amalgams. Urine was collected for 3 hours after the challenge compounds were given, except that urine was collected for only 2 hours after the DMPS. The different collection time for the DMPS prohibits valid comparisons of the effects of the other agents with that of DMPS. The high bolus doses of *N*-AC and K-citrate significantly increased urinary mercury, by 131% and 83%, respectively, compared with basal values. Under these conditions of different collection times, DMSA and DMPS increased mercury excretion by 163% and 135%, respectively. No mention was made of the urine volumes associated with the different test groups, and clearly, the data would have been easier to interpret had the results been standardized per gram urinary creatinine.

Grossly misleading values for urinary metals can be associated with expression of excreted metals per unit volume because urinary output can vary considerably. No other data are currently available to permit further evaluation of the value of the nonpharmaceutic compounds as provocation agents. These two compounds also should be tested in animal models to determine whether they are associated with significant redistribution of metals among various tissues, because neither is a true chelator and their stability constants are relatively low. Currently, no definitive studies are available to assess the utility of parentally administered reduced glutathione as a metal complexing agent. As a final note about other routes of administration of various authentic and potential metal detoxification agents, particularly with respect to provocation testing: the author has not been able to find any published research addressing the systemic bioavailability or efficacy of any agent that is given via a transdermal delivery system.

FECAL METALS ANALYSIS

Several toxic metals, including mercury, lead, thallium and cadmium, are naturally excreted primarily or partially in bile. Therefore, under certain conditions analysis of fecal metals, without provocation, may provide at least qualitative information about the rate of biliary excretion of assimilated metals. However, contaminated foods present a significant source of exposure to metals, and metals that have not been assimilated by the GI tract can contribute to a significant percentage of the total amount of metals measured in a fecal specimen.

In addition to dietary contamination, fecal mercury is very much influenced by the amount of mercury that is present in the mouth in the form of mercury amalgams.[90] Fecal mercury concentrations, expressed per gram of dry weight, are roughly an order of magnitude higher in people who have an average of six to eight medium-sized amalgams than in individuals who are amalgam free.[90] Day-to-day variability in fecal mercury levels in amalgam bearers is remarkably low. Fecal mercury levels are highly correlated with the number of amalgams (Figure 23-1). Further, it has been demonstrated that fecal mercury levels decline significantly after extraction of amalgams.[91] Therefore, levels of fecal metals generally are more a representation of exposure to metals than an indication of total body retention. Current research efforts are focusing on the identification of metal complexing agents or phytonutrients that increase the biliary or fecal excretion of metals.

Fecal metals have been analyzed in autistic children (n = 54), and on average, metal levels were significantly higher compared with those in age-matched, nonautistic controls (n = 83).[84] The reason for the higher levels in association with autism is not known, and pica is a possible issue that may contribute to higher levels of exposure in autistic patients.

CONCLUSION

Long-term, low-level exposure to environmental toxins is a growing global problem, and evidence is accumulating to link the bioaccumulation of toxic metals in humans to subtle and overt health effects. Increasing numbers of patients dissatisfied with the care provided by clinicians who rely only on methods for the assessment of acute metal poisoning are seeking out progressive clinicians who are aware of the value of tools that are yet to be accepted for the assessment of subacute metal toxicity. Analyses of metals in hair, blood, and urine all have advantages and disadvantages, and no single test is likely to enable unequivocal diagnosis of "subclinical" metal toxicity. However, consideration of the results of the various tests discussed in this chapter as well as a complete medical examination, exposure history, and other findings can be used to design a comprehensive therapeutic detoxification program. Table 23-1 provides an overview of the value of the various tests for assessing a patient's potential problem with metals.

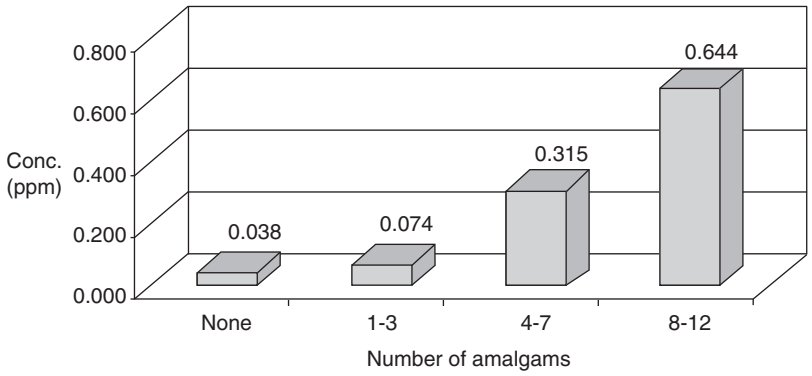


FIGURE 23-1 Fecal mercury levels versus the number of dental amalgams. Fecal mercury (microgram per kilogram dry weight) was plotted against number of amalgams for 200 subjects. (Data from Bass DA, Urek K, Quig D. Clin Chem 1999;45:A164. Poster presented at American Association of Clinical Chemistry Conference, Measurement of Mercury in Feces, New Orleans, July 1999.)

TABLE 23-1 **Summary of the Potential Value of Hair Analysis and Urinalysis**

		Urine (Retention)			
METAL/METALLOID	**HAIR (EXPOSURE)**	**NO PROVOCATION**	**DMSA**	**DMPS**	**CA-NA_2-EDTA**
Aluminum	Fair	Poor	Poor	Poor	Fair, best with deferoxamine
Antimony	Good	Poor	Good	Good	Good
Arsenic	Good	Poor	Good	Excellent	Poor
Cadmium	Fair	Poor	Fair	Fair	Excellent
Lead	Good	Poor	Good	Fair	Excellent
Inorganic mercury	Poor to fair	Poor	Excellent	Excellent	Poor
Organic mercury	Excellent	Poor	Excellent	Excellent	Poor
Nickel	Poor	Poor	Fair	Fair	Good
Tin	Poor	Poor	Good	Good	Good
Iron	Poor	Poor	Poor	Poor	Good, best with deferoxamine
Tungsten	?	Poor	Fair	Fair	Poor
Uranium	Good	Poor	Poor	Poor	?, Poor

Summary of the potential value of hair analysis (exposure), and the most commonly used provocation agents used in conjunction with urinalysis for the detection of retention of specific metals. It is emphasized that retention is not necessarily associated with overt toxicity. The qualitative guidelines are based on the author's perception of affinities (in vivo) derived from examination of thousands of test results, and stability constants as determined under highly defined conditions in vitro. The information provided does not include the potential use of adjunctive agents and/or protocols and does not cover all known metal complexing agents.

Ca-Na_2-EDTA, calcium-disodium ethylenediaminetetraacetic acid; DMSA, meso-2,3-dimercaptosuccinic acid; DMPS, Dimaval,-(R,S)-2,3-dimercapto-propane-1 sulfonate.

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CHAPTER 24

Mineral Status Evaluation

L. Charles Masur, MD

CHAPTER CONTENTS

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INTRODUCTION

Studies assessing the bioavailability of minerals in humans first appeared in the scientific literature in the 1960s,[1-3] and over the ensuing years it became clear that minerals play an important role in the biochemistry of the human body.[4,5] Abnormal levels of minerals can have deleterious effects on multiple enzyme systems, neuronal structures, and organs, including the brain, heart, thyroid, liver, kidneys, and skin.[4] Thus, mineral analysis can be an important health assessment tool for many patients. Opinions vary considerably as to which tissue or body fluid may be "best" for the assessment of any or all nutritional element(s).

In general, nutritional elements are better evaluated in blood or in urine. Blood mineral status can be assessed from an intracellular (e.g., potassium in erythrocytes, zinc in leukocytes) or extracellular (e.g., copper in serum) perspective, or overall in whole blood (total cellular components and serum). Levels of elements in serum will vary day-to-day depending on dietary intake. Many factors, such as specific protein carriers and the ionic charge of an element and its capacity to be in equilibrium, may affect the usefulness and reproducibility of a specific assay method and the appropriateness of a chosen tissue. The life span of the cellular components of blood is about 3 to 4 months, so any analysis using these cellular components must be interpreted with this time frame in mind; reported values will reflect exposure and absorption that occurred during that period.

When mineral analyses involve the cellular components of blood, the clinician must ensure that samples are spun down immediately after collection, thereby separating the cells from the serum. If whole blood is allowed to sit for an extended period or is shipped without such separation, some of the cellular components will break down, allowing their contained elements to disperse into the liquid component of the sample. Subsequent centrifugation will remove all of the liquid component, leaving the remaining intact cells to be analyzed for their elements. In that scenario, erroneously low levels of intracellular elements would be reported.

Although hair analysis (see Chapter 17) does have the benefit of convenience and low cost, interpretation is made difficult by the ease with which hair can be contaminated from external sources of exposure. With that proviso, hair analysis can accurately reflect exposure to, and absorption of, a limited number of elements (e.g., chromium) or deficiencies of others (e.g., copper). The most appropriate use of hair analysis appears to be in the assessment of toxic metal exposure but even then, its utility remains highly controversial ("an unproven practice" according to the American Medical Association).[6]

Most clinicians employ whole blood or urine analysis in the evaluation of mineral status since these fluids are the simplest and most economical to collect and transport. Whole blood requires no centrifugation and, like urine, requires no special treatment, other than collection and shipping in approved containers. Red blood cell (RBC) analysis might best be utilized in the assessment of elements that are more commonly represented intracellularly (e.g., iron, potassium). Reputable laboratories use current technology (e.g., induction-coupled plasma mass spectroscopy) operated by highly trained personnel to perform these tests and to produce accurate and precise results. Excellent reference range data are available to allow appropriate interpretation of analytic findings.

MINERALS AND DISEASE

Serum levels of various minerals have been implicated as clinical markers of disease.[4] Patients with cirrhosis have demonstrated low serum selenium,[7] calcium,[8] magnesium,[9] and zinc.[10] Those with emphysema and cancer have shown elevated serum copper concentrations; copper and manganese levels are often elevated in congestive heart failure, infection, and psychoses.[11] Other associations have been observed between trace minerals and breast cancer,[12] gastrointestinal malignancy,[13] and malignant ascites,[14] although in other studies, selenium, copper, zinc, and magnesium seemed to have no diagnostic value for distinguishing malignant from nonmalignant effusions[15] or cervical cancer.[16] Heart tissue levels of selenium, iron, copper, zinc, and phosphorus have been associated with ejection fraction and cardiac index.[17] In men infected with human immunodeficiency virus, helper T-type 4 cells seemed closely correlated with serum magnesium concentration.[18]

The ratios of trace elements may be indicators for various disease states. The concentrations of copper, zinc, and selenium, and their relative levels in whole blood and thyroid tissue, follow specific patterns for various thyroid disorders, including thyroid cancer. Further, and although the mechanisms are unclear, the copper-to-zinc ratio was found to be significantly increased in patients with breast cancer but not in patients with benign breast diseases.[19] In one study, serum copper-to-zinc ratios were shown to be of diagnostic and prognostic value in head, face, and neck cancer, with alterations in copper, zinc, and copper-to-zinc ratio related to the stage of the disease.[20] Other studies identified distinct differences in copper/zinc ratios among various levels of skin disease severity.[21]

ESSENTIAL MINERALS

There are a number of minerals that are common to all living organisms, in that they support biochemical processes in structural and functional roles. These essential elements are calcium, chloride, copper, iodine, iron, magnesium, manganese, molybdenum, phosphorus, potassium, selenium, sodium, and zinc (and perhaps, boron, cobalt, nickel, and sulfur). Other minerals, although not discussed here, have also been described as "essential," including chromium,[22] fluoride,[23] and vanadium.[24]

Calcium

Dietary sources of calcium include dairy products, canned fish with bones (e.g., salmon, sardines), green leafy vegetables, nuts, and seeds. Assessment of dietary intake of calcium is confounded by multiple factors that affect absorption, such as the quantity of fiber and other natural chelators in the diet; gastric acidity; the ratio of dietary calcium to phosphorus (and dietary magnesium); as well as gut transit time and other factors.

Serum calcium is so closely regulated (by the parathyroid gland) that its use as an indicator of calcium balance is not reliable when considered in isolation. Measurement of ionized calcium may be useful in evaluation of calcium status. Urinary calcium is of value in a patient with a known low total calcium intake and persistent calciuria. Hair calcium levels are subject to considerable variability and should not be taken as a quantitative determination of calcium status (although a relationship between hair calcium level and coronary disease has been reported).[25,26] In patients with high phosphorus and low calcium intakes, hair calcium level was consistently reported as much as three times higher than normal. Hair calcium returned to normal with proper supplementation and dietary changes.[27]

In one study that evaluated intracellular, plasma, and membranous levels of calcium and magnesium in hypertensive patients, there were no differences between controls and patients. However, the absolute levels of calcium and magnesium were lower, and the calcium/magnesium ratio in membranes was significantly higher in patients with essential hypertension than in healthy subjects.[28]

The best test to evaluate body calcium sufficiency may well be whole blood analysis, since this will assess calcium present in serum, intracellularly, and in the cell membranes.

Chloride

Chloride is necessary for the production of hydrochloric acid in the stomach and is also essential in cellular pump functions. The main dietary source of chloride is table salt. Chloride is readily assessed in serum and in urine.

Increased serum chloride may be associated with dehydration but could be present with either a metabolic acidosis or a respiratory alkalosis. High chloride can also be present along with elevated sodium in conditions such as Cushing disease. Urine chloride analysis, and often the analysis of urine sodium as well, may be important when considering alkalosis or acidosis or when assessing high or low serum chloride levels. Low serum chloride accompanies low serum sodium; low chloride may be associated with metabolic alkalosis and is often seen with prolonged emesis or in conditions causing respiratory acidosis, such as chronic obstructive pulmonary disease.

Body chloride levels are best evaluated in serum along with other electrolytes such as sodium. Urine chloride is a necessary component of a full electrolyte assessment and/or a metabolic panel.

Cobalt

Cobalt is essential in the production of vitamin $B_{12,}$ which is synthesized by bacteria. Cobalt metabolism and testing is better discussed elsewhere, especially in the context of vitamin B_{12} deficiency.

Copper

Under normal conditions, far more copper is absorbed than is needed by the body. Dietary sources include beans, eggs, fish, fresh fruits, liver, milk, mushrooms, nuts, oysters, peas, poultry, and whole grains. Nearly all dietary copper is stored initially in the liver, leaving only a small percentage in the blood. The principal mechanism for the control of copper homeostasis is excretion through the biliary system.

Because 95% of copper in serum is bound to the protein ceruloplasmin, there is almost no ionic copper so urinary copper output usually is minimal. At present, analysis of copper in serum may be the best indicator of body copper levels, provided that clinical conditions known to cause abnormal copper metabolism (e.g., Wilson's disease, cirrhosis of the liver) have been ruled out.[27] Some studies have shown hair copper measurement to be an acceptable method of assessing copper status[29,30] with the same provisos as mentioned previously regarding the ruling out of other illnesses known to affect copper metabolism and retention. When high copper levels are seen on hair analysis, external copper contamination (e.g., exposure to swimming pool and hot tub water, which are often disinfected with copper-containing chemicals) always should be considered.

Iodine

Iodine is necessary for the synthesis of thyroid hormones; iodine deficiency may lead to enlargement of the thyroid gland (goiter). Although iodine is readily measurable in urine, levels are highly variable[31]; thus, evaluation of urine iodine is not a reliable method to assess body iodine status. In contrast, it has been suggested that whole body sufficiency of iodine may be assessed in urine using an "iodine loading test."[32] Interpretation of the results of this test presupposes specific receptor/storage sites that take up and store iodine/iodide. When body storage of iodine/iodide is optimal, the percentage excretion of an oral loading dose of iodine/iodide excreted in urine is maximal; some authors purport that body stores are optimal when excretion is 90% or more.[33] An emerging assessment of iodine status is serum thyroglobulin, which appears to be a better measure of iodine status over weeks and months.[34]

Iron

Iron is essential for the function of many enzymes and has a role in the production of proteins (e.g., hemoglobin). Dietary sources include beans, dark green leafy vegetables, dates and figs, dried fruits, egg yolk, fish, molasses, nuts, organ meats, red meat, shellfish, as well as whole and enriched grains. Serum iron concentration has long been used as an indicator of iron deficiency. In practice it is not of much value when taken in isolation because there is considerable variation in serum iron levels, even when samples are taken from the same person at the same time each day. Serum iron measurement is much more reliable when combined with other indicators, such as serum transferrin or ferritin.

Ferritin is an iron storage protein accounting for 20% of the total body iron in normal adults. It is found principally in the cytoplasm of reticuloendothelial and liver cells, and, to some degree, in developing red cell precursors in bone marrow. This protein is involved in both absorption and recycling of iron and is a convenient and generally reliable indicator of total body iron stores.

A decrease in serum ferritin level (normal 12 to 300 ng/mL) is an early sign that body iron stores are low. As iron deficiency progresses, anemia (normal hemoglobin 13 to 15 g/100 mL), decreased serum iron concentration (normal 75 to 150 mcg/100 mL), and elevated iron-binding capacity (normal 300 to 400 mcg/100 mL) become apparent.[35,36] Serum ferritin may not be completely reliable in several common conditions, including cancer, infections, inflammation, and acute and chronic liver diseases, where it might be elevated. When iron overload is associated with hemochromatosis, hemosiderosis, or thalassemia, serum ferritin is also elevated.

The best way to evaluate body iron stores may well be with RBC analysis coupled with serum iron, serum ferritin, and total iron binding capacity.

Magnesium

Magnesium is essential for adenosine triphosphate (ATP) production and as a structural component of bones. Good dietary sources include nuts, soy beans, and cocoa mass. Measurement of magnesium status presents some difficulties, but the magnesium retention test is probably the most accurate, though cumbersome, method of assessment.[37] However, analysis of white blood cell magnesium content may be nearly as accurate as the magnesium retention test.[38]

Serum magnesium concentration may be influenced by many factors; it constitutes about only 1% to 3% of total body magnesium and does not reflect magnesium levels in other tissues.[39] The level of binding, complexing, or chelating of magnesium to serum proteins and other fractions is subject to many uncontrollable variables. Serum magnesium levels as low as 1.2 mEq/L have been measured in patients with normal total body magnesium.[40]

Erythrocyte membrane tests may also be useful in testing magnesium status (see previous discussion of calcium) and may be more clinically relevant than either plasma or intracellular studies.[19] Although the calcium/magnesium ratio in erythrocyte membranes was shown to be high in essential hypertension patients, it is unclear whether this finding is a cause or an effect of hypertension. However, it has been suggested that magnesium levels are low in hypertensive patients.[40]

The best test to evaluate body magnesium sufficiency may well be whole blood analysis since this will assess total magnesium in serum, intracellularly, and in the cell membranes of both red and white blood cells.

Manganese

Manganese is a trace element. It serves as a cofactor in enzyme functions (e.g., superoxide dismutase) and is essential in carbohydrate metabolism and production of skeletal and connective tissue development, and is a catalyst in fatty acid and cholesterol production. Dietary sources include dark green leafy vegetables, dried fruits, dried legumes, nuts, and whole grains. Assessment of body status for manganese is difficult as it is normally present in trace amounts (1% of the level of copper or zinc in blood).

Whole blood manganese concentration is a valid indicator of body manganese and soft tissue levels.[41] Proper technique is essential in the collection procedure as well as the actual analysis. Hair manganese level may be a rough indicator, especially in chronic toxicity, but whole blood manganese is the most reliable measurement tool.

Molybdenum

Dietary sources of molybdenum include beans, peas, red meats, and whole grains. It is a trace element important in xanthine, aldehyde, and sulfite oxidase (metabolism of sulfur-containing amino acids) systems. Xanthine oxidase catalyses oxidative hydroxylation of purines and pyridines; aldehyde oxidase oxidizes purines, pyrimidines, and pteridines and is involved in nicotinic acid metabolism. Sulfite oxidase deficiency or absence leads to neurologic symptoms and early death. Reduced dietary intake may result in low urinary molybdenum excretion, low serum uric acid, and excessive urinary xanthine excretion.[6] Molybdenum deficiency has been reported as occurring in in-born errors of metabolism and in patients receiving total parenteral nutrition.[42] Body sufficiency of molybdenum is best assessed by erythrocyte or whole blood analysis.

Nickel

Nickel is generally accepted as being a trace element in animals,[43] but its importance in humans requires further study.[44] Food sources of nickel are limited except perhaps in the case of high-acid prepared foods. It has been reported to be involved in iron metabolism and in stabilizing the structures of nucleic acids and proteins,[45] and it may be a cofactor of some enzymes.[46] Recent nickel exposure is best assessed by whole blood analysis. Nickel is rapidly

cleared by urinary excretion, so acute exposure to excessive nickel can be readily assessed by urine element analysis.

Phosphorus

Phosphorus serves a multiplicity of roles in human metabolism. Phosphorus is readily available in most foods, even in fast foods and especially in soft drinks. It is used as a structural component of bones (hydroxyapatite is a combination of ionic calcium and phosphorus). It is important in DNA, RNA, and energy production (ATP); in cell membrane structure (phophoslipids); and in most second messenger signaling pathways. It is involved in the renal production and serum concentration of 1,25-dihydroxy vitamin D.[47] High serum phosphorus is a predictable component of end-stage renal disease where no dietary restriction or other mitigating treatment is provided.[48] Intracellular phosphorus levels can be assessed with RBC analysis. Serum analysis provides an excellent evaluation of extracellular phosphorus levels, and whole blood element analysis provides a simple and straight forward method of assessing overall body phosphorus status.

Potassium

Potassium is an electrolyte and, along with sodium, essential to the regulation of ATP and the triggering of nerve and muscle activity. Dietary sources include bananas, legumes, potatoes (skins), and tomatoes. Consumption of a diet high in sodium (e.g., fast food items) can predispose to a potassium deficiency. Potassium is primarily an intracellular ion, and so serum measurements may not accurately reflect body stores. A low serum potassium level usually indicates an advanced intracellular deficit; however, an intracellular deficit may also occur with normal or high serum potassium concentrations.

RBC potassium content has been shown to mirror the potassium content of other tissue cells.[43,49] Although RBCs do not have nuclei, the sodium–potassium membrane pump that maintains the proper influx and efflux of these ions is intact. Whole blood potassium concentration is almost as accurate as the RBC potassium level because 98% of potassium is intracellular. The validity of intracellular potassium levels was demonstrated in a study where the electrocardiographic repolarization phase in elderly subjects was measured; alterations of repolarization correlated well with intracellular potassium levels but showed no correlation with serum levels.[50]

Selenium

Selenium is a trace element. Dietary sources of selenium include red meat, seafood, Brazil nuts, and whole grains. It is a cofactor essential to the activity of antioxidant enzymes such as glutathione peroxidase. Selenium may replace sulfur in cysteine to produce selenocysteine. Polypeptides containing selenocysteine include such selenoproteins as glutathione peroxidases and thioredoxin reductases (increases metallothionein redox capacity; supports vitamin E regeneration). Selenium deficiency may be associated with metal toxicity symptoms (due to lack of reduced metallothionein capacity).

After absorption, selenium is distributed throughout the tissues but does not seem to equilibrate with blood selenium levels. Blood selenium levels do not correlate with selenium intake, except at extremes.[51] Furthermore, serum levels of selenium do not appear to be associated with mortality and morbidity in relationship to infectious disease,[52] although one study found low serum levels of selenium and zinc to be associated with advanced gastrointestinal cancer.[6]

RBCs are high in glutathione peroxidase and could provide a means of assessing selenium levels, but may not give a good picture of total body status. Whole blood is generally the choice for assessment of selenium sufficiency.

Sodium

Sodium is an electrolyte and is essential, along with potassium, in the regulation of ATP. Sodium and chloride ions are the major electrolytes of the body. Dietary sources include table salt, sea vegetables (e.g., kelp, seaweed), milk, and spinach. Sodium and water depletion (e.g., dehydration, heat stroke, prolonged and excessive diarrhea or vomiting) can lead to hypotension; excessive long-term sodium intake (e.g., diets high in fast foods, prepared foods) is associated with hypertension. Sodium status is best assessed in serum.

Sulfur

Sulfur is essential for amino acid production and is obtained from cysteine and methionine contained in dietary protein sources. Sulfur sufficiency is best assessed with analysis of urine for essential elements. High urine sulfur may be seen in dehydration, recent use of thiol-containing complexing agents (e.g., dimercaptosuccinic acid, 2,3-dimercapto-1-propanesulfonic acid), high intake of sulfur-containing foods, and/or nutritional supplements (e.g., *N*-acetylcysteine, lipoic acid), and if there is impaired capacity to reabsorb cysteine (cystinuria). The possibility of cystinuria can be evaluated through urine amino acid analysis.

Zinc

Zinc is essential to the production and function of many enzymes, such as carboxypeptidase, alcohol dehydrogenase, and carbonic anhydrase. It is an intracellular ion, and some research shows that serum zinc concentrations are not sensitive indicators of depletion.[53] Urinary zinc level is also not a good indicator. Low hair zinc levels may indicate depletion, but normal values do not rule out low body stores.[24,54,55] Leukocyte zinc level has been investigated and found to be an accurate index of body stores.[56] In one investigation, 16 young women were given high and then low zinc dietary intake for specified periods. Low zinc intake status was not correlated with plasma zinc levels. Plasma zinc concentration was not significantly lower during the low dietary intake period than during the high dietary intake period. However, there was no significant change in fractional zinc absorption or urinary zinc excretion.[57]

The best test to evaluate body zinc sufficiency may well be whole blood analysis, since this will assess zinc present in serum, intracellularly, and in the cell membranes of both red and white blood cells.

CONCLUSION

The increasing availability of reliable laboratory methods for mineral analysis undoubtedly will better assist clinicians in evaluating disease status, progression, and prognosis as well in helping to make better treatment decisions. However, no analytic test is better than the laboratory performing it. Proper collection and analytic procedures must be used, and each step in the

preparation and processing of a sample must be carefully performed and monitored. In hair analysis, proper sample preparation and the use of ultrahigh purity digesting acid and distilled water are extremely important. In blood and urine analysis, collection tubes specially designed for the specific tissues being sampled and the minerals being collected must be used. Where analysis of cellular components of blood is involved, care must be taken to separate these components from serum without delay and definitely before transport.

Ultimately, it is the clinician's responsibility to verify the validity of an analytic procedure and to choose a reputable laboratory well known for its expertise, accuracy, and precision of its results. These steps will allow the clinician to confidently interpret and apply the results of any analysis. Finally, and most importantly, treat the patient, not the laboratory work!

It should be noted that many of the articles listed in the Reference section are reviews, and thus can serve as sources of additional information.

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CHAPTER 25

Oral Manifestations of Nutritional Status

Michael T. Murray, ND

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INTRODUCTION

The structures and lining of the oral cavity offer valuable and easily accessible information on the nutritional status of an individual. Lesions may indicate a nutrient deficiency or may be manifestations of gastrointestinal or other disease.[1] Because of the very rapid cell turnover of the oral mucosa, these lesions often may precede other manifestations of nutrient deficiency or systemic disease. Some typical lesions are mucosal ulceration, cheilosis, gingivitis, and glossitis. Between 5% and 10% of the people in the United States are deficient in one or more nutrients, so signs of nutritional deficiency are common.

THE HEALTHY MOUTH

The ventral surface of the healthy tongue is covered with a smooth, pink mucous membrane and lymphoid follicles. On the dorsal surface, the filiform, fungiform, and circumvallate papillae (which contain the organs of taste) produce a rough, grayish red appearance. The thick epithelial tufts of the filiform papillae give the tongue its characteristic grayish white coating, whereas the globular, pale red fungiform papillae give it a speckled pink appearance. Furrows are not characteristic of the healthy tongue.

The buccal mucosa has a grayish red color and may be crossed by fine grayish ridges where it touches the closed teeth.

Healthy gums have a light reddish appearance and cover the roots of the teeth completely.

The assessment of oral health, obviously, must include the health and status of the teeth. Patients should be asked about their dental history and encouraged to have regular dental checkups. Here are some key nutritional considerations for examination of the teeth[2]:

- Having fewer than 20 teeth as an adult is associated with a significantly reduced capacity to eat nutritious foods, such as salads, raw fruit and vegetables, nuts, and whole grain products. The same applies even to denture wearers.
- Bulimia may manifest as erosive tooth wear.
- Osteoporosis may manifest initially as changes in jaw structure and/or loose teeth.
- Presence of mercury amalgams may be associated with systemic disease, especially neurologic conditions.

ABNORMALITIES OF THE ORAL MEMBRANES

Table 25-1 summarizes the typical oral manifestations associated with a particular nutrient deficiency, and Table 25-2 summarizes common disorders associated with oral manifestations.[1-12]

In general, ulceration should be considered a nonspecific expression of a disease state. A search for the etiology will usually result in a specific therapy. Aphthous stomatitis is a common example of a mucosal ulceration and is discussed in detail in Chapter 146.

Similarly, cheilosis is a common expression for acquired nutrient deficiency. Gingivitis is associated with the classic signs of scurvy, but other nutrients have now been shown to play a role in gingival health; this subject is discussed in Chapter 199. Glossitis is associated with numerous vitamin deficiency states, each with a characteristic appearance.

TABLE 25-1 **Oral Signs of Nutrient Deficiency**

NUTRIENT	SIGNS OF ORAL DEFICIENCY
Vitamins	
Biotin	Geographic tongue, atrophy of lingual papillae
Folic acid	Gingivitis, glossitis with atrophy, or hypertrophy of filiform papillae, cheilosis
Niacin	Intraoral burning, canker sores, halitosis, glossitis, tongue swollen with red tip and sides, swollen red fungiform papillae, filiform papillae becoming inflamed and losing their epithelial tufts (giving the characteristic slick red appearance)
Pyridoxine	Intraoral burning, glossitis, mucosal ulcerations and erosions, cheilosis
Vitamin B_{12}	Intraoral burning, mucosal ulcerations and erosions, painful glossitis with a beefy red or fiery appearance, eventually resulting in an atrophic (smooth and shiny) tongue
Riboflavin	Soreness and intraoral burning, cheilosis, angular stomatitis, glossitis with a magenta tongue
Vitamin C	Sore and bleeding gums, deep blue-red color to gums, loose teeth, follicular hyperkeratosis
Vitamin D	Intraoral burning
Vitamin E	Glossitis
Minerals	
Calcium	Periodontal disease, tooth decay
Iron	Cheilosis, atrophic glossitis, gingivitis, candidiasis, intraoral burning or pain, mucosal ulcerations and erosions, pallor
Zinc	Cheilosis, atrophic glossitis, gingivitis, candidiasis, intraoral burning or pain, mucosal ulcerations and erosions, pallor

Data from references 1-12.

TABLE 25-2 **Common Disorders Associated with Oral Manifestations**

ORAL MANIFESTATION	DISORDER(S)
Cheilosis	Crohn's disease, acrodermatitis enteropathica, alcoholism, celiac disease, malabsorption syndrome
Gingivitis	Crohn's disease, anorexia nervosa, celiac disease, scurvy
Erythroplakia	Dysplasia or carcinoma
Glossitis	Crohn's disease, diabetes, alcoholism, celiac disease, malabsorption syndrome, pernicious anemia, iron-deficiency anemia, amyloidosis, carcinoid syndrome, cigarette smoking, anemia
Intraoral burning	Menopause, diabetes mellitus, esophageal reflux, Sjögren's syndrome
Leukoplakia	Chronic irritation, dysplasia, early invasive squamous cell carcinoma
Ulcerations, erosions	Crohn's disease, ulcerative colitis, celiac erosions disease, corticosteroid use, acrodermatitis enteropathica, anorexia nervosa, pernicious anemia, iron-deficient anemia, mercury poisoning, nicotine withdrawal

Data from references 2-12.

Like glossitis, intraoral burning represents a nonspecific expression of a possible nutrient deficiency or systemic disease.[3-5] Possible causes in addition to those listed in Table 25-2 are as follows:

- Xerostomia
- Dentures
- Deficiencies of iron, vitamin B_{12}, folic acid, vitamin B_6, and protein
- Steatorrhea
- Antibiotic use
- Changes in mucosal innervation
- Anxiety states

In people who do not wear dentures, nutritional disorders are the most common causative factors.[2]

Leukoplakia is any white lesion of the oral cavity that cannot be removed by rubbing the mucosal surface. Although lesions are usually only a sign of chronic irritation, 2% to 6% represent either dysplasia or early invasive squamous cell carcinoma.[4]

Erythroplakia is similar to leukoplakia, except that it has a definite erythematous component. This is a far more serious sign, with 90% of such lesions representing dysplasia or carcinoma.

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CHAPTER 26

Rapid Dark Adaptation Test

Dirk Powell, BS, ND

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INTRODUCTION

The earliest sign of vitamin A deficiency is a decrease in dark adaptation, or poor night vision. Serum retinol levels are not sensitive enough to reliably identify mild deficiency states. A dark adaptation test has the advantage of more reliably identifying marginal vitamin A deficiency; however, classic dark adaptation testing is a cumbersome and time-consuming process (usually taking 45 minutes or longer).

A rapid dark adaptation test (RDAT) was described by Thornton[1] and evaluated by Vinton and Russell.[2] This rapid (6 minutes) test has significant clinical utility. The basis for the test is the measurement of the time of the so-called Purkinje shift. This term refers to the shifting of peak retinal wavelength sensitivity from the red toward the blue end of the visual spectrum during the transition from day (cone-mediated) vision to night (rod-mediated) vision. When color vision is nonfunctional, this shift causes the intensity, not the color, of blue to appear brighter than red under dim lighting.

CLINICAL APPLICATION

Although dark adaptation testing has the advantage of being an in vivo test, and therefore directly related to function, it is somewhat less specific. Box 26-1 lists conditions that may give abnormal dark adaptation results with a normal vitamin A status.

PROCEDURE

Equipment and Supplies

- Lightproof room
- A standard darkroom light fixture fitted with a 7.5 W bulb and a neutral-density filter (allowing 1% transmittance). The bottom of the fixture is suspended 1.2 m above the work surface, so that the target brightness on the work area is approximately 0.0068 candela/m^2.
- Munsell color disks with matte finish: five white disks (N9.5/-), six blue disks (5PB5/10), and seven red disks (5R5/10) (available from Munsell Color and Macbeth Division, Baltimore, Md.)
- A nonreflective work surface
- A stopwatch
- A standard x-ray viewbox

Method

1. The procedure is explained to the subject.
2. The subject's vision is light-adapted by fixation on a standard x-ray viewbox for 1 minute at a distance of 0.5 meters. The x-ray viewbox is then turned off (the darkroom light remains on).
3. The subject is given all 18 disks mixed in random order, and the stopwatch is started.
4. The subject separates the white and then the blue disks as fast as possible. Under these controlled lighting conditions, the subject will not be able to recognize the colors, because the cones cannot distinguish color with the limited light available. The ability to separate the disks by brightness therefore depends on

BOX 26-1 Conditions Causing Abnormal Rapid Dark Adaptation Test Results in Subjects with Normal Levels of Vitamin A

- Zinc deficiency
- Cataract
- Retinitis pigmentosa
- Diabetic retinopathy
- Severe errors of refraction
- Miosis caused by pharmaceutical agents
- Tinted corrective lenses

the rods. Any disk mistakenly separated by the subject is returned to the original pile until 100% accuracy of sorting is achieved, at which point the stopwatch is stopped and the time is recorded as the result.

5. The first test performed by a subject should be redone to allow for learning and standardization.

Results

Vinton and Russell[2] reported the following results.

In subjects with normal vision, results are given according to age group:

- 20 to 39 years old: 3.03 ± 1.00 minutes
- 40 to 60 years old: 4.41 ± 0.83 minutes

Results in subjects who are vitamin A deficient average 7.63 ± 1.79 minutes.

INTERPRETATION

The RDAT time depends largely on the individual setting. However, the difference in the RDAT time between normal and vitamin A deficient individuals is significant, and therefore standardization is easily achieved. The normal values depend on the age of the subject, with older subjects having an increased RDAT time. An increased RDAT time may also indicate a zinc deficiency.

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CHAPTER 27

Biomarkers for Stool Analysis

Andrea Girman, MD, MPH

INTRODUCTION

Gastrointestinal (GI) dysfunction is a remarkably common experience in the United States.[1] The popular media are saturated with advertisements promising to soothe a wide variety of complaints, including (but by no means limited to) constipation, indigestion, reflux, bloating, and cramping. Those seeking relief beyond that offered on their local pharmacy shelves are substantial in number: GI-related complaints account for a significant percentage of visits made to primary care providers' offices.[2] As a group, many GI diseases carry significant morbidity and mortality—and many are currently poorly treated or in some cases completely untreated.[3] Yet the burden of GI diseases goes beyond individual physical costs: one survey estimated that over 40 billion dollars are dedicated to addressing GI-related issues annually.[4] Given the substantive toll that GI-related illnesses place on patients and the health care system—and given that current treatment methods to address them may be less than effective—it must be asked: what options do clinicians have to fully support their patients?[5]

Laboratory diagnostics that assess the stool for insight into the state of health of the gut have existed for decades, yet the evolution of technology is such that more sensitive and specific tools now exist for easy clinical application. Biomarkers for stool analysis measure key physiologic aspects of the gut: digestion/absorption (D), immunology/inflammation/infectious processes (I), and gut microflora balance (G) (or DIG). This physiologic assessment of DIG mirrors functional status, and provides a critical noninvasive way to evaluate and clinically approach the patient with GI complaints (Figure 27-1). Assessed together, stool analysis biomarkers provide an effective means of capturing underlying physiologic disruption that manifests as disease: eliminating the need for costly diagnostic testing where unnecessary; highlighting those individuals specifically at risk for organic disease who require immediate specialty referral; and identifying the source of gut dysfunction to apply simple, cost-effective treatments.

OVERVIEW OF THE GASTROINTESTINAL TRACT

A popular adage expounds, "You are what you eat." Over the course of a lifetime, it is estimated that a well-nourished adult will consume between 25 and 50 tons of food.[6] Yet given that these macronutrients—fats, carbohydrates, and proteins—must ultimately be broken down, taken up, and assimilated, perhaps the more appropriate maxim is, "You are what you digest and absorb."

Once taken in, dietary foodstuffs undergo a series of complex digestive processes in this tube within a tube. The human gut has a massive absorptive surface area to capture macronutrients and micronutrients critical to optimal physiologic function, yet the impact of its processes are increasingly understood to go beyond traditionally defined roles of digestion and absorption. The mucosal surface of the GI tract is the primary interface with our external environment, and gut commensal microflora interaction with this mucosal surface is critical for differentiating self from nonself—a phenomenon known as "oral tolerance." In addition, more than 70% of the body's immune tissue sits within the gut, and is both closely interconnected to—and continuously interacting with—the largest concentration of nervous tissue outside of the central nervous system (CNS). These immunomodulatory and neuroendocrine functions give credence to clinical concern that gut dysfunction may be a root cause not only at the level of local digestive issues

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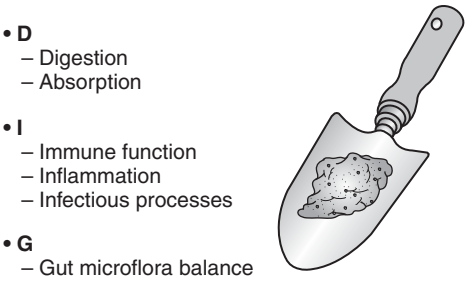


FIGURE 27-1 Key Physiologic and Functional Processes of the Gastrointestinal Tract: DIG

like constipation, gastroesophageal reflux disease, and irritable bowel syndrome (IBS), but also for many chronic, systemic illnesses like inflammatory bowel disease (IBD), Hashimoto thyroidits, systemic lupus erythematosus (SLE), rheumatoid arthritis, and migraine.

The following sections provide a broad-based overview of digestive physiology, followed by an in-depth look at key aspects of the gut utilizing the DIG framework—digestion/absorption (D), immunology/inflammation/infectious processes (I), and gut microflora balance (G)—and the biomarkers that provide insight into their function and/or dysfunction.

DIGESTIVE PHYSIOLOGY 101

Brain

As anyone watching a late-night food commercial may attest to, the process of digestion begins long before any food enters the mouth or stomach. The cephalic phase of digestion begins when anticipatory, visual, gustatory, and/or olfactory stimuli activate CNS centers, and result in parasympathetic stimulation of gastric activity.[7]

Mouth

Homogenization of ingested food first occurs in the mouth via the grinding and mixing action of the teeth. Salivary glands provide hydration to form a bolus and protect the pharyngeal and esophageal mucosa, primarily with secretory immunoglobulin-A (IgA) antibodies. The process of starch and fat hydrolysis is initiated with the release of lingual lipase, salivary amylase, and ptyalin.[8,9]

Esophagus

As the food bolus is swallowed, the epiglottis closes, providing a one-way valve that allows the food to pass into the GI tract and not the respiratory tract. Food is then transported down the esophagus in peristaltic waves past the lower esophageal sphincter into the stomach.

Stomach

The stomach produces churning action, and initiates protein and lipid hydrolysis. Peptides, amino acids, and fatty acids released in this process synchronize the release of pancreatic juice and bile into the small intestine.[8] About 2 L of gastric juice are produced each day, containing several important components.[10] Hydrochloric acid (secreted by the parietal cells) activates pepsinogen to convert to pepsin, which renders some minerals (e.g., calcium and iron) more absorbable. It also creates an essentially sterile environment to prevent bacterial overgrowth. Mucus forms an acid- and pepsin-resistant coating for the stomach lining. Gastric lipase secreted by gastric mucosa begins to hydrolyze triglycerols, producing 1,2-diacylglycerols and fatty acids. The optimal pH of gastric lipase is about 4, but the enzyme is active up to pH 6 or 6.5.[11]

Liver and Biliary System

The liver is the largest gland in the body, and performs an extraordinary number of tasks that impact every system of the body. Although the liver has critical vascular and metabolic functions, its secretory and excretory functions—especially as related to the synthesis and secretion of bile acids—are those that most directly impact digestion.

Because the by-products of lipid digestion have limited ability to dissolve in water, they have difficulty reaching the epithelial surface of the small intestine, which is covered by the unstirred water layer. To be more effectively absorbed, they must form aggregates (micelles) with bile acids (which act as biologic detergents) that can penetrate the unstirred water layer. Without bile acids, only a small number of lipid molecules permeate through the water layer to be taken up by the brush-border membrane of the enterocytes. Finally, fat soluble antioxidants (vitamins A, D, E, and K, as well as lutein and lycopene) also require bile acids for optimal absorption and utilization.

Pancreas

The pancreas plays a vital role in supporting the ongoing breakdown of the semi-fluid mass of partially digested food that flows from the stomach to the small intestine (chyme). Pancreatic duct cells secrete bicarbonate, which is critical for rapidly neutralizing gastric acid to preclude damage to the duodenal mucosa. In addition, pancreatic exocrine function results in the secretion of proteases, amylases, and lipases that further breakdown macronutrients (proteins, carbohydrates, and lipids) so that their components are readily absorbed across the intestinal mucosa.

Primary pancreatic exocrine insufficiency results from organic diseases of the pancreas (e.g., chronic pancreatitis, cystic fibrosis, severe acute necrotizing pancreatitis, pancreatic cancer). Secondary pancreatic exocrine insufficiency results from extra-pancreatic diseases such as celiac disease and Crohn's disease, GI and pancreatic surgical resection, as well as any condition that results in a compromise or blunting of the small intestinal brush border. These include inflammatory processes, infectious agents, food allergies, and dysbiosis and/or small bowel bacterial overgrowth. Whether of primary or secondary etiology, any compromise of pancreatic exocrine function can result in significant malnutrition related morbidity and mortality.[12]

Small Intestine

Most digestion and assimilation occur in the small intestine. Digestion is mediated chiefly by pancreatic enzymes, including proteolytic enzymes, nucleolytic enzymes, lipases, α-amylase, and phospholipase A_2, which hydrolyze macromolecules to oligomers, dimers, or monomers.[8] Pancreatic enzymes are most active in the neutral pH range,[10,13] and bicarbonate begins the process of neutralizing stomach acid. Pancreatic proteases are secreted into the duodenum as inactive precursors, trypsinogen,

chymotrypsinogen, and proelastase, and are activated by brush-border enzymes, such as enterokinase, to form trypsin, chymotrypsin, and elastase, respectively.[10]

The digestive and absorption capacities of the small intestine are greatly enhanced by circular folds and fingerlike projections of the intestinal mucosa called microvilli. This region, dubbed the "brush border," increases the luminal surface area of the intestinal wall by about 600 times, creating a total absorptive surface of approximately 200 to 250 m^2, essentially the size of a tennis court.[10,13,14]

Even after prolonged contact with pancreatic enzymes, a substantial portion of ingested carbohydrates and amino acids depend on hydrolytic enzymes (disaccharidases such as maltase, sucrase, lactase, enterokinase, and peptidases) produced by the brush-border membrane to complete their digestion.[10]

For this reason, damage to the intestinal brush border—resulting from inflammation, trauma, parasitic infection, bacterial overgrowth, long-term nonsteroidal anti-inflammatory drug use, and other factors—may interfere significantly with the proper absorption of nutrients. Such damage also can disrupt the intracellular tight junctions that are vital to the protective barrier function of the gut mucosal layer, increasing the intestinal permeability of potentially harmful macromolecules, such as bacteria and toxins, into the systemic circulation. This state of increased intestinal permeability, sometimes referred to as "leaky gut," has been cited as a potential contributory or causative factor in gluten enteropathy, Crohn's disease, food allergy, various arthritides and autoimmune diseases, chemotherapy complications, and a variety of other clinical conditions.[15-19]

Large Intestine

A primary role of the large intestine is to absorb water, about 1 L/day. The large intestine also provides an environment for microbial fermentation of soluble fiber, starch, and undigested carbohydrates. Soluble fibers are more readily fermented than insoluble fibers.[20]

Nondigestible carbohydrates (e.g., fiber), polysaccharides, and oligosaccharides contain chemical bonds that make them incapable of complete digestion by pancreatic or brush-border enzymes. As they move through the digestive tract, these undigested compounds play an important role in intestinal transport mechanisms. Once in the colon, they are cleaved and modified by enzymes produced by resident colonic bacteria to form short-chain fatty acids (SCFAs) and various gases, such as methane, hydrogen, and carbon dioxide.[11]

ASSESSING GASTROINTESTINAL HEALTH: DIG

As noted previously, a clinical approach to evaluating the functional state of gut health can be one that is based on the primary physiologic roles of the gut. This approach is captured by the mnemonic DIG: digestion/absorption (D), immunology/inflammation/infectious processes (I), and gut microflora balance (G).

DIGESTION/ABSORPTION

Digestive Dysfunction

The first step in optimizing GI health is optimizing digestive function. Because numerous organs are involved in the digestive process, maldigestion can occur with malfunction at any level of digestive physiology, resulting in both local and systemic signs and symptoms. Maldigestion may result from an inadequate cephalic phase, leading to inadequate secretion of salivary amylases and proteases; insufficient mastication; hypochlorhydria; pancreatic insufficiency; bile insufficiency; small intestinal villous atrophy; and brush-border enzyme destruction.

As an example, hypochlorhydria has been hypothesized to be the root cause of a number of clinical conditions, including reduced mineral and amino acid absorption, depression, and other syndromes.[21,22]

In addition, interest has been expressed in the medical literature about the connection between the robust use of pharmaceuticals promoting gastric acid blockade and chronic clinical complaints. Research indicates that small bowel bacteria overgrowth, and associated disorders such as blunting of brush-border enzyme activity and decreased pancreatic exocrine function, may be an iatrogenic consequence of overprescribing of proton pump inhibitors.[23-25] Given that long-term use of drugs that markedly reduce gastric acid secretion may negatively affect dietary and nutriceutical calcium absorption, concern has also been raised about their potential to increase the risk of fracture in individuals with osteoporosis, although the greatest potential for this may be in patients already at risk for loss of bone mineral density.[26-29]

Maldigestion associated with pancreatic exocrine insufficiency results in an inadequate delivery of enzymes to the small intestine, and can lead to inadequate breakdown of fats, carbohydrates, or protein. The net effect is poor nutrition and an unhealthy environment for the flora of the large intestine. Significant decreases in exocrine pancreatic secretion have been associated with the aging process,[30] and clinically, may be associated with osteoporosis[31,32] and diabetes.[33-35]

Absorptive Dysfunction

Malabsorption can be characterized by abnormal fecal excretion of fat (steatorrhea); abdominal pain; and variable malabsorption of fats, fat-soluble vitamins, other vitamins, proteins, carbohydrates, minerals, and water. Common causes include:

- Maldigestion
- Hypochlorhydria
- Small bowel bacterial overgrowth
- Deficient bile production, resulting in inadequate solubility of fatty acids[11]
- Chronic inflammation of the small intestine
- Rapid transit, which does not allow adequate time for absorption

Malabsorption often increases with age[36]: atrophic gastritis is estimated to affect 10% to 30% of individuals more than 50 years old and often leads to inadequate absorption of key nutrients such as vitamin B_{12}.[37]

General malabsorption syndromes are associated with many disorders of the intestinal tract, including celiac disease, gluten enteropathy, IBD, infectious processes such as giardiasis and cryptosporidiosis, lactose intolerance, and eosinophilic gastroenteritis. Because amino acids, carbohydrates, vitamins, and minerals are absorbed through different processes, individuals with malabsorption are at risk for development of a wide range of nutrient deficiencies.

Biomarkers for Digestion/Absorption

Pancreatic Elastase 1

Pancreatic elastase 1 (PE1) is a proteolytic enzyme secreted exclusively by the human pancreas, and as such, reflects overall pancreatic exocrine function.[38] It is an extremely stable, reliable, and specific marker,[39] and correlates well with gold-standard,

stimulated pancreatic function tests.[40] PE1 is concentrated five- to six-fold higher in feces than when it enters the duodenum, reflecting an overall stability of this biomarker in the GI tract.[41] It is not degraded during intestinal transit, and is generally not affected by increases or decreases in intestinal transit time,[42] although its sensitivity may be diminished in cases of liquid diarrhea.[43] Unlike other pancreatic markers, such as chymotrypsin, PE1 results are not affected by pancreatic enzyme replacement therapy,[39,40] a feature that makes it a valuable marker for monitoring and adjusting exogenous enzyme replacement.[39]

PE1 appears to have less sensitivity when diagnosing mild exocrine pancreatic insufficiency, and may have limited use in differentiating pancreatic from nonpancreatic steatorrhea or diarrhea.[44]

Although research typically indicate levels of PE1 less than 200 mcg/g to be consistent with normal pancreatic exocrine function, healthy individuals produce on average 500 mcg/g of PE1. Given that, PE1 levels greater than 200 mcg/g and less than 500 mcg/g suggest a deviation from optimal pancreatic function. PE1 values between 100 and 200 mcg/g suggest moderate pancreatic insufficiency, and values less than 100 mcg/g are considered to be consistent with severe pancreatic insufficiency.[45,46] Enzymatic support of pancreatic insufficiency is warranted, and strength of supplementation–typically based on the level of lipase units–should be modulated based on the degree of pancreatic insufficiency indicated by the PE1 level (Table 27-1).

Reduced PE1 has been reported clinically in patients with type 1 and type 2 diabetes.[47,48] chronic pancreatitis,[49,50] osteoporosis,[32] cystic fibrosis,[51] trauma states,[47] and in intestinal malabsorption states associated with mucosal atrophy such as celiac disease.[52,52a]

Putrefactive Short-Chain Fatty Acids

Valerate, isovalerate, and isobutyrate are produced exclusively by bacterial fermentation of proteinaceous material (polypeptides and amino acids). These SCFAs are putrefactive, and their presence suggests underlying maldigestion and/or malabsorption from dysfunctional states such as hypochlorhydria or exocrine pancreatic insufficiency,[53] or bacterial overgrowth in the small intestine. Other causes are GI disease (resulting from the fermentation of blood or mucosal cells delivered to the colon)[54] and rapid transit time (resulting from inadequate time for digestion and absorption of peptides and amino acids).[55]

Fecal Fats

Fecal fats include triglycerides, long chain fatty acids, cholesterol, and phospholipids, and are derived primarily from the dietary ingestion of fat. Elevated levels of fecal fats in the stool suggest fat malabsorption (steatorrhea), which can occur as a result maldigestion and/or impaired uptake of fatty acids. In addition, any condition that results in impairment of lipase activity and bile acid production and release may result in fat malabsorption. These include pancreatic insufficiency, cholestatsis, short bowel syndrome, and celiac disease.[56]

TABLE 27-1 **Pancreatic Elastase 1 Levels, Degree of Pancreatic Insufficiency, and Enzyme Supplementation**

>500 mcg/g	Optimal
351-500 mcg/g	Normal, but not optimal
201-350 mcg/g	Mild insufficiency
101-200 mcg/g	Moderate insufficiency
<100 mcg/g	Severe insufficiency



IMMUNOLOGY/INFLAMMATION/INFECTIOUS PROCESSES

As noted previously, more than 70% of the body's immune tissue sits within the GI tract.[57] This immune tissue has a complex and dynamic relationship with the commensal microflora that colonize its surface—the primary interface with an external environment rich in both supportive dietary antigens as well as pathogenic agents. The gut commensal microflora exist in this macronutrient dense intestinal environment, and are significant contributors to the process of digestion, building of essential nutrients, and holding nonbeneficial bacterial counts in check. How is it then that host immune function is modulated to allow for the acceptance of self (as well as supportive commensal organisms and dietary antigens), even as it is vigilantly surveying for and combating against pathogenic microorganisms?

The answer appears to lay with an exquisitely balanced, ongoing inflammatory response by the intestinal immune system: it is capable of mounting strong inflammatory responses against pathogenic agents while concomitantly providing inhibitory signals that preclude responses against commensal bacteria.[58,59] Any alteration of this equilibrium, for example, as a result of gut microflora imbalance, genetic predisposition, or immune dysregulation, will result in an upregulation of the gut inflammatory response. Diagnostically, this may be reflected by the release of the biomarker calprotectin from neutrophils.[60] Clinically, the breakdown of this intestinal immune balance has been implicated in the development of diseases marked by significant inflammation, such as IBD,[61-63] and has been postulated to play a role in the development of extraintestinal allergic and autoimmune disorders.[64] Microflora imbalance has also been reported in patients with IBS.[65]

Biomarkers for Immune Function/Inflammation/Infectious Processes

Eosinophil Protein X

Eosinophil protein X (EPX) is a basic cellular protein with potent cytotoxic and neurotoxic properties, and is a marker of eosinophil activation and degranulation. Mobilization of eosinophils in the gut appears to occur in response to immune-mediated inflammatory responses.[66,67]

Clinically, fecal elevations of EPX have been described in IBD, IgE-mediated food allergy, parasitic infections, and collagenous colitis.[68-79]

Calprotectin

Calprotectin belongs to a group of calcium-binding neutrophil-derived proteins. Because neutrophils are typically mobilized in response to increased mucosal permeability, cell or tissue damage, and infectious processes, elevations in calprotectin may be seen in the presence of inflammatory, neoplastic, and/or infectious disease processes.[80,81]

Clinical application of this biomarker has been directed toward discerning the best approach for the patient with functional abdominal symptomology. Specifically, calprotectin has been evaluated (in conjunction with Rome criteria) as a diagnostic biomarker to distinguish between IBS and IBD.[82-84] Surveys indicated that up to 12% of primary care visits were comprised of IBS-related complaints and accounted for 28% of referrals to gastroenterologists.[85,86] Because

symptoms often overlap, early IBD may be inappropriately labeled as IBS. At least one study reported that more than 25% of patients with Crohn's disease had been misdiagnosed as having IBS in the prodromal stages of their disease.[87] Attempts to define organic disease in patients with IBS inevitably results in the application of more invasive diagnostic imaging procedures and escalated health care costs.[5]

Calprotectin has been found to correlate closely with IBD activity[88] and provides a highly sensitive, specific, and noninvasive alternative for assessing inflammatory activity in IBD.[84,89] Fecal calprotectin levels have been shown to correlate significantly with histologic and endoscopic assessment of disease activity in ulcerative colitis[90] and with indium-111–labeled white blood cells (the gold standard for assessing gut inflammation) in patients with Crohn's disease.[91] In one report, more than 95% of patients with IBD had elevated fecal calprotectin levels.[92]

Calprotectin has been used to predict relapse in patients with established IBD and to evaluate the effectiveness of therapeutic regimens as well.[68,93,94]

Because severity of inflammation is indicated by varying levels of calprotectin, treatment options and urgency of diagnostic intervention vary as well (see Table 27-2).

Infectious Agents

Helicobacter pylori. *Helicobacter pylori* remains a prevalent worldwide infection, with infection rates in middle-aged adults reaching more than 80% in areas of low socioeconomic status and 20% to 50% in most industrialized countries.[95] *H. pylori* continues to be a causal link for the development of peptic ulcer disease (an estimated 10% to 20% lifetime risk in infected individuals),[96] as well as a variety of other GI concerns ranging in severity from dyspepsia to gastric malignancy.[97,98]

Several diagnostic options exist in assessing possible *H. pylori* infection. Although histologic confirmation remains the gold standard, noninvasive measures such as urea breath testing, *H. pylori* stool antigen (HpSA) testing, and *H. pylori* polymerase chain reaction (PCR) are currently available.

HpSA diagnostics have been approved by the U.S. Food and Drug Administration for the detection of *H. pylori* pre- and posteradication therapy. This biomarker indicates the presence of *H. pylori* antigens shed directly into the stool, and provides increased ease of clinical use as well as diagnostic performance characteristics comparable to urea breath testing in both adult and pediatric populations.[99,100] It has been shown to accurately indicate treatment failure at 7 days after completion of eradication therapy (compared with 4 weeks for urea breath testing),[100-102] an important consideration for directing additional clinical intervention in patients who remain symptomatic or develop recurrent symptoms posttherapy.

Although PCR testing for *H. pylori* is currently offered as a noninvasive diagnostic alternative to endoscopy and biopsy as well, concerns have been raised about the high degree of false-positive results with this methodology.[103,104]

Clostridium difficile. *Clostridium difficile* is an anaerobic, spore-forming, gram-positive bacterium that can be part of the normal intestinal flora. Although typically considered an opportunistic infection occurring after antibiotic therapy, the epidemiology of *C. difficile* infection has shifted significantly. Its incidence has increased dramatically worldwide in the past decade, and new at-risk populations include individuals with community-acquired infection and no previous exposure to antibiotics, children, and pregnant women.[105]

C. difficile produces two toxins, A and B, which are its main virulence factors, and human infection can take many forms. These range from asymptomatic carrier states[106] and recurrent mild-to-moderate IBS-like manifestations, to severe symptoms indistinguishable from colitis (cramping, diarrhea, urgency, mucus, and blood) that may result in a misdiagnosis of IBD.[107]

Parasitic Agents

Research suggests that parasitic organisms may also act as etiologic agents of gut inflammation and dysfunction, including abdominal pain, diarrhea, and constipation.[108] One study found *Blastocystis hominis* to be present four times more frequently in IBS patients compared with control subjects. In addition, symptoms resolved in 80% of subjects with IBS when *B. hominis* was treated.[109]

Other parasitic agents identified by stool analysis that have been isolated from patients with clinical symptomology include *Dientamoeba fragilis*, *Entamoeba spp.*, *Endolimax nana*, and *Giardia lamblia.*[110-112] A recent review by an American diagnostic laboratory routinely surveying stool for parasitic agents found that 23.5% of nearly 14,000 clinical samples meeting *International Classification of Diseases 9th Edition* criteria for IBS tested positive for the presence of at least one parasite.[113] *B. hominis* was the most commonly identified organism (12.5% of positive samples), followed by *D. fragilis* (3.8%), *Entamoeba* spp. (3.4%), *E. nana* (2.2%), and *G. lamblia* (0.7%). Similar results have been reported by laboratories outside of the United States as well.[114]

TABLE 27-2 **Calprotectin Levels, Inflammation Severity Clinical Intervention**

<50 mcg/g	No inflammation
50-120 mcg/g	Mild inflammation
• Evaluate for dybiosis, allergies, infection	
120-250 mcg/g	Moderate inflammation
• Evaluate aggressively for source of inflammation	
>250 mcg/g	Severe inflammation
• Refer for diagnostic imaging (i.e., colonoscopy)	
• Begin treatment in patients with IBD. Therapy should persist until biomarker indicates that inflammation has resolved and mucosal healing has occurred.	

GUT MICROFLORA BALANCE

At birth, the human GI tract is sterile. Bacterial colonization begins within days of delivery, and evolves continuously over the first 1 to 2 years of life.[115] Early gut microflora development is impacted by a variety of factors: location and type of birthing, breast-feeding versus formula-feeding, and antibiotic use in infancy and childhood.[116-119] *Bifidobacteria* are typically the first organisms to populate the newborn gut, and research suggests that any event that results in inadequate gut colonization during early life may lead to an increased risk of infectious, allergic, and autoimmune disorders later in life.[120] Once established, the bacterial composition of the gut tends to remain relatively constant over the lifetime of an adult,[121] although environmental (pharmaceuticals, toxins, infectious agents), lifestyle (stress), and dietary (glycemic load, fiber content, essential fatty acid composition, macronutrient/micronutrient composition, and pH balance) factors may induce shifts in commensal flora balance.[122,123]

Bacteria are present at every level of the GI tract and can be found in increasing density as one progresses from the upper gut (esophagus and stomach 10^3 to 10^5 organisms/mL luminal content) to the lower gut (large intestine 10^{10} to 10^{12} organisms/mL luminal content; feces 10^9 to 10^{11} organisms/mL luminal content). In addition, the human gut hosts a massive diversity of microflora species—more than 400 have been described to date. Anaerobic species comprise the vast majority of the microbiome in healthy individuals: these include obligate anaerobes such as *Bacteroides*, *Bifidobacterium*, *Lactobacillus,* and *Clostridium*, as well as facultative anaerobes such as *Escherichia coli*, *Citrobacter*, *Enterobacter*, *Proteus,* and *Klebsiella*.[124] At counts of greater than 100 trillion bacteria colonizing the GI tract, these nonhuman cells vastly outnumber the total number of human cells in the body. With a metabolic capacity greater than the liver—and accounting for roughly 3 lbs of body mass—this dynamic population of organisms could be considered a hidden organ in its own right.[125]

As noted previously, the bacteria that inhabit the human GI tract play a significant role in metabolic processes in the body. These include fermentation, SCFA and undigested dietary fiber metabolism, primary bile acid deconjugation, vitamin synthesis, and energy production. In addition, they are key immunomodulators, exert trophic effects on intestinal epithelia, and are a critical defense against pathogens—not only by competing for nutrients, space, and adherence intraluminally, but also by producing bacteriocidal substances.[126] For this reason, alterations in gut microbial balance (dysbiosis) may result in health-related consequences at both intestinal and extra-intestinal levels.[65,127-129]

In dysbiosis, organisms of typically low intrinsic virulence, including bacteria, yeasts, and protozoa, may grow or migrate beyond their normal limitations. This can result in intensified microbial competition for nutrients, damage to the gut mucosal layer, and alterations of host immune function,[130] and as a consequence, may increase the risk for nutritional deficiencies, inflammation, autoimmune disorders, and neoplasia.[126,131-135]

Given the potential for disease that results from altered host-flora dynamics, restoration of balance as a means of restoring health has been a fundamental tenet of natural medicine and an increasing area of research in traditional medical spheres. However, the question should be asked: what defines optimal gut ecology?

Analysis of stool samples has been historically used to provide insight into the microbial composition of the gut. Specifically, levels of growth on plated culture media can be quantified and reflect the density of bacteria in the distal colon. Studies comparing electron microscopic evaluation of the microflora with fecal culture suggest that 50% to 80% of total microscopic composition is recovered with stool culture methodologies. Limitations presented with the utilization of culture techniques include selectivity of growth based on media used and challenges posed by recovering strict anaerobes in a standard culture environment. Despite these limitations, use of molecular probes suggests that there is good agreement on the degree of biodiversity when fecal culture is compared with 16S rDNA sequence analysis. In addition, biomarkers that reflect the metabolic activity of the GI microflora provide insight into the optimal functioning of the microbiome.[136]

With the advent of the Human Microbiome Project, increased focus has been placed on use of molecular probe technology to characterize the microbial populations of the human body.

Given ongoing evidence linking the GI microflora, health, and disease, these research initiatives have sought to identify a core gut microbiome. A limited number of common species have been demonstrated in the human intestinal microbiota to date and indicate the promise of applying molecular probe techniques in defining beneficial bacterial composition. Given that research consistently demonstrates significant interindividual diversity and high intraindividual specificity, variability of microflora composition between individuals appears to be the norm, especially with aging.[137,138] In addition, although molecular probes have the capability of identifying the vast pool of species inhabiting the human gut, questions have been raised about the clinical relevance of such identification, as was noted previously with *H. pylori* PCR versus stool antigen testing. This is of particular concern when parasitic and/or pathogenic organisms are identified, because probe technology does not currently have the capacity to differentiate between the DNA of living organisms (active infection) and DNA fragments indicative of past infectious processes or incidental exposure.

Ultimately, characterization of the microflora is undertaken to correct imbalances that may be contributing to acute or chronic states of illness. Supportive therapies such as prebiotics and probiotics (see Chapters 115 and 116 on Prebiotics and Probiotics) are standard clinical tools for optimizing gut health, and supplementation has been shown to be of benefit in an array of medical conditions, including atopic dermatitis[124,139]; acute infectious and antibiotic-associated diarrhea[140-142]; cancer prevention[133]; IBS[143,144]; prevention of necrotizing enterocolitis[145]; prevention and treatment of pouchitis[146]; and ulcerative colitis.[147-149,150]

Although evidence exists that demonstrates clinical benefit, there is little consensus regarding what constitutes the most optimal therapeutic strain(s), concentrations, or timeline of treatment. With the emergence of molecular technology, there may be a point in the near future that allows individual targeting of probiotic therapies. Until that time, phenotypic markers that provide insight into the health of the microbiome—biomarkers reflecting digestion/absorption (D), immunology/inflammation/infectious processes (I), and gut microflora balance (G)—may be utilized to identify and monitor patients needing support.

BIOMARKERS FOR GASTROINTESTINAL MICROFLORA BALANCE AND METABOLIC FUNCTION

Beneficial Bacteria

Bifidobacterium, Lactobacillus, and nonpathogenic *E. coli* are the predominant strains of beneficial flora,[117] with the obligate anaerobic *Bifidobacteria* constituting about one fourth of the microbial flora found in adults.[151] In the distal colon, *Bifidobacteria* outnumber *Lactobacilli* by 1000:1.[152] Given that, quantification of *Bifidobacteria* via stool culture typically demonstrates recovery in the 3+ or 4+ ranges in a healthy microbial milieu. The facultative aerobe *Lactobacilli* and nonpathogenic *E. coli* are both typically recovered in the 1+ or 2+ ranges.[153]

Adequate amounts of *Bifidobacterium, Lactobacillus,* and nonpathogenic *E. coli* are essential for the maintenance of optimal digestive functioning, and as such, these species are utilized in culture diagnostics as indicators of gut microflora health. Recovery of their numbers in less than optimal ranges suggests alterations in gut microbial balance, and indicates a clinical need to ascertain the underlying etiology of the disruption, and ultimately, to assess the need for therapeutic support. The composition and distribution of the GI flora are impacted by a variety of factors as noted previously, including dietary intake, infectious agents, pharmaceuticals, and age. Stress also exerts a profound impact on gut flora and physiology, including increasing intestinal permeability, increasing bacterial adherence, and decreasing intraluminal levels of *Lactobacilli*.[123]



FIGURE 27-2 Probiotic recommendations by disease. From Isolauri E, Kirijavainen PV, Salminen S. Probiotics: a role in the treatment of intestinal infection and inflammation? Gut 2002 50: iii54-iii59http://gut.bmj.com/content/50/suppl_3/iii54.full.pdf.) Used with permission from BMJ Publishing Ltd.

Restoration of balance and improvement of clinical symptoms may be achieved by probiotic supplementation. As indicated in the peer-reviewed literature, increasing levels of probiotic support may be required with increasing levels of disease state severity (see Figure 27-2).[154]

Additional Bacteria

Bacterial cultures are capable of identifying any number of additional organisms present in the individual human gut. These organisms may or may not exert a pathogenic effect depending on the state of balance or imbalance of the gut microbial milieu in toto. Putting it another way: sometimes these agents are the source of gut dysfunction, and sometimes their presence is merely a reflection of underlying gut dysfunction.

Overgrowth of additional bacteria may cause clinical and subclinical malabsorption and increase bowel permeability to large molecules. Abnormalities of the immune or mechanical barriers can lead to enhanced uptake of inflammatory luminal macromolecules and pathogenic bacteria. Bacterial antigens are capable of inducing antibodies, which cross react with host antibodies, forming systemic immune complexes.[155,156] This process has been implicated in the etiology of chronic gut inflammation, as well as SLE and other connective tissue diseases.[157,158]

Bacterial species such as *Klebsiella* and *Proteus* are not routinely surveyed as components of standard microbiological assessments, but both have demonstrated antigenic cross reactivity to human leukocyte antigens (HLAs). *Klebsiella* has been associated with ankylosing spondylitis when cross reactivity occurs with the HLA-B27 antigen. Similarly, *Proteus mirabilis* has been associated with rheumatoid arthritis and is known to cross react with the HLA-DR4 antigen.[159,160]

Mycology

The GI tract in healthy individuals normally harbors small amounts of yeast. However, colonic yeast infections have attracted attention and controversy as a possible cause of chronic complex illnesses.[161] Investigators have hypothesized that *Candida albicans* may be involved in the etiology of allergic disorders such as scleroderma and asthma,[131,162] chronic fatigue,[163] chemical sensitivity,[161] and IBD.[164]

Biomarkers for Microflora Metabolic Activity

As mentioned previously, biomarkers that reflect the metabolic activity of the GI microflora can provide an adjunctive assessment of the microbial status of the gut. Diagnostic assays utilized include those that evaluate SCFAs, β-glucuronidase, and bile acid metabolism.[140]

Beneficial Short-Chain Fatty Acids

SCFAs are produced by the anaerobic bacterial fermentation of primarily nonabsorbed dietary fiber.[165] The rate and amount of SCFA production depends on the composition and density of microflora present in the colon, the substrate source, and GI transit time.[166]

There are three primary beneficial SCFAs—acetate, n-butyrate, and propionate—yet most clinical and research emphasis has been placed on n-butyrate. Butyrate plays a major role in the physiology of the colonic mucosa and serves as the major energy source for the colonocyte.[167] In addition, research suggests that it may modulate inflammation in IBD via regulation of proinflammatory cytokines[168,169] and may play a role in the prevention of colon cancer.[170]

Beta-Glucuronidase

Beta-glucuronidase is an inducible enzyme elaborated by anaerobic *E. coli, Peptostreptococcus, Bacteroides,* and *Clostridium*.[171,172] By uncoupling glucuronides (xenobiotics and endogenous compounds detoxified via the glucuronidation pathway), this enzyme can deconjugate potential toxins, enhancing the formation of local carcinogens in the bowel[173] and promoting the enterohepatic recirculation of toxins, hormones,[174] and various drugs[175] in the body. For this reason, excess amounts of the enzyme may promote higher risk of colon cancer. Both the incidence of colon cancer and levels of β-glucuronidase tend to be higher in individuals consuming Western diets (high in saturated fat, low in fiber) than in individuals consuming diets high in fiber and low in saturated fat.[176]

However, an adequate amount of β-glucuronidase activity is probably important to maintain normal enterohepatic recirculation of endogenous compounds, such as vitamin D,[177] thyroid hormone,[178] and estrogen.[179]

Bile Acids

The relationship between dietary fat and increased risk of colon cancer is believed to hinge on the excess production of bile acids and the bacterial conversion of conjugated primary bile acids to potentially dangerous unconjugated secondary bile acids.[180] Studies have found that a higher ratio of secondary bile acids, specifically, an elevated ratio of lithocholic acid to deoxycholic acid (LCA/DCA ratio), is associated with higher susceptibility to polyps and colorectal cancer.[181] Increased secondary bile acid excretion and a rise in the LCA/DCA ratio have also been observed in patients with gallstones.[182]

Bacterial overgrowth markedly increases the concentration of unconjugated bile acids, and this mechanism may play an important role in the pathophysiology of gut mucosal injury.[183] Probiotic treatment with *L. reuteri* has been demonstrated to lower the bioavailable concentration of toxic bile acids.[180]

SUMMARY

The philosophical framework that describes GI health to be the foundation of optimal health is not a new one. The *Sushruta Samhita*, an ancient Ayurvedic text, alludes to this in the following passage: "A person whose basic emotional and physical tendencies are in balance, whose digestive power is balanced, whose bodily tissues, elimination functions and activities are in balance, and whose mind, sense and soul are filled with vitality, that person is said to be healthy." If we hold this tenet to be true, then tools that allow us to diagnostically illuminate the imbalances that create symptoms and disease states in our patients—and ultimately lead to interventions to support them—are clinically important. Biomarkers for stool analysis provide a useful approach to identify the underlying pathologies that present as gut dysfunction, thus eliminating the need for costly diagnostic testing where unnecessary, highlighting those individuals specifically at risk for severe disease who do require significant diagnostic intervention, and identifying the source of gut dysfunction to apply simple, cost-effective treatments (Boxes 27-1 and 27-2).

BOX 27-1 Biomarkers for Stool Analysis Clinical Vignettes

A 21-year-old woman presents with a history of intermittent recurrent abdominal cramping, bloating and/or gas, and occasional diarrhea over the past 2 years. She has been evaluated by her college health clinic on numerous occasions, has been told that her symptoms were primarily "stress related," and has been advised to cut back on her coffee intake during the day. She has recently been evaluated for complaints of fatigue, and has been diagnosed with hypothyroidism (including elevated thyroid antibodies), for which she is now being treated. While home during a break, the patient was asked to submit a stool analysis by her primary care doctor who was concerned that some underlying etiology had not been determined. Results were significant for the following:

Pancreatic Elastase = 150 (normal level, more than 200)

- At this level, the pancreatic elastase clinically indicates moderate pancreatic insufficiency and need for pancreatic enzyme support. Evaluation of the underlying cause of pancreatic insufficiency is warranted.

Calprotectin = 22 (normal level, less than 50)

- A normal calprotectin level indicates no inflammation due to neutrophilic activity in the gastrointestinal tract.

Eosinophil Protein X = 13.1 (normal level, less than 7.0)

- An elevated eosinophil protein X may be associated clinically with celiac disease, parasitic infections, and/or immunoglobulin-E mediated food allergies.

Microscopy = No Evidence of Parasite Infection or Altered Gut Flora

Given that celiac disease can be consistent with the patient's clinical symptoms, and may be suggested on stool analysis by an elevated eosinophil protein X and compromised pancreatic exocrine function (low pancreatic elastase), the doctor decided to evaluate the patient for celiac disease. Blood serologies (positive tissue transglutaminase immunoglobulin-A and positive anti-endomysial antibody) confirmed the diagnosis of celiac disease. The patient was placed on a gluten-free diet and given pancreatic digestive enzyme support. At follow-up, the patient reported that her symptoms had markedly improved—appearing only during times of dietary indiscretion.

BOX 27-2 Biomarkers for Stool Analysis Clinical Vignette

A 42-year-old woman presents with a 3-year history of irregular bowel movements and intermittent lower abdominal pain, for which she has seen her primary care provider many times. She also has been diagnosed with depression, and is currently using a tricyclic antidepressant, which she notes does not make a significant difference in her abdominal pain. She has used fiber, antidiarrheals, probiotics, and diet changes in the past to no avail. Upon evaluation, her new primary physician chooses to use stool analysis to evaluate the root cause of her illness. While waiting for the stool test to return, empiric use of probiotics at 10 billion colony-forming units per day has made no difference. The following results were noted:

Pancreatic Elastase = 482 (normal level, more than 200)

- At this level, the pancreatic elastase clinically indicates normal pancreatic function and no need for pancreatic enzyme support.

Calprotectin = 286 (normal level, less than 50)

- This level of elevation of calprotectin level indicates severe gastrointestinal tract inflammation and warrants referral to a specialist for further investigation (i.e., colonoscopy).

Microscopy = No Evidence of Parasitic Infection or Altered Gut Flora

The patient is referred for colonoscopy for inflammatory changes in the gastrointestinal tract. She is diagnosed with ulcerative colitis and placed on steroids and 5-aminosalicylic acid. For this patient, stool analysis allowed for early detection and appropriate referral to a gastroenterologist. Subsequent evaluations of gastrointestinal inflammation with the calprotectin biomarker can be used to monitor mucosal healing and determine if repair is sufficient and/or complete, or to monitor for relapse in patients with IBD.

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CHAPTER 28

Urinary Organic Acids Profiling for Assessment of Functional Nutrient Deficiencies, Gut Dysbiosis, and Toxicity

J. Alexander Bralley, PhD, and Richard S. Lord, BS, PhD

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INTRODUCTION

Urinary organic acid analysis for metabolic profiling was used initially to assess inborn errors of metabolism that can cause severe mental retardation or death within the first year of life. The identification of isovaleric acidemia in 1966 was followed quickly by numerous additional acidurias, because the severe enzyme impairments of genetic diseases were found to result in urinary excretion of highly elevated amounts of organic compounds.[1] Profiling of organic acids in urine as a routine laboratory evaluation of chronic diseases is a relatively recent addition to clinical assessment procedures.

Levels of organic acids in urine can be used to detect functional nutritional deficiencies, to identify genetic variants, and to establish the source of toxicants from the environment and gut.[2-4] For example, elevated methylmalonic acid (MMA) in urine is a sensitive indicator of functional vitamin B_{12} deficiency because the vitamin plays a critical role in metabolic clearance of MMA.[5,6] Similarly, levels of other organic acids in urine are markers of multiple nutritional deficiencies. Organic acid profiling of urine has been found useful in numerous clinical evaluations, as shown in Table 28-1.

URINARY ORGANICS PROFILING

The test is performed on an overnight urine sample and the concentrations of 40 or more compounds are measured by gas chromatography/mass spectrometry (GC/MS) or liquid chromatography (LC)/MS-MS methods. The information content of the profile is high, but the interpretation is simplified if one keeps in mind that the results answer six questions of clinical relevance:

1. Is mitochondrial energy production adversely affected?
2. Are functional nutrient deficiencies present?
3. Are neurotransmitters displaying abnormal turnover rates?
4. Is antioxidant protection status insufficient?
5. Is toxicant exposure elevated?
6. Are there elevated growth rates of upper intestinal bacteria or fungi?

Table 28-2 shows compounds that might appear on a typical quantitative report of organics in urine with some interventions that have been found to help rectify conditions associated with abnormal levels. The supplementary nutrient amounts are given as guides to starting points that might improve clinical outcomes for adults.

FATTY ACID OXIDATION

Adipate, Suberate, and Ethylmalonate

Adipate and suberate are short-chain dicarboxylic fatty acids produced by an alternate oxidation pathway called ω-oxidation, which occurs in peroxisomes. Their production is normally low because the predominant pathway is β-oxidation in the mitochondria. However, transport of fatty acids into the mitochondria requires carnitine as a carrier. Suboptimal levels of carnitine result in inadequate transfer of fatty acids into the mitochondria and subsequent

TABLE 28-1 **Clinical Applications of Organic Acids in Urine Testing**

CONDITION	COMPOUND(S)	REFERENCE(S)
Acidosis with metformin	Lactate	81, 82
Acute appendicitis	5-Hydroxyindoleacetate	83
Adult neurologic complaints and breathing problems	Pyroglutamate	84
Alcoholic delirium tremens	Vanillylmandelate, homovanillate	85
Anemia	Methylmalonate	86
Arginine-responsive hyperammonemia	Orotate	88
Attention deficit hyperactivity disorder	Homovanillate	87, 89
Bacterial overgrowth syndromes in acutely ill infants and children	*p*-Hydroxyphenylacetate	90
Biotin-responsive orificial skin lesions, lethargy, hypotonia, and alopecia	3-Hydroxyisovalerate	91
Birth asphyxia	Lactate, pyruvate, 3-hyroxybutyrate, 4-hydroxyphenyllacetate, 2-hydroxybutyrate, 2-oxo-isocaproate, 2-oxo-3-methylvalerate	92
Calcium urolithiasis	Citrate	93
Carnitine-responsive familial Reye-like syndrome	Pyruvate, α-ketoglutarate, α-ketoadipate	94
Cerebral palsy	Fumarate	95
Chronic fatigue syndrome	Succinate	96
Chronic lactic acidosis (weakness, shortness of breath)	Alpha-ketoglutarate, α-hydroxybutyrate	97
Encephalomyelopathy	Alpha-ketoglutarate, succinate, adipate, suberate	98
Encephalopathy	D-Lactate	99
Folate deficiency developmental disorders	5-Hydroxyindoleacetate, homovanillate	100
Glycine-responsive malnutrition	Pyroglutamate	101
Gut flora and *Klebsiella*-specific metabolites	Benzoate, phenylacetate, *p*-hydrophenylpropionic, dihydroxyphenylacetate	102, 103
Hemoblastoses and nephroblastoma	*p*-Hydroxyphenyllactate	104
Hepatic detoxification	Pyroglutamate	105
Phenol exposure	*o*-Cresol	106
Pregnancy decrease of biotin status	3-Hydroxyisovalerate	107
Recent alcohol use	5-Hydroxyindoleacetate	108
Riboflavin-responsive inspiratory stridor	Ethylmalonate	109
Sleep-waking rhythm	Tartrate	110
Thiamin-responsive maple syrup urine disease	Alpha-ketoisovalerate	111
Toluene exposure	Hippurate	112
Vitamin deficiency in the elderly	Homocysteine, 2-methylcitrate	113
Xylene exposure	2-Methylhippurate	114

TABLE 28-2 **Quick Reference to Clinical Significance of Abnormal Levels of Organics in Urine**

NAME	ABNORMALITY	POTENTIAL INTERVENTION*	METABOLIC PATHWAY
Carbohydrate Metabolism			
Lactate	H	CoQ_{10}, 50 mg tid	Mitochondrial electronic transport system
Pyruvate	H	B complex, 1 capsule tid; B_1, 100 mg tid; lipoic acid, 100 mg tid	Aerobic/anaerobic energy production
Beta-hydroxybutyrate	H	Chromium picolinate, 200 mcg bid	Ketosis
Fatty acid oxidation			
Adipate, suberate, ethylmalonate	H	L-Carnitine, 250 mg tid; B_2, 100 mg bid; B_5, 500 mg bid; choline, 100 mg tid; vitamin C, 1000 mg tid; CoQ_{10}, 150 mg	Mitochondrial vs peroxisomal fatty acid oxidation
Energy Production			
Citrate	L	Aspartic acid, 500 mg	Anaplerotic
Cis-aconitate	H	Arginine, 1000 mg; iron, 18 mg; *N*-acetylcysteine, 1000 mg bid	Citric acid cycle

TABLE 28-2 Quick Reference to Clinical Significance of Abnormal Levels of Organics in Urine—cont'd

NAME	ABNORMALITY	POTENTIAL INTERVENTION*	METABOLIC PATHWAY
Isocitrate	H	Arginine, 1000 mg; B_3, 100 mg Magnesium, 400 mg; manganese, 20 mg	Citric acid cycle
Alpha-ketoglutarate	L	Alpha-KG, 300 mg; glutamine, 1-5 g	Anaplerotic
	H	B-complex, 1 tid; lipoic acid, 100 mg	Citric acid cycle
Succinate	L	Isoleucine, 1000 mg tid; valine, 1000 mg tid	Anaplerotic
	H	Magnesium, 500 mg	Citric acid cycle
Fumarate	L	Tyrosine, 1000 mg bid; phenylalanine, 500 mg bid	Anaplerotic
Malate	H	B_3, 100 mg tid	Citric acid cycle
Specific Vitamin Indicators			
Alpha-ketoisovalerate, α-ketoisocaproate, α-keto-β-methylvalerate	H	B complex, 1 capsule tid; B_1, 100 mg tid; lipoic acid, 100 mg tid	BCAA catabolism
Kynurenate	H	B_6, 100 mg	Kynurenin
Xanthurenate	H	B_6, 100 mg	Kynurenin
Beta-hydroxyisovalerate	H	Biotin, 5 mg bid; magnesium, 100 mg bid	Isoleucine catabolism
Methylmalonate	H	B_{12}, 1000 mcg tid	Leucine catabolism
FIGLU	H	Folic acid	Histidine catabolism
Hydroxymethylglutarate	H/L	CoQ_{10}, 50 mg tid	Cholesterol and CoQ_{10} biosynthesis
Detoxification indicators			
Glucarate	H	Glycine, GSH, NAC, 500-5000 mg/day	Detoxifying liver enzyme induction
Orotate	H	Alpha-KG, 300 mg tid; arginine, 1-3 g/day; aspartic acid, 500 mg bid; magnesium, 300 mg	Ammonia clearance by urea cycle vs pyrimidine synthesis
p-Hydroxyphenyllactate	H	Vitamin C up to 100 mg/kg	Prooxidant and carcinogen
2-Methylhippurate	H	Avoidance of xylene	Hepatic glycine conjugation
Alpha-hydroxybutyrate	H	NAC, 1000 mg; glutathione, 300 mg; lipoic acid, 600 mg Taurine, 500 mg bid; glutathione, 300 mg	Hepatic glutathione synthesis
Pyroglutamate	H		Glutathione-requiring γ-glutamyl pathway
Sulfate	L		Glutathione turnover
Neurotransmitter Metabolism			
Vanilmandelate, homovanillate	L/H	Tyrosine may stimulate rates of catecholamine production; contraindicated for patients taking MAO inhibitors	Catecholamine catabolism, neurotransmitter metabolites
5-Hydroxyindolacetate	L	5-Hydroxytryptophan can stimulate rates of serotonin production; contraindicated for patients taking SSRI	Serotonin catabolism by monoamine oxidase
Quinolinate	H	Magnesium, 300 mg	Kynurenin
Dysbiosis Markers (Products of Abnormal Gut Microflora)			
Products of bacterial growth: benzoate, hippurate, phenylacetate, phenylpropionate, *p*-hydroxybenzoate, *p*-hydroxyphenylacetate, tricarballylate, *p*-hydroxyphenylproprionate D-lactate Products of yeast growth D-Arabinital	H	If any of these compounds is high, the possibility of dysbiosis is reinforced. Glutamine, 10-30 g daily, and free-form amino acids normalize gut permeability. Take appropriate steps to ensure favorable gut microflora population.	Numerous interferences in pathways and cellular energy control mechanisms

BCAA, branched chain amino acids; bid, twice daily; CoQ_{10}, coenzyme Q_{10}; FIGLU, formiminoglutamate; GSH, glutathione; H, high; KG, ketoglutarate; L, low; MAO, monoamine oxidase; NAC, N-acetyl-L-cysteine; SSRI, selective serotonin reuptake inhibitor; tid, three times a day.

*Supplemental dosages are in the upper range of aggressive repletion.

compensation via ω-oxidation, producing elevated urinary levels of adipate and suberate. Similar carnitine transport impairment leads to elevation of urinary ethylmalonate. Urinary concentrations of all three of these compounds are elevated in overt enzyme failure, but the patterns of elevations in milder carnitine deficiencies vary.

Symptoms include periodic mild weakness, nausea, fatigue, hypoglycemia, "sweaty feet" odor, recurrent infections, and increased free fatty acids. Patients may also exhibit a Reye-like syndrome with dicarboxylic aciduria, which has been associated with various metabolic toxins generated from viral infections that affect mitochondrial function. Mild heterozygotic forms of dicarboxylic aciduria may be commonly seen clinically and may go unrecognized. The enzymes involved also respond to environmental toxin exposure with altered lipid metabolism, which can lead to impaired immune responsiveness.[7,8] Supplementation of carnitine and riboflavin is indicated when urinary adipate, suberate, or ethylmalonate is elevated. (See Chapter 74 for a full discussion of this useful nutrient.)

CARBOHYDRATE METABOLISM

Lactate and Pyruvate

For each molecule of glucose carried through the glycolytic pathway, two molecules of pyruvate are produced. The conversion of pyruvate into acetyl-coenzyme A requires the pyruvate dehydrogenase enzyme complex that is dependent on cofactors derived from thiamin, niacin, riboflavin, pantothenic acid, and lipoic acid. Elevations of pyruvate may reflect failure of the enzyme because of a functional need for increased B vitamins, particularly thiamin and pantothenic acid. Levels of pyruvate in the tissues are further controlled by the biotin-containing protein pyruvate carboxylase, which controls the first step in the formation of glucose from pyruvate. Multiple forms of pyruvate carboxylase deficiency, some of which are biotin responsive, have been reported.[9]

Any accumulation of pyruvate can lead to concurrent elevations of lactate through the action of lactate dehydrogenase. Lactate accumulates when there is a block in the final oxidative phosphorylation (ox/phos) stage of energy production. Such a block results in inactivation of the citric acid cycle (CAC). Coenzyme Q_{10} (CoQ_{10}) has been used in cases of lactic acidosis associated with ox/phos impairments.[10,11] Increased lactate is a common acidotic condition that can be caused by a variety of metabolic problems. Decreased lactate is seen in people who are physically inactive. Highly trained athletes have such efficient conversion of lactate to glucose that they have lactate levels below the 2.5 percentile.

Beta-Hydroxybutyrate

Beta-hydroxybutyrate is a ketone body that becomes elevated in conditions of impaired glucose oxidation, where free fatty acids are used as the predominant energy source. Ketone bodies can be thought of as a transportable form of acetate resulting from oxidation of fatty acids. Elevations of β-hydroxybutyrate seen in overnight collection urine specimens might indicate inefficient use or mobilization of carbohydrate stores. Excessive fatigue on exertion is the most common symptom associated with ketosis. Chromium and vanadium supplementation may support carbohydrate use by improving insulin receptor activation.

CENTRAL ENERGY PATHWAY INTERMEDIATES

Citrate, Isocitrate, Alpha-Ketoglutarate, *cis*-Aconitate, Succinate, and Fumarate

Citrate, isocitrate, α-ketoglutarate (α-KG), *cis*-aconitate, succinate, and fumarate are intermediates in the CAC. Most of the enzymes of the CAC require specific vitamin-derived cofactors and minerals for their function. When the enzyme rates slow due to deficiency of their cofactors, abnormal spilling of CAC intermediates into urine can occur. For example, in cytochrome C oxidase deficiency, there is inefficient removal of the primary product of the CAC, reduced nicotinamide adenine dinucleotide, and citrate, malate, fumarate, and α-KG all increase.[12] CoQ_{10} deficiency can also result in elevations of CAC intermediates (see section on Hydroxymethylglutarate). Aggressive dosing with carnitine, CoQ_{10}, and other nutrients has been used to help normalize mitochondrial function in genetic mitochondriopathies.[23]

Mild inborn errors of energy metabolism that may be compatible with survival, at least into young adulthood, but not with normal development of mental and neurologic functions, have been associated with the excretion of elevated α-KG.[24] The clinical heterogeneity of neurometabolic disorders and the importance of organic acid analysis in the diagnosis of static encephalopathy were underscored by the finding of excretion of excess fumaric acid in a 5-year-old girl with a previous diagnosis of cerebral palsy.[25]

Urinary levels of citrate, a marker of acid-base status, normally decrease with age.[26] Metabolic compensation in glycogen storage disease type 1a leads to low urinary citrate concentration and higher incidence of nephrolithiasis. Citrate supplementation may help avoid urinary calculi in patients with low urinary citrate levels.[27] Drinking bicarbonate-rich mineral water has also been shown to help raise urinary citrate concentration, and this dietary change has been suggested to prevent the recurrence of calcium oxalate and uric acid stones.[28]

Intermediates of the cycle can also be derived from amino acids. This may explain the energy-boosting effect that some individuals report when they take free-form amino acid supplements. The effect results from the conversion of specific amino acids directly into CAC intermediates needed for the energy-producing cycle. The fatigue-reducing effect of supplementation of aspartate salts and α-KG acid has been attributed to such a mechanism.[9,20] Supplementation of the precursors serves to drive the cycle and generate reducing equivalents used in the electron transport chain in which adenosine triphosphate is produced via oxidative phosphorylation.

Hydroxymethylglutarate

Hydroxymethylglutarate (HMG) is the metabolic precursor of cholesterol and CoQ_{10}. Low levels may reflect inadequate synthesis and possible deficiency of CoQ_{10}. The statin drugs lower cholesterol by blocking the conversion of HMG into mevalonate. They cause elevated urinary HMG and lowered serum CoQ_{10} levels.[21] CoQ_{10} is used in the mitochondrial oxidative phosphorylation pathway for adenosine triphosphate synthesis and is a potent antioxidant because it lowers the undirected flow of electrons onto molecular oxygen. It has been employed extensively as a cardiovascular protective agent.[22]

CoQ_{10} has also been used successfully to improve mitochondrial function in clinical situations of cardiac and skeletal muscle weakness and cramping, and in the extreme, mitochondrial encephalomyopathy.[23,24] The coenzyme has been found helpful in the treatment of fatigue, particularly when both lactate and

pyruvate are elevated. Such responses reflect the inability of mitochondrial oxidative phosphorylation to proceed efficiently, possibly because of CoQ_{10} deficiency.

B-COMPLEX INSUFFICIENCY MARKERS

Alpha-Ketoisovalerate, Alpha-Ketoisocaproate, and Alpha-Keto-Beta-Methylvalerate

Ketoacids derived from the branched chain amino acids isoleucine, leucine, and valine are α-ketoisovalerate, α-ketoisocaproate, and α-keto-β-methylvalerate, respectively. They are formed by the removal of the amine group in branched chain amino acid catabolism and are excreted in large amounts along with their amino acid precursors in the inherited disorder known as maple syrup urine disease. There are several known metabolic disorders in the pathways of catabolism of the ketoacids. The reactions require enzymes similar to pyruvate dehydrogenase that use the B-complex cofactors B_1, B_2, B_3, B_5, and lipoic acid. Elevations of the branched chain ketoacids provide a functional assessment of the sufficiency of these vitamins, especially thiamin.[25]

INDICATORS OF A SPECIFIC VITAMIN DEFICIENCY

Beta-Hydroxyisovalerate

Beta-hydroxyisovalerate is an ideal marker compound for evaluating biotin status because it is produced in the high-flux pathway for degradation of the most abundant dietary amino acid, isoleucine. The carboxylase enzyme that is necessary for the step that clears β-hydroxyisovalerate requires the active form of biotin; human biotin deficiency has been shown to quickly produce elevation of urinary β-hydroxyisovalerate.[26] Beta-hydroxyisovalerate is elevated in inherited disorders of multiple carboxylase insufficiency because biotin is the cofactor for the mitochondrial carboxylase enzymes.[27] Symptoms of multiple carboxylase deficiencies include alopecia, rash, *Candida* dermatitis, unusual odor to the urine, immune deficiencies, and muscle weakness. Biotin deficiencies of various degrees develop in a substantial minority of normal pregnancies and in patients receiving long-term therapy with anticonvulsants.[26,28] Other possible indications of biotin deficiency are elevations of lactate and alanine in urine and accumulations of odd-chain fatty acids in plasma or red cell membranes.[29] Supplementation of biotin may improve these conditions.

Methylmalonate

Methylmalonate is converted into succinic acid by means of a vitamin B_{12}–dependent enzyme, methylmalonyl CoA mutase. The lack of vitamin B_{12} impairs this conversion, leading to elevation of urinary methylmalonate.[30] If both homocysteine and methylmalonate are elevated, both vitamin B_{12} and folate functional deficiencies are indicated. Folate supplementation is suggested if homocysteine alone is high, and vitamin B_{12} supplementation is needed if methylmalonate alone is elevated.

Formiminoglutamate

Formiminoglutamate (FIGLU) is a biochemical marker of folic acid deficiency. Histidine metabolism is interrupted in the absence of adequate levels of folic acid, causing accumulation of FIGLU acid elevation of levels in urine.[31] Because of the linkage between folate and vitamin B_{12}, FIGLU may be a more sensitive marker for vitamin B_{12} deficiency than methylmalonate. In a cohort of 15 leukemia cases, three patients showed elevated FIGLU, whereas the entire group had normal methylmalonate levels.[32] A child with failure to thrive and vomiting had a genetic variant in the vitamin B_{12}–dependent FIGLU transferase enzyme in which normal serum folate and vitamin B_{12} values were present with gross excretion of FIGLU.[33]

Kynurenate and Xanthurenate

The hepatic kynurenin pathway that is responsible for clearing excess tryptophan is impaired by vitamin B_6 deficiency in such a way that the intermediates, kynurenate and xanthurenate, accumulate and spill into urine. These two markers are much higher in the kidney than in blood. The precursors kynurenine and 3-hydroxykynurenine are formed in the liver, but they appear in urine as total kynurenine.[34] As xanthurenate excretion increases, niacin production from tryptophan decreases.[35] Pregnancy may have independent effects on kynurenine excretion, and studies in rats indicate that the effects of pregnancy and diet are additive.[36]

NEUROTRANSMITTER METABOLISM

Vanilmandelate and Homovanillate

Vanilmandelate (VMA) (also called vanillylmandelate) is the principal metabolite of the catecholamine epinephrine. Low urinary levels have been associated with low central nervous system (CNS) levels of the neurotransmitter. Symptoms associated with this condition are depression, sleep disturbances, inability to deal with stress, and fatigue. Treatments aimed at improving protein digestion and supplementation of the amino acid precursors can normalize neurotransmitter levels in the CNS.[37] The much more commonly encountered conditions of elevated adrenal gland output resulting from chronic stress produce high urinary levels of VMA. Because of the rapid clearance rate for this hormone, high VMA indicates an elevated catecholamine turnover rate, but does not necessarily indicate elevated concentration of the hormones in blood.

Homovanillate (HVA) is the principal product of dopamine catabolism. Elevated urinary values indicate increased production and turnover of dopamine. VMA is highly elevated by pheochromocytomas, and both VMA and HVA are measured in screening and prognosis for hemoblastoses and neuroblastoma.[38,39]

5-Hydroxyindolacetate

Catabolic breakdown of serotonin leads to excretion of 5-hydroxyindoleacetate (5-HIA). Abnormally high levels of this metabolite result from increased rates of serotonin release from the CNS, argentaffin cells in the gut, or platelets. Carcinoid tumors composed of chromaffin tissue can also release large amounts of serotonin. Serotonin is necessary for control of gut motility because it activates smooth muscle activity. Inadequate production of serotonin leads to constipation. Low levels have also been associated with depression, fatigue, insomnia, suicide, attention deficit disorder, and behavioral disorders. When 5-HIA levels are low, dietary therapy should focus on improving protein digestion and increasing consumption of foods high in tryptophan. (See Chapter 58 for discussions of hypochlorhydria and pancreatic insufficiency.) These actions minimize the need for oral tryptophan or 5-hydroxytryptophan use.

Quinolinate and Picolinate

The hepatic kynurenin pathway that was previously mentioned as the origin of urinary xanthurenate and kynurenate is also operative in the brain. However, the normal end products in the brain are quinolinic and picolinic acids that serve to modulate brain activity via regulating *N*-methyl-D-aspartate (NMDA) receptors. In contrast to the unreliability of other neurotransmitter levels in urine for assessing CNS status, urinary quinolinate and picolinate are directly related to their concentrations in the brain, where their formation is specifically stimulated by the inflammatory cytokine interferon-γ.[12] Urinary quinolinate rises in parallel with neopterin as both compounds reflect the process of inflammation.[40] However, quinolinate is a specific agonist for glutamatergic *N*-methyl-D-aspartate receptors, thus contributing directly to the hyperexcitation of inflammation in the brain.[41]

INDICATORS OF DETOXIFICATION FUNCTION

Glucarate

Glucaric acid (glucarate) is the oxidation product of glucuronic acid. It is a by-product of the predominant liver Phase II detoxification reactions involving glucuronic acid conjugation. A great variety of drugs, environmental toxins, food components, and products of gut microbial metabolism are prepared for excretion by glucuronidation. Decreased glucarate is an indicator of reduced overall hepatic function, whereas elevation of this compound is an indication of enzyme induction caused by potentially toxic exposures.[42,43]

The excretion of D-glucarate is considered a marker of the viability of hepatocytes and is a useful clinical prognostic predictor in biliary atresia.[44] Most exposures that result in stimulation of hepatic cytochrome P-450 activity result in increased excretion of glucarate. For example, urinary D-glucarate is elevated in pesticide-exposed groups.[45] Patients with clinically quiescent chronic pancreatitis also show elevations of urinary glucarate, indicating a relationship of toxic metabolite stress to heightened free radical activity and hence to the genesis of chronic pancreatitis.[46] Glucarate measurements have been advanced as useful biomarkers to xenobiotic exposure, being particularly useful as a screening tool in reproductive epidemiology.[47]

Orotate

Orotic acid accumulation is a sensitive marker of ammonia buildup. Ammonia (via glutamine) is normally disposed of by forming carbamoyl phosphate, which enters the urea cycle. When there is insufficient capacity for detoxifying the load of ammonia, carbamoyl phosphate leaves the mitochondria and stimulates the synthesis of orotic acid.[48] Increased orotic acid production is a sensitive indicator of arginine availability. Most of the symptoms that develop after arginine deprivation can largely be accounted for by a diminished efficiency of ammonia detoxification. Greater orotic biosynthesis was observed with rising ammonia concentrations in rat, mouse, and human livers, and was reduced by in vitro arginine supplementation.[49]

Genetic medium-chain acyl CoA dehydrogenase deficiency and other disorders of fatty acid oxidation may appear long after infancy in some patients, such as those with a clinical diagnosis of Reye's syndrome. These disorders may mimic defects in the urea cycle, such as that reported for a 13-year-old girl with hyperammonemic encephalopathy and orotic aciduria caused by ornithine transcarbamylase deficiency.[50] Responses should include steps to stimulate ureogenesis, including α-KG, magnesium, and aspartic and glutamic acids.

p-Hydroxyphenyllactate

p-Hydroxyphenyllactate (HPLA) is a carcinogenic metabolite of tyrosine that increases lipid peroxidation in the liver.[51] Methyl *p*-hydroxyphenyllactate (MeHPLA) is an important cell growth–regulating agent, and tumor cells contain esterase enzymes that hydrolyze the compound to the free acid, HPLA.[52] HPLA is an important regulator of normal and malignant cell growth, and it appears to mediate the cancer-promoting effects of estrogen. MeHPLA blocks uterine growth in vivo and inhibits growth of MCF-7 human breast cancer cells in vitro.[53] High doses of ascorbic acid (100 mg/kg body weight daily) were shown to arrest or significantly inhibit the excretion of HPLA in patients with hemoblastoses and nephroblastoma.[54] HPLA may also be produced by some microbes that could inhabit the gut, but the cell proliferative and prooxidant functions are of greater clinical relevance.[55]

2-Methylhippurate

2-Methylhippurate is a biotransformation metabolite of the common solvent xylene. Elevations indicate an exposure to this potentially toxic compound.[56,57] Although there are three positional isomers of xylene, the ortho form is virtually always present, so only the 2-methyl isomer of hippurate is necessary for detecting and monitoring exposure to the solvent.[58] A study of spray painters showed elevated methylhippurate, indicating recent exposure to xylene.[59] Patient counseling in avoidance of these compounds is indicated. Glycine supplementation may also be considered to ensure maximal rates of conjugation to clear body burdens of xylene. This is especially the case when benzoate is found elevated in urine (see discussion of benzoate later).

Alpha-Hydroxybutyrate

Alpha-hydroxybutyrate is a by-product of the conversion of cystathionine to cysteine for hepatic glutathione synthesis. When demand for glutathione increases due to oxidative stress or detoxification requirements, the flow through this pathway increases with concomitant increases in the excretion of α-hydroxybutyrate. The enzyme α-hydroxybutyrate dehydrogenase occurs at high concentrations in cardiac muscle tissue, and its elevation in serum is widely used to estimate infarct size and reperfusion effectiveness.[60] A series of urinary organic acid profiles performed on an autistic child exposed to xylene indicated that α-hydroxybutyrate was excreted at higher levels when epinephrine was stimulated.[61] These findings are consistent with observations of α-hydroxybutyrate dehydrogenase changes in mice caused by acute stress.[62]

Pyroglutamate

Pyroglutamate (sometimes called 5-oxoproline) is a cyclic form of glutamic acid. Small amounts are always present in overnight urine because the substance is produced as an intermediate in the γ-glutamyl cycle used in a renal recovery pathway involving active transport of amino acids.[63] This process uses glutathione as a carrier and requires glycine to reform glutathione. When glycine is insufficient, there is net conversion of glutathione to pyroglutamate, so this pathway conserves amino acids at the expense of glutathione. Pyroglutamaturia in an adult receiving antibiotic therapy is evidence for a renal-associated mechanism.[64] Other

cases of pyroglutamaturia accompanying homocystinuria indicate a glutathione-wasting mechanism leading to elevated urinary pyroglutamate.[65] Supplemental glycine and *N*-acetylcysteine can replenish the intermediates in the γ-glutamyl cycle and help rebuild total body glutathione.[66,67]

Sulfate

Urinary sulfate is an inorganic compound sometimes reported on profiles of organic acids. It is measured in a separate assay and is included because of its added value in assessing the functioning of the detoxification pathways. Sulfation pathways are used in Phase II liver detoxification for the biotransformation of drugs, steroid hormones, and phenolic compounds, among others. Urinary sulfate has been used to assess the body's reserve of sulfur-containing compounds (especially glutathione) used in Phase II pathways. These stores need replenishment when the sulfate/creatinine ratio is low. Administration of glutathione, in combination with oral cysteine, taurine, and salts of sulfate, is used to replenish sulfur pathways and restore the hepatic supply of inorganic sulfate.[68,69] Glutathione levels in the liver can be increased 35% in normal individuals by supplementation of *Silybum marianum* (see Chapter 123).

PRODUCTS OF GUT MICROFLORA

Several studies have used the appearance of unique products of microbial metabolism in urine as an indicator of the abnormal overgrowth of unfavorable intestinal microflora, a condition sometimes called "gastrointestinal dysbiosis." Such a condition has been related to a wide variety of symptoms due to pathogenic toxins produced by the populations of microflora. For example, no false-negative results and only 2% of false-positive results for small bowel disease and bacterial overgrowth syndrome were found in a study of urinary *p*-hydroxyphenylacetate in 360 acutely ill babies and children.[70] Some compounds are absorbed and enter the detoxification pathways of the liver to be excreted as products that can serve as sensitive indicators of changes in gastrointestinal flora.[71]

Phenylacetate, Phenylpropionate, *p*-Hydroxybenzoate, *p*-Hydroxyphenylacetate, *p*-Hydroxyphenylpropionate, and Tricarballylate

For individuals with normal, healthy intestinal function, the compounds phenylacetate, phenylpropionate, *p*-hydroxybenzoate, *p*-hydroxyphenylacetate, *p*-hydroxyphenylpropionate, and tricarballylate should not appear as more than background concentrations in urine. Except for tricarballylate (derived from dietary carbohydrates), they are produced by microbial action on dietary polyphenolic compounds and all are markers of bacterial growth in the gut. *p*-Hydroxyphenylacetic aciduria has been found useful in detecting small bowel disease associated with *Giardia lamblia* infestation, ileal resection with blind loop, and other diseases of the small intestine associated with anaerobic bacterial overgrowth.[70] Use of antibiotics such as neomycin, which acts primarily against aerobic bacteria, can encourage the growth of *Giardia* and anaerobic bacteria, which then produce greater amounts of these compounds.[72]

Other gastrointestinal disorders, including cystic fibrosis of the pancreas, celiac disease, and unclassified enteritis, have been associated with increased excretion of *p*-hydroxybenzoate, phenylacetate, and *p*-hydroxyphenylacetate. Patients with cystic fibrosis had elevations of *p*-hydroxyphenylacetate even while undergoing pancreatin therapy. Variations in the relative amounts of these compounds observed with this type of gastrointestinal disturbance are an indication that the patterns of excretion are apparently determined by the microbial flora present in the patient's intestinal lumen.[73] Tricarballylate is produced by aerobic bacteria that quickly repopulate in the gut of germ-free animals.[74] Tricarballylate build up due to overgrowth of *Acidaminococcus fermentans* or *Selenomonas ruminantium* in the lumen of sheep produced magnesium deficiency that could be fatal.[75] Tricarballylate lowers magnesium because of tight binding in the gut and in blood. Magnesium absorption is reduced and excretion is increased.

D-Arabinitol Versus Arabinose

Arabinitol is a sugar alcohol that is a product uniquely produced by anaerobic fungal growth in the gut. D-Arabinitol is produced by fungal metabolism, and detection of elevated urinary D-arabinitol is considered the optimal way of monitoring immunocompromised patients for invasive candidiasis.[76,77] In contrast, arabinose is a carbohydrate that has no relationship to growth of any form of yeast or fungi in or on the human body, although some laboratories may report the compound as a marker.

D-Lactate

Like many other normal human intestinal bacteria, *Lactobacillus acidophilus* produces the D-isomer of lactic acid from the fermentation of undigested dietary carbohydrate. *L. acidophilus* is usually regarded as a favorable organism because moderate amounts of D-lactate can be racemized to L-lactate and oxidized to carbon dioxide by intestinal and hepatic enzymes. The organism produces other desired products and helps discourage colonization by pathogens. Under conditions of carbohydrate malabsorption, however, D-lactate output can exceed metabolic conversion capacity and accumulate, causing systemic acidosis and encephalopathy.[78,79] Elevated urinary D-lactate is characteristic of this condition. Other bacteria, such as *Bacteroides fragilis* and *Klebsiella,* also can produce D-lactate, but they lack the ability to proliferate in the highly acidic environment created by high accumulations of lactic acid. D-Lactic encephalopathy has been found in a high percentage of patients with short bowel syndrome after intestinal resection, and high D-lactate excretion has been found in antibiotic-associated diarrhea.[80]

SUMMARY

Measurement of organics in the urine has become an indispensable clinical tool. The profile provides a wide array of metabolic functional markers at a relatively low cost. Multiple factors involved in energy production, carbohydrate metabolism, functional nutritional status, fatty acid metabolism, detoxification, gut biosis, and neurotransmitter metabolism can be assessed from a single overnight urine specimen. Many of the detected abnormalities can be corrected through the appropriate use of dietary changes, lifestyle improvements, and nutritional and botanical supplements.

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CHAPTER 29

Urinary Porphyrins for the Detection of Heavy Metal and Toxic Chemical Exposure

J. Alexander Bralley, PhD, and Richard S. Lord, BS, PhD

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INTRODUCTION

Toxic chemicals affect human biochemistry at any level of long-term exposure. Fortunately, the body has mechanisms for transforming, eliminating, or compartmentalizing the many toxic chemicals encountered over a lifetime. Nonetheless, these "safety" mechanisms may be inadequate or even inappropriate in modern industrialized society, especially for susceptible people such as the elderly, individuals with poor nutritional habits, and others who are physiologically stressed.[1,2]

Recognizing and identifying offending chemical(s) can present a difficult challenge for the clinician. Many chemicals exert their effect at such low concentrations that they escape detection except by very sophisticated laboratory methods. Although measuring effects of toxicity by observing symptoms is a time-honored procedure, determination of the actual toxicant often requires the use of laboratory methods that measure biomarkers, which are specific indicators of the toxicant's action.

Porphyrins measured in urine serve as such a biomarker. Porphyrins are particularly well suited as biomarkers for two reasons. First, they are produced in the highly active heme pathway, so any disturbance tends to cause rapid and relatively large accumulations of intermediates. Second, some of the enzymes of the porphyrin-producing pathway are highly sensitive to the presence of various toxins, and they are rapidly turned over. Their short half-lives of minutes or hours cause a demand for rapid synthesis in response to changing environmental signals. The enzymes normally associate with nutrient metal ions to produce heme and cobalamin (and, in plants, chlorophyll), sometimes called the pigments of life.[3]

The presence or elevation of various urinary porphyrin species can flag a potentially toxic condition. Metals and other toxic chemicals with prooxidant reactivity can inactivate porphyrinogenic enzymes, deplete glutathione and other antioxidants, and increase oxidant stress, all of which lead to damage to membranes, enzymes, and other proteins in cells.[4,5] In addition, porphyrinogens (precursors to porphyrins in the reduced state) themselves are easily nonenzymatically oxidized to porphyrins by toxic metals such as mercury. Thus, the distribution pattern of porphyrins in the urine serves as a functional fingerprint of toxicity.[6]

The utility of urinary porphyrin measurement as a diagnostic tool is not new; its use has been documented in the literature since 1934. Specific diseases collectively known as the *porphyrias*, which can be inherited or acquired (e.g., acute intermittent porphyria, porphyria cutanea tarda, variegate porphyria), are often diagnosed with the aid of information about the distribution profile of individual porphyrin species in human urine.

DEFINITIONS

Porphyrins are oxidized by-products that have escaped from the heme biosynthetic pathway, an essential pathway occurring in all nucleated mammalian cells. Heme is the all-important iron-binding molecule essential for the proper function of many proteins, including hemoglobin (oxygen transport), cytochrome c (energy production), and cytochrome P-450 (detoxification). Biosynthesis of heme involves eight enzymes (Figure 29-1), five of which produce intermediate molecules that are collectively called *porphyrinogens*. Some porphyrinogens escape the

intracellular pathway to become oxidized by other cellular processes to porphyrins. In turn, some porphyrins are excreted in urine and feces.

The different molecular species of porphyrins that occur in the urine of healthy individuals form a predictable, characteristic pattern. An elevation of one or more porphyrins is designated *porphyrinuria*. The term *porphyria* is reserved for primary conditions exhibiting specific clinical symptoms caused by an inherited defect in one or more of the heme biosynthetic enzymes. *Porphyrinopathy* is an umbrella term for any disorder in porphyrin metabolism. Enzymatic defects associated with common porphyrias are listed in Table 29-1.

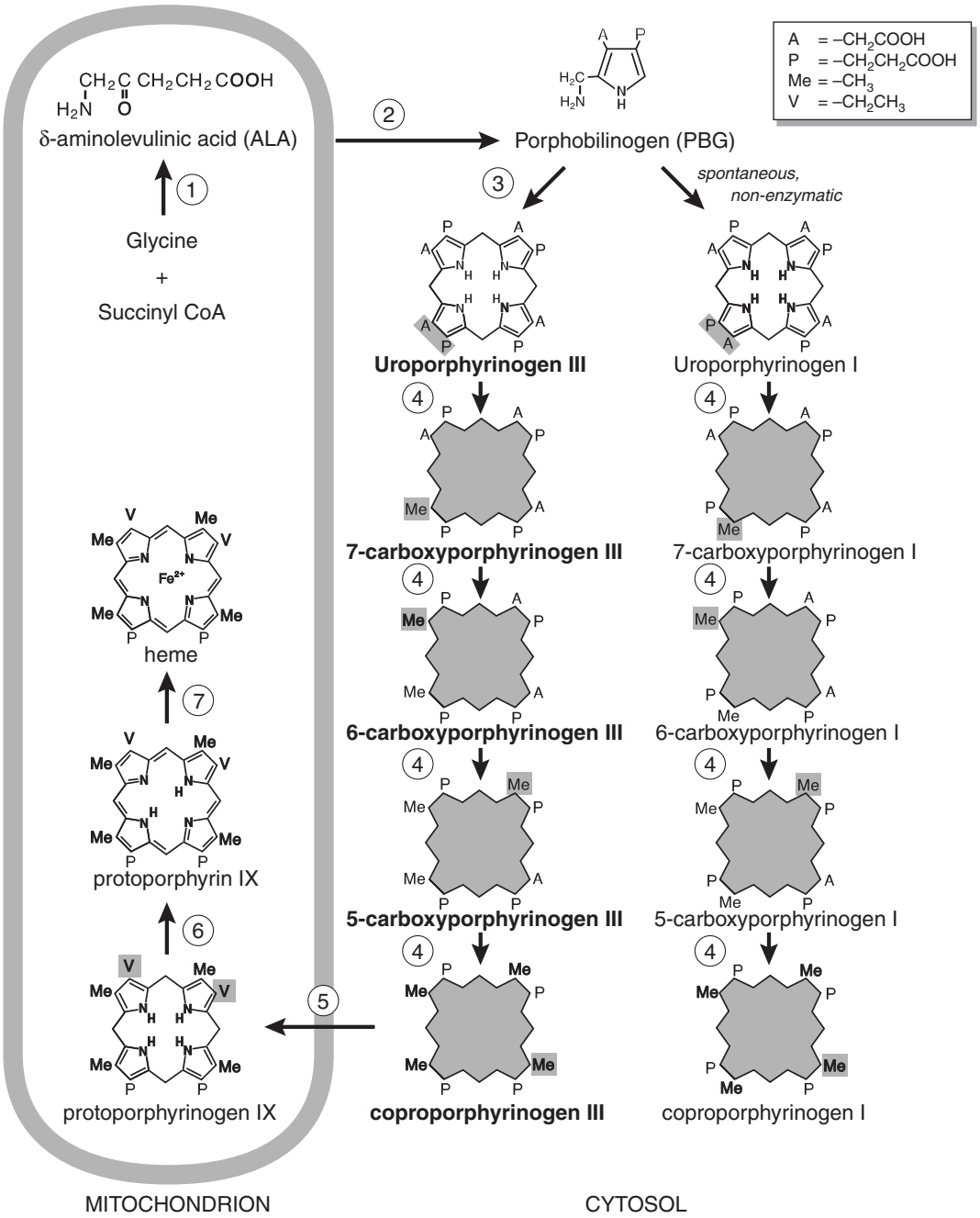


FIGURE 29-1 Biosynthesis of heme. The enzymes that drive the heme pathway are: (1) δ-aminolevulinate (ALA) synthetase; (2) ALA dehydratase; (3) uroporphyrinogen I synthetase (porphobilinogen deaminase) and uroporphyrinogen III cosynthetase, two enzymes that work in concert; (4) uroporphyrinogen decarboxylase; (5) coproporphyrinogen oxidase; (6) protoporphyrinogen oxidase; and (7) ferrochelatase (heme synthetase). Spilled porphyrins derived from porphyrinogens with 8-, 7-, 6-, 5-, and 4-carboxyl groups are largely excreted in the urine, whereas the less polar 2-carboxyporphyrin (protoporphyrin) is excreted exclusively in the feces. The physiologically relevant pathway leading to heme is via uroporphyrinogen III, in which the propionyl and acetyl groups are "reversed" compared with the type I pathway, which "dead-ends" with coproporphyrinogen I. The physiologic significance of the type I pathway remains unclear; however, coproporphyrin I is elevated in hepatobiliary diseases.

PORPHYRIAS

The porphyrias have been classified in the literature in several different ways. Most commonly, porphyrias are presented in textbooks with specific biochemical reference to the principal enzyme deficiency (e.g., δ-aminolevulinate [ALA] dehydratase deficiency) and the site of the deficiency (e.g., hepatic, erythropoietic, or both). Furthermore, the temporal pattern of appearance of overt clinical signs (acute vs chronic) and the primary presentation of symptoms (neuropathic, dermatopathic, or mixed) are valid classifications that arrange porphyrias according to symptomatology. It is useful also to organize porphyrias according to etiology (hereditary vs acquired or toxicant-induced). This review will focus on only those porphyrinurias associated with toxic chemical or heavy metal exposures.

PORPHYRINOPATHIES

Inhibition of an enzyme for heme biosynthesis can result in the inappropriate accumulation of that enzyme's substrate. The more severe the enzyme's inhibition becomes, the greater the tissue accumulation of porphyrins, which sometimes becomes severe enough to cause clinical porphyria.

TABLE 29-1 **Enzymatic Defects of the Common Porphyrias**

ENZYMATIC DEFECT	PORPHYRIA
δ-Aminolevulinic acid (ALA) synthetase	Aminolevulinic aciduria (porphyrinogen precursor)
ALA dehydratase	Plumboporphyria
Porphobilinogen deaminase	Acute intermittent porphyria
Uroporphyrinogen cosynthetase	Congenital erythropoietic porphyria
Uroporphyrinogen decarboxylase	Porphyria cutanea tarda and hepatoerythropoietic porphyria
Coproporphyrinogen oxidase	Hereditary coproporphyria
Protoporphyrinogen oxidase	Variegate porphyria
Ferrochelatase	Protoporphyria

One class of toxic chemicals capable of subtle yet insidious health effects that may mimic other disorders, especially in children, is the heavy metals. Lead, mercury, arsenic, aluminum, and cadmium are well-documented examples. Long-term exposure to these metals often results in organ-specific accumulation that compromises target organ physiology. Similarly, long-term exposure to organic chemicals such as herbicides, pesticides, and industrial and manufacturing by-products can have a deleterious effect on the body's biochemistry that results in the decline of cellular function.[4] Whatever the cause, porphyrins induce oxidative cellular damage when they accumulate.

Clinical Applications

The effect of chemicals on the porphyrin pathway has been the subject of many scientific reports. Lead, mercury, or arsenic toxicity induces porphyrinuria,[7] as do polychlorinated phenyls (e.g., dioxin, polychlorinated biphenyls)[8] and many drugs[9] (Table 29-2). In long-term cultures of adult rat hepatocytes, exposure to submicromolar concentrations of lead increased porphyrin excretion after a delay of 15 to 22 days.[10] A study of practicing dentists reported correlations between elevations of urinary 5-carboxyporphyrin, precoproporphyrin, and coproporphyrin, and behavioral changes that were related to urinary excretion of mercury.[11,12] Together, elevations of these porphyrins served as biomarkers of mercury toxicity.

Upregulation of the heme biosynthetic pathway, with the concomitant increase in ALA, is another mechanism by which porphyria can be precipitated. Increased ALA production is usually a normal physiologic response to provide enough of this preporphyrin precursor to meet the body's demand for heme. However, overproduction of ALA can overwhelm even a normally functioning heme biosynthetic pathway, resulting in the inappropriate accumulation of ALA or the porphyrins.[6] Active porphyria commonly occurs when overproduction of ALA coincides with inhibition of one or more of the porphyrinogenic enzymes. Often porphyria is the result of a chemical insult to a porphyrinogenic enzyme combined with an external stressor that provokes dysregulation of the heme biosynthetic pathway. It is estimated that among patients with a porphyrinogenic enzyme deficiency, as many as 90% are healthy throughout adulthood, until porphyria is triggered midlife

TABLE 29-2 **Interpretation of Abnormal Urinary Porphyrin Test Results: Relationship to Heme Pathway Defects and Possible Causes (with Emphasis on Toxic Metals)**

ABNORMAL TEST RESULT*	HEME PATHWAY ENZYME AFFECTED	POSSIBLE ENVIRONMENTAL CAUSE†
Uroporphyrin and 7-carboxyporphyrin (sometimes)	Uroporphyrinogen decarboxylase	Arsenic[2] or certain organic chemicals
5-Carboxyporphyrin and coproporphyrin	Uroporphyrinogen decarboxylase	Mercury[6]
6-Carboxyporphyrin (sometimes)	Coproporphyrinogen oxidase	Certain organic chemicals
Precoproporphyrin‡ (almost always accompanied by elevated coproporphyin III)	Uroporphyrinogen decarboxylase (possibly)	Mercury[6]
Coproporphyrin III, coproporphyrin I (sometimes)	Coproporphyrinogen oxidase	Lead or mercury[2] Certain organic chemicals
Coproporphyrin I/III ratio >1	Hepatobiliary dysfunction[4] Porphobilinogen deaminase	Arsenic

*Reference ranges vary depending on the laboratory doing the analysis. The reference range for the particular laboratory conducting the analysis should be used. Inherited disorders in the enzymes of heme biosynthesis are relatively rare, but such a possibility should be considered if urinary porphyrins are greatly elevated. A specialist in inherited disorders should be consulted if such a disorder is suspected.

†When urinary porphyrin results are being evaluated to arrive at a diagnosis of metal or chemical toxicity, the following should be ruled out: use of ethanol, estrogens, oral contraceptives, antibiotics, sedatives, analgesics, dietary brewer's yeast; also pregnancy, liver disease, malignancies, and hematologic diseases such as pernicious or iron deficiency anemias.

‡The detection of precoproporphyrin is specifically diagnostic for mercury toxicity.[6]

by toxic chemicals or drugs, an acute illness or worsening chronic condition, or a major dietary change (Table 29-2).[11]

CONCLUSION

Use of porphyrin measurements as biomarkers of chemical toxicity is reasonable in combination with other laboratory tests of toxicant concentrations in body fluids or hair. The clinician should realize that many conditions unrelated to primary or toxicant-induced porphyria can cause porphyrinuria.[13] When considering a urinary porphyrin result, the clinician should be mindful that the distribution of normal urinary porphyrin values, representing healthy individuals, overlaps significantly with values representing those who have had porphyria at one time or another.

Any patients in whom a urinary porphyrins test result is positive should receive more specific testing for a differential diagnosis. Tests that assay toxic metals directly in biologic samples (e.g., blood, urine, and hair) are essential for confirming whether the toxicity symptoms are caused by a metal. Identification of toxic organic chemicals by laboratory methods is also possible. Profiles are available for measuring series of volatile solvents, polychlorinated biphenyls, and chlorinated pesticides in blood or phthalates and parabens in urine. Ruling out porphyria as the primary cause of porphyria-like symptoms requires tests for porphyrinogenic enzyme activities (e.g., uroporphyrinogen decarboxylase), as well as tests for blood, fecal, and urine porphobilinogen and ALA.

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CHAPTER 30

Urine Indican Test (Obermeyer Test)

Dirk Powell, BS, ND

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INTRODUCTION

The essential amino acid tryptophan is converted to indole by intestinal bacterial cleavage of the tryptophan side chain. After absorption, indole is converted to 3-hydroxy indole (indoxyl or indican) in the liver, where it is conjugated with potassium sulfate or glucuronic acid. It is then transported by the blood to the kidneys for excretion. Increased urinary excretion of indican can be an indicator of gastrointestinal bacterial overgrowth and dysbiosis.

CLINICAL APPLICATION

Because most of the endogenous indoles have a side chain that prevents cleavage and are instead metabolized to skatole, the production of indicans (indoxyl potassium sulfate and indoxyl glucuronate) reflects bacterial activity in the small and large intestines. Box 30-1 lists conditions in which increased levels are found.[1–4] Elevations of indicans are considered an indicator of gastrointestinal dysfunction and overgrowth of anaerobic bacteria (dysbiosis). The indican test can be used to monitor the efficacy of treatment of gastrointestinal dysbiosis.

Procedure

Detection of indican depends on its decomposition to indoxyl and subsequent oxidation to indigo blue. It is then concentrated in a layer of chloroform for easier measurement.

Method

1. Place 5 milliliters of fresh urine in a test tube.
2. Add 5 milliliters of Obermeyer reagent under a hood to exhaust vapors, and cork securely.
3. Invert several times to mix.
4. Add 2 milliliters of chloroform, cork securely, and invert several times.
5. Allow the chloroform to settle, and then observe.
6. The results are then graded according to the color present in the chloroform layer.

Reagents

- Obermeyer reagent is prepared by dissolving 0.8 grams ferric chloride in 100 milliliters concentrated hydrochloric acide (*caution:* caustic).
- Chloroform (*caution:* volatile and toxic; keep tightly capped).

Results

- Urine color: 0 (negative)
- Light blue: +1
- Blue: +2
- Violet: +3
- Jet black: +4

BOX 30-1 Conditions Associated with Elevations of Urinary Indican[1-4]

- Irritable bowel syndrome
- Small intestinal bowel overgrowth
- Inflammatory bowel disease
- Celiac disease
- Hypochlorhydria
- Gastric ulcer
- Biliary and intestinal obstruction
- Jejunal diverticulosis
- Scleroderma
- Postgastrectomy
- Hartnup disease
- Pancreatic insufficiency
- Diminished peristalsis
- Blue diaper syndrome

INTERPRETATION

A positive result may indicate one of several underlying disorders, any of which can lead to bacterial dysbiosis and/or overgrowth, including hypochlorhydria, maldigestion, pancreatic insufficiency, malabsorption of protein, and excessive dietary protein intake (see Box 30-1). Occasionally a positive test can be caused by increased dietary protein prior to testing, which can be prevented by the institution of a moderate protein diet for 2 days before testing.

False-negative results occur when formalin, methenamine, or sulfasalazine (Azulfidine) is present.[2] Indigo red may occasionally form from slow oxidation. The presence of iodine, salicyluric acid, methylene blue, or thymol causes a violet color that can be removed with the addition of a crystal of sodium thiosulfate. Bile pigments can interfere with the reaction, but can be removed by shaking the urine with barium chloride and filtering.

CONCLUSION

This simple in-office diagnostic test can be used to determine gastrointestinal dysfunction or dysbiosis. A positive test can indicate the need for additional testing for gastrointestinal pathogens or altered GI function. The test for urine indicant can be a clinically useful tool for identifying and treating dysbiosis and optimizing GI health. A limitation of this test arises from the caustic nature of the test reagents, which require a hood to exhaust fumes and care to avoid skin contact.

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SECTION 3

THERAPEUTIC MODALITIES

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This section presents a historic, scientific, and practical review of the schools of thought and modalities of natural medicine. We have compiled the work of experts in their fields into what we hope the reader will find a concise, yet useful, description of these practices and modalities. Because of the clinically oriented and alternative nature of these disciplines, the scientific evaluation of their theories and efficacy has been limited in the past. Happily, published research in natural medicine has increased dramatically since *A Textbook of Natural Medicine* was first published in 1985.

Although this textbook is strongly oriented to the scientific method and the use of the peer-review literature for documentation of the efficacy of a therapy, these modalities' widespread clinical use and long history of patient satisfaction demand that they be given a place here even though the mechanisms of action of several have yet to be elicited.

CHAPTER 31

Acupuncture

Mark H. Nolting, ND, LAc, DiplAc, DNBAO

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INTRODUCTION

Acupuncture is arguably the most recognizable and widely practiced complementary and alternative medicine (CAM) therapy in the world today.[1] Public acceptance and utilization steadily increased across the globe between 1980 and 2011. In America, where the growth of acupuncture has been most dramatic (outside of China) during these years, we have seen the numbers of licensed, mainly nonphysician practitioners expand rapidly. In Washington State, for example, the number of acupuncture licensees jumped by 227% during the 10 years from 1997 to 2007, the most of any of the CAM professions, including chiropractic. The same report showed the growth of chiropractic licenses was only 14%, whereas that of physicians was 34%. Naturopathic physician licenses also increased considerably, by 134%.[2]

There are several key organizations leading the growth of the acupuncture profession in America as of late 2010:

- NCCAOM: National Certification Commission for Acupuncture and Oriental Medicine
- AAAOM: American Association of Acupuncture and Oriental Medicine
- CCAOM: Council of Colleges of Acupuncture and Oriental Medicine
- ACAOM: Accreditation Commission for Acupuncture and Oriental Medicine

These organizations were formed during 1981 and 1982. The NCCAOM was formed to provide testing for the certification of acupuncturists across America. "The mission of the NCCAOM is to establish, assess, and promote recognized standards of competence and safety in acupuncture and Oriental medicine for the protection and benefit of the public."[3]

The ACAOM was formed to provide accreditation to schools and colleges developing programs of study for the training of acupuncturists. "ACAOM's primary purposes are to establish comprehensive educational and institutional requirements for acupuncture and Oriental medicine programs, and to accredit programs and institutions that meet these requirements."[4]

The CCAOM was formed "to advance acupuncture and Oriental medicine by promoting educational excellence within the field. The philosophy of the Council is based on respect for the broad range of traditions of acupuncture and Oriental medicine and a commitment to academic freedom."[5]

The AAAOM was the first major professional organization to lead this budding profession. "The AAAOM is the national professional association promoting and advancing high ethical, educational, and professional standards in the practice of acupuncture and Oriental medicine (AOM) in the U.S. The AAAOM mission statement is: To promote excellence and integrity in the professional practice of acupuncture and Oriental medicine in order to enhance public health and well-being."[6]

As a result of the ongoing work of these organizations, the following milestones were achieved as of late 2010:

- Licensure: 44 states plus Washington, DC[7]
- Licensed acupuncturists: estimated 25,000–30,000[8]
- CCAOM Schools and Branches: 60[9]
- NCCAOM Diplomates since 1982: 22,000[10]
- Students in acupuncture schools: 8000[11]

There are several types of providers that receive training in acupuncture as noted in Box 31-1.[12] On occasion, professionals such as medical doctors, naturopathic physicians, and chiropractors undergo extensive training in acupuncture, but it is more common to receive professional specific training composed of far fewer hours.

BOX 31-1 Acupuncture Training Comparisons

Acupuncture Training	Physician Training	Other
• Licensed Acupuncturist (LAc standard) • 3-4 Years Professional, post bachelors standard • 1500 to 2000 hours acupuncture specific	• MD, DO, ND, DC • 300 hours or less, acupuncture specific • 100 hours for chiropractic add on	• Physical therapist • 40-50 hours of "dry needling" • National Acupuncture Detox Association detoxification technicians • 100 hours or less

TABLE 31-1 China Acupuncture Statistics

CHINESE ACUPUNCTURE AND TCM STATISTICS	
TCM doctors	218,044
TCM clinics	35,477
TCM hospitals	2688
Beds	350,257
Acupuncture hospitals	6
TCM doctors per 10,000 population	2.69 (0.69-0.83 USA)
Chinese investment in TCM	1.7 billion yuan

TCM, Traditional Chinese Medicine.

For perspective and comparative purposes, Table 31-1 provides numbers from mainland China showing traditional Chinese medicine (TCM) statistics for the years 2007 and 2008. Acupuncture is considered a key component of the practice of "modern" TCM, along with herbal medicine, massage, nutrition, qigong, and health promotion.[13–16]

The World Health Organization stated in 2001 that "Chinese Medicine, particularly acupuncture, is the most widely used traditional medicine. It is practiced in every region of the world." Although this statement has not been revised as of 2011, there is every reason to believe that this remains true.[17]

Western acupuncture terminology is evolving. Even the term "acupuncture" is considered ambiguous and deserves qualifiers to better guide consumers and professionals engaged in the practice. The following statement reflects this opinion: "The term 'acupuncture' in and of itself is ambiguous. It has been used to refer to either a specific procedure involving acupuncture needling or a multicomponent treatment that also involves history taking, physical examination, diagnosis, and education. In some cases, nonneedling procedures (e.g., laser, TENS) conducted at acupuncture points are also referred to as acupuncture."[18]

Even the acupuncture credential that this author states in *Textbook of Natural Medicine* reflects the changing practice landscape. In 2010, the legislature of Washington State approved major scope changes and terminology concerning the licensure of acupuncturists. The widely excepted term L.Ac. (licensed acupuncturist) in the United States was removed and replaced with the term East Asian Medical Practitioner (EAMP) to reflect a long-standing opinion within the field of acupuncture practice that acupuncture is an ambiguous term "in and of itself" and is a "multicomponent treatment."[19]

In the state of California, acupuncture licensure was also expanded to reflect this trend. "The theory and practice of acupuncture is based on Asian medicine (also known as traditional, classical Chinese or Oriental medicine), a comprehensive natural health care system that has been in use in Asian countries for thousands of years to preserve health and diagnose, treat, and prevent illness."[20]

Contrasting biomedicine and Chinese Medicine in his 2002 article in the *Annals of Internal Medicine*, Kaptchuk stated that "Chinese medicine relies on the veracity of the senses, the person-centered experience either as reported by the patient or perceived by an observant practitioner."[21]

The definition of acupuncture is not as firmly agreed upon as one would imagine. Acupuncture as simply "a Chinese medical practice or procedure that treats illness or provides local anesthesia by the insertion of needles at specified sites of the body" is an oversimplification of a practice that has evolved over many generations with many variations and can describe an entire field of medical practice rooted in ancient classics.[22] A more comprehensive definition agreed upon by the greater acupuncture community helps in the transmission of acupuncture principles to the world at large, aiding in the support of new research and advances in the field.

As for historical perspective on the actual term, according to George Lewith's writings, "acupuncture, or needle puncture, is a European term invented by Willem Ten Rhyne, a Dutch physician who visited Nagasaki in Japan in the early part of the seventeenth century. The Chinese describe acupuncture by the character 'Chen,' which literally means 'to prick with a needle,' a graphic description of this therapeutic technique."[23]

The California Acupuncture Board, which licenses more than 8500 acupuncturists, states the following:

> *Acupuncture means the stimulation of a certain point or points on or near the surface of the body by the insertion of needles to prevent or modify the perception of pain or to normalize physiological functions, including pain control, for the treatment of certain diseases or dysfunctions of the body and includes the techniques of electroacupuncture, cupping, and moxibustion.*[24]

The practice of acupuncture, according to Business and Professions Code section 4937 (b) of California, is as follows: "to perform or prescribe the use of oriental massage, acupressure, breathing techniques, exercise, or nutrition, including the incorporation of drugless substances and herbs as dietary supplements to promote health."[25]

In November 1997, the National Institutes of Health (NIH) convened a consensus development conference on the subject of acupuncture. After discussion among a board of experts, the following working definition was included in the NIH Consensus Statement:

> *Acupuncture describes a family of procedures involving stimulation of anatomical locations on the skin by a variety of techniques. There are a variety of approaches to diagnosis and treatment in American acupuncture, which incorporates medical traditions from China, Japan, Korea, and other countries. The most studied mechanism of stimulation of acupuncture points employs penetration of the skin by thin, solid, metallic needles, which are manipulated manually or by electrical stimulation.*[26]

The NIH conference has had a lasting positive impact on the growth of acupuncture in America and probably in the world. The definitions and recommendations for further research have sparked wider acceptance within the medical profession. No longer is acupuncture merely a novelty practice from the East.

HISTORY

The historical timeline of Chinese medicine spills over thousands of years to the present. This vast expanse of history can only be captured in mere snapshots of traditional practice, some of it legend, some of it practiced to this day. A rich folk medicine survives in the dozens of minority cultures making up the whole of China. Some attempt exists today to revive an element of these practices. Chinese medicine begins with a legend about the infamous Yellow Emperor, Huangdi (approximately 2698-2598 BC).[27,28] The so-called "Father of Chinese Medicine," Huangdi reigned over a vast Chinese empire. The core of Chinese medicine, acupuncture, and pharmaceutics is traced to the greatest and oldest medical text on earth, the Yellow Emperor's *Canon of Medicine.* Unknown medical scholars of the Warring States period (221 BC and 220 AD) wrote the text that is fixed to Huangdi's name.[29]

Nevertheless, this book is attributed to the reign of Huangdi and is said to highlight questions and answers among the emperor and his ministers, particularly a physician named Qi Bo. Huangdi discoursed on medicine, health, lifestyle, nutrition, and religious tenets of the times. He is ascribed such a high place in Chinese history that many Chinese people consider themselves descendants. Huangdi is viewed as the "symbol of vital spirit of Chinese civilization."[30] Probably the most important text in the history of Chinese medicine, often overshadowed by the "reputation and authority of the original classic," the *Huangdi Nei Jing,* was the *Nan Jing (The Classic of Difficult Issues),* thought to have been compiled around the first or second century AD. According to Unschuld,[31] the *Nan Jing* was "a significant and innovative work that was the apex and conclusion of the developmental phase of the conceptual system unknown as the medicine of systematic correspondence." He went on to describe the importance of the *Nan Jing,* saying "the Nan-ching (jing in pinyin romanization) is comprehensive . . . discusses the origins and the nature of illness; outlines a system of therapeutic needling; and develops—in great detail—an innovative approach to diagnosis." The *Nei Jing* predates the historically available writings of ancient China and delves strongly into "demonological medicine and religious healing," whereas the *Nan Jing* is homogeneous and highly systemized, basically intact, and well focused.[32]

In terms of acupuncture, Unshuld[33] cites no "reliable" references before 90 BC appearing in Chinese literature. Ancient works as a whole were written on bamboo strips and silk. These went through countless hands and copies, creating a body of written work that contained numerous errors and omissions. It was not until 26 BC that the Chinese government organized medical officials to collate and revise the royal collection of medical works preserved at the Mifu Natnal Royal Library.[34] The earliest recorded physician reputed to be versed in pulse-taking and acupuncture was Bian Que (approximately 500 BC). Several medical works ascribed to him have been lost.[35] Su Ma Qian, historian of the Han dynasty (206 BC-220 AD), wrote a chapter on the biography of Bian Que in the *Historical Note* about 100 BC. This was the first reliable reference documenting acupuncture and moxibustion in Chinese. He told many stories of Que's ability to treat with acupuncture. Zhang Ji (150-219 AD), referred to as the sage of Chinese medicine, authored the classic work *Shanghanlun.* Statues of the legendary Zhong Ji are common on many of the TCM college campuses in mainland China today. Another of the famous ancient masters of Chinese medicine was Hua Tuo (?-208 AD), a surgeon and practitioner of an eclectic range of therapies, including acupuncture and hydrotherapy, and an originator of the therapeutic exercises called the "five animals."[36]

Huangfu Mi (214-282 AD), a famous acupuncturist, compiled *Zhen Jiu Jia Yi Jing (A Classic of Acupuncture and Moxibustion),* the first monograph on acupuncture in history, around 282 AD. These 12 volumes covered all aspects of acupuncture practice and theory and are considered a monumental work.[37]

The first usage of the English term "acupuncture," meaning needle puncture, is attributed to a Dutch physician, Rhyne, who visited Japan sometime in early seventeenth century.[38] Dr. Berlioz of the Paris Medical School was attributed with the first recorded use of acupuncture in the West. John Churchill, in 1821, was the first British acupuncturist to publish works highlighting treatment of tympany and rheumatism. Acupuncture is also mentioned in *Lancet's* first edition in 1823. Dr. Elliotson published results of 42 cases of acupuncture treatment of rheumatism, concluding that acupuncture was effective as a treatment.[39]

In 1825, Franklin Bache, MD (Benjamin Franklin's great grandson) published an article on acupuncture in the *North American Medical and Surgical Journal*, detailing his clinical trials utilizing acupuncture on prisoners with various conditions. Michael Devitt wrote a wonderful account about this early pioneer of acupuncture in the *American Acupuncturist*.[40]

As noted earlier, in 1849, the Gold Rush in California helped to spark a large immigration of mostly male Chinese people into Western America. Heading for "Gold Mountain," they brought all elements of their culture, including their traditional medicine with its acupuncture and Chinese herbs. Writing in his book, *Chinese Medicine on the Golden Mountain,* Paul Buell stated the following: "[There] was an acute shortage of any form of medical care in Western America where most Chinese settled. Well practiced Chinese medicine was often superior to contemporary Western practice. Western medicine did not gain any real advantage over well practiced Chinese medicine until the coming of any 'wonder drugs' in the 1930s, and in some respects, as in many chronic ailments, (traditional) Chinese medicine is still superior."[41]

In an interesting mention of acupuncture in 1892, William Osler wrote, in his *Principles and Practice of Medicine,* about the use of acupuncture in the treatment of sciatica.[42] There would be few other mentions of the subject in American medical literature for many years to come.

FUNDAMENTALS OF ACUPUNCTURE

Acupuncture is a technique involving the insertion of fine needles into the skin at select points or points of tenderness. As discussed earlier, the theory, or acuology, that surrounds the practice dates back as many as 4000 to 5000 years. Possible historical links to India and even other areas have been suggested. For many contemporary practitioners, their practices of acupuncture are defined by the theory of the fundamental principles: five elements (e.g., phases, movements), Yin, Yang, Qi, and Zang Fu. For still others, these ancient theories remain just that—ancient and removed from modern science—and they practice acupuncture solely on the basis of recent theories of mechanism and anecdotal evidence.[29,43]

Yin and Yang, on which all diagnosis and treatment in TCM is based, is the central theory in the practice of acupuncture. In perfect balance, in optimal health, Yin and Yang are harmonious, the ebb and flow of the tides, day and night, male and female. The theory, when translated, can be set in quite poetic terms. A deficiency of liver and kidney Yin, for example, might result in clinical symptoms

such as dizziness, vertigo, insomnia, dry throat, and lumbago, whereas a deficiency of spleen and kidney Yang may manifest clinically as cold limbs, lumbago, diarrhea, and scanty urine. Excess is usually seen as a relative state due to the deficiency of the other, as in deficient Yin resulting in an apparent excess of Yang.

Qi

Qi is the energy and potential energy that courses throughout the organism and defines what we call life. The lack of proper Qi flow in the system results in numerous maladies. Qi stagnation often manifests as pain. Rebellious Qi manifests as belching, burping, and vomiting, a reversal of the normal downward movement of Qi digestively. Potential Qi is that energy that is bound up in inanimate objects, such as rocks and furniture, that can become more active if expressed or liberated. Then there is the Qi that weaves through space, connecting us to the web of the universe—a concept that begins to sound like theories in quantum physics.

Zang Fu

The Zang Fu are the Chinese organs, five solid Yin and six hollow Yang. In the West, English names are used for the organs—liver, heart, spleen, kidneys, and lungs—but depending solely on the Western name without a thorough understanding of the traditional Chinese meaning leads to much confusion clinically. A complete and clinically sound synthesis of the Western biomedical understanding with the traditional Chinese understanding has not occurred to date. For example, the liver as known in the West is defined according to its anatomical structure and function (i.e., it is a large glandular organ that secretes bile and metabolizes blood-borne compounds). The Chinese gan (liver) stores blood and Qi, and is responsible for the smooth transmission of Qi and blood throughout the body. Moreover, it has a chief role in emotions; an unbalanced gan (liver) results in anger, high blood pressure, and a general state of agitation. The liver in the Chinese sense is much more a functional system with many body-wide interactions. The hollow organs are the gallbladder, large and small intestines, "triple burner," urinary bladder, and stomach. The triple burner is a good example of how different the Western and Chinese views are, because this has no meaning in the West. In the Zang Fu system, the triple burner corresponds to the thoracic and abdominal regions, including all of the organs within these regions. It has a specific function that distinguishes it as a Fu organ, namely, to transport water.

The Five Elements

The five elements (also called the five phases or in Chinese, wu xing) are fire, metal, wood, earth, and water. The correspondences among these elements have led to a method of diagnosing and treating patients.

In the West, a school of thought following the teachings of Dr. Worsley in England evolved and grew into a worldwide system of schools and practitioners associated with the so-called law of five elements. There is a stark contrast between this system of acupuncture practice and the TCM systems.

Points and Meridians

The other key aspect of the fundamentals of acupuncture is, of course, the theory of the channels. There are the basic 365 mapped acupuncture points along the 12 major and 8 extra channels, as well as more than 1000 extra points and special use points, including the microsystems, such as the hand, ear, and scalp, all with specialized functions. The so-called ashi points, or pain points, can literally be located anywhere on the body where there is a pain locus. Qi and blood flow throughout the channels, and this is where the proper manipulation of the needle is critical in properly moving this flow.

ACUPUNCTURE SCOPE OF PRACTICE

Similar to the challenges in universal acceptance of an exact definition of the term acupuncture, the clinical practice of acupuncture also varies across the world and in different American jurisdictions. There are 45 American State and District of Columbia acupuncture practice acts as of early 2011. Although there is a core of therapeutic acceptance from state to state, there are wide variations in expanded scopes. Although most states use the designation "L.Ac." a few have begun to use other credentials such as "Doctor of Acupuncture" in Rhode Island and "Doctor of Oriental Medicine" in a few other states.[44]

New Mexico is a good example of perhaps the broadest acupuncture scope in America. The practice of "Oriental Medicine" includes homeopathy, prescriptive drug authority (with expanded practice certification), laser therapy, injection, and IV therapy, all within its Doctor of Oriental Medicine (DOM).[45]

Although California law has in many ways set the pace for the profession through the years with a scope that now defines acupuncturists as primary health care professionals with a practice inclusive of Asian massage, acupuncture, herbal medicine, exercises, breathing techniques, and dietary supplements, among others, it is the Washington State law that forged entirely new ground for acupuncturists in America.

The stage was set for the renaming and overhaul of the state acupuncture law for a number of reasons, including the strong desire by a Korean Washington State legislator to rid the Western world of the term "Oriental," an upcoming sunset review, and several confusing and deficient parts of current acupuncture law. What resulted was the insertion of the term Asian in place of Oriental in the Washington State acupuncture regulations. "East Asian medicine means a health care service utilizing East Asian medicine diagnosis and treatment to promote health and treat organic or functional disorders and includes the following: Acupuncture (or lancets), Electrical, mechanical, magnetic devices, moxibustion, acupressure, cupping, dermal friction technique, infra-red, sonopuncture, laserpuncture, point injection therapy (aquapuncture), dietary advice (including recommendation and sale of herbs, vitamins, minerals), breathing, relaxation and East Asian exercise, Qi Gong, East Asian massage and Tui na, and superficial heat and cold therapies."

Acupuncturists in the State of Washington now can use the credential EAMP.[46]

ACUPUNCTURE SAFETY

Acupuncture therapy is a safe and relatively pain-free procedure. There are many forms and styles of acupuncture therapy practiced; some have a reputation for potentially being more painful at times, but generally the procedure is painless. Millions of treatments have been performed by licensed acupuncturists in America with very little reporting of adverse effects. Most licensed acupuncturists in America have taken "clean needle" training as part of their basic acupuncture training. For the past 15 years, it has been the standard of care in acupuncture practice that single use disposable needles are used in all treatments.

In the past year there has been renewed discussion about the safety of acupuncture sparked by a *British Medical Journal* (*BMJ*) editorial piece that put a cautionary spin on the view that acupuncture needling is entirely safe, or at least has virtually no side effects.

The article, "Acupuncture Transmitted Infections," although highlighting the skin infection risk of acupuncture needling, also identified only "more than 50 cases" to date (2010) worldwide. Nevertheless, the authors' main opinion stated that these type of infections were underreported.[47] An older report also published in the *BMJ* by Vincent seems appropriately titled, "The Safety of Acupuncture; Acupuncture Is Safe in the Hands of Competent Practitioners." Vincent stated, "The conclusion that acupuncture is a very safe intervention in the hands of a competent practitioner seems justified on the evidence available."[48] A large review study published in 2008 focused on acupuncture safety and efficacy in pediatrics. The authors "found evidence of some efficacy and low risk associated with acupuncture in pediatrics." They stated some caution as well, noting "the safety of acupuncture is a serious concern, particularly in pediatrics. Because acupuncture's mechanism is not known, the use of needles in children becomes questionable." They also stated, "nevertheless, it seems acupuncture is a safe complementary/alternative medicine modality for pediatric patients on the basis of the data we reviewed."[49]

The NCCAOM and the AAAOM jointly authored a response to the *BMJ* editorial, stating that "the article neglected to mention that the incident of infections is drastically reduced when a consumer seeks a qualified practitioner who has met the rigorous standards of the NCCAOM certification which includes passing of the Council of Colleges of Acupuncture and Oriental Medicine (CCAOM's) clean needle technique course, a prerequisite to becoming an NCCAOM certified practitioner."[50] They stated in another article that, "while acupuncture is a highly effective and valuable form of healthcare, it is not an entirely risk-free medical procedure, and should be administered by practitioners with the proper training who follow accepted guidelines of practice."[51]

EVIDENCE-BASED ACUPUNCTURE

The defining moment for acupuncture research came with the conclusion of the NIH Consensus Conference in 1997. For the first time, a Western panel of medical experts gathered to review, critique, and set guidelines for the use of acupuncture in the medical field in America. Before this conference, research in acupuncture was acknowledged by some Western doctors but largely dismissed. The view of Asian studies and of studies from other countries in general did not make an impact on the American radar. The conference helped focus the attention, collect what research had been completed to date, and concluded that there was merit in the use of acupuncture for certain conditions and, most importantly, that there was a real need and demand that acupuncture be better studied and used. Acupuncture was finally "on the map" in the West.[52]

Progress was made in the 10 years after the NIH conference, as was detailed by the 2007 Society for Acupuncture Research (SAR) International Symposium.[53] The symposium detailed a number of important research conclusions, highlighting growing evidence for the effectiveness for chronic pain while detailing the issues concerning sham acupuncture in trials, as well as a number of basic science trials demonstrating the physiologic effects of needling. Paradoxes in acupuncture research are the focus of increased discussion and remain an issue important in 2011.

Box 31-2 highlights the state of evidence-based acupuncture as of late 2010.[54-57] These conditions have been well researched, and the evidence is there for their inclusion in the list. For many acupuncturists who still tout the dated WHO list of conditions for application to acupuncture, this list would appear inadequate and incomplete. To the medical skeptics who doubt the blogosphere and appear 100% opposed to anything CAM, this list is probably highly suspect. This is the state of CAM in 2011. Somewhere between the true believers and the skeptics lies the truth. The research community that is honestly trying to attain that truth for the betterment of science and human health deserves respect for their efforts.

Western medical practice has grown within a system of great scrutiny and self-analysis. A massive research culture spins off studies by the thousands. The double-blinded, placebo-controlled trial has become the hallmark of the "appropriately conducted research trial." Acupuncture evolved in a completely different culture, that of China, where, ironically, as we were "discovering" the Chinese traditional system of acupuncture, not so many years ago, the Chinese began a wholesale discovery of traditional Western medicine. Acupuncture and all that is TCM have been extensively researched in China. What is the quality of that research? Does it meet the scrutiny of Western "gold standard" research?

Large research academies, the largest being the China Academy of Traditional Chinese Medicine in Beijing, and various universities and schools of TCM, have created a huge research culture in China since the 1970s. Although there is considerable emphasis on herbal research, there is still quite a lot of research examining the other areas of TCM, including acupuncture. What does this Chinese research culture mean for Western medicine? This is a big question that is being sorted out in numerous ways today. The issues still at hand regarding Chinese research are the following:

- Too few numbers of English-translated TCM journals[58]
- Lack of studies using "approved" Western research standards
- Terminology issues
- Major design issues
- Inflated outcome assumptions
- Lack of Western acceptance of Chinese studies

BOX 31-2 Evidence-Based Acupuncture: Medically Necessary Indications

- Chronic pain
- Low back pain
- Chronic neck pain
- Osteoarthritis
- Postoperative pain
- Fibromyalgia
- Postoperative nausea/vomiting
- Chemo-induced nausea
- Dental pain
- Endoscopy pain

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CHAPTER 32

Ayurveda: The Science of Life and Mother of the Healing Arts

Virender Sodhi, MD, ND

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INTRODUCTION

Ayurveda is one of the most ancient systems of medicine known today. The origins of this science of life (*Ayu*—life and *Veda*—knowledge), although difficult to pinpoint, have been placed by scholars of ancient Indian Ayurvedic literature somewhere around 6000 BC.[1]

Ayurveda is a holistic science of health and a balance in lifestyle. Disease is seen as an imbalance, and its treatment involves diverse strategies to restore optimal function and balance. Using dietary alterations, yoga, and exercise, along with elaborate surgical techniques and complex, integrated herbal formulas, the Ayurvedic physician treats the whole person, removing disease completely by ending the imbalance that created it.

HISTORY

In ancient India, it was custom for a teacher's instruction to be recorded by his students, who would eventually repeat the same information orally to their own disciples. Thus, according to the different interpretations given by various disciples of Ayurveda, a number of treatises were written. Although specific instructions differed, the basic principles remained the same.

Ayurvedic teachings were orally transmitted for thousands of years and then written down in melodious Sanskrit poetry. The contents of a number of Sanskrit verses, or *shlokas*, although written many centuries ago, still sound a note of familiarity in today's scientific environment. Ayurveda, in its first recorded form (*vedas:* the world's oldest literature), is specifically called *Atharveda.*

The Development of Ayurvedic Medicine

Hindu legend holds that, after seeing the suffering of human beings, Lord Brahma, the god of creation, elaborated ways to ease that suffering to Daksha, who, in turn, taught them to the Ashwin twins. Figure 32-1 presents the chronology of Ayurveda's development.

Dhanvantari and Bhardwaj separately developed the surgical and medical aspects of Ayurveda around the ninth century BC. Their students recorded these principles in great detail in compendia that are called *Samhitas.*

The *Sushruta Samhita*, one of the most widely accepted Ayurvedic texts, emphasizes the surgical aspects of therapy. Its author, Sushruta, is considered the father of surgery (particularly of plastic and reconstructive surgery). The medical teachings of Charak were a synthesis of earlier work. His material has become a classic text of the nonsurgical medical wisdom of Ayurveda. Successive generations have modified his work, the *Samhita.*

THE MAJOR SCHOOLS AND SPECIALTIES

School of Physicians *(Atreya Sampradaya)*

Charak wrote a complete text on Ayurvedic medicine in which he revised the work of Agnivesh. Charak's text described the *Tridosh* physiology *(Vat, Pit,* and *Kaph)*, seven *Dhatus* (tissues), and three *Malas* (excretions). His text covered the pathophysiology and treatment of diseases, human constitution *(Prakriti),* classifications

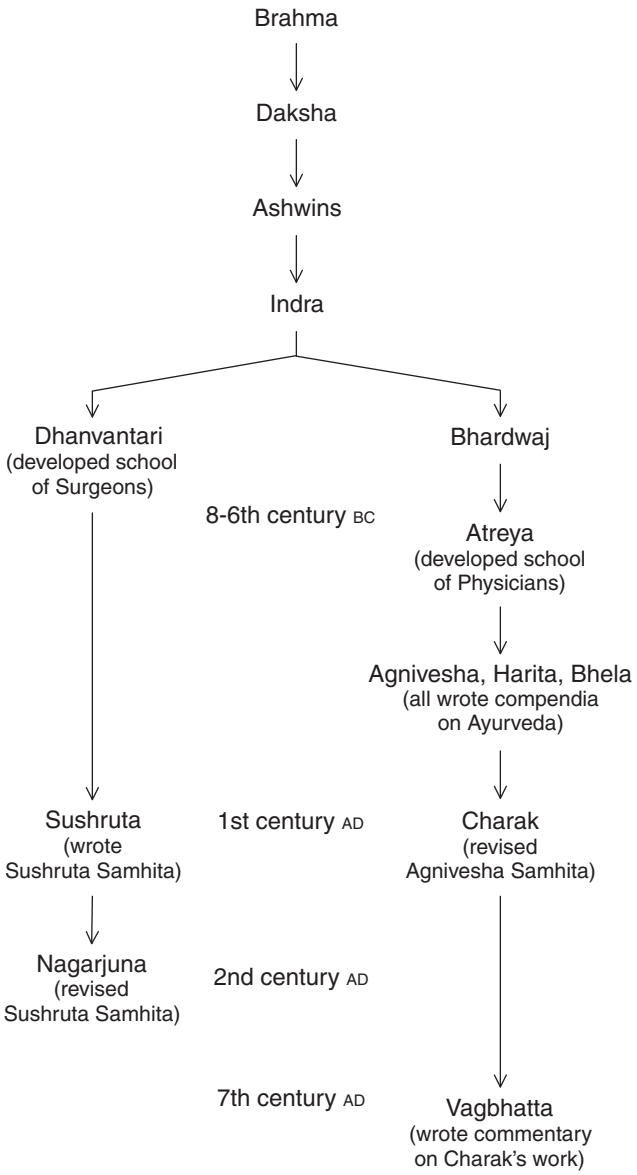


FIGURE 32-1 The chronology of Ayurveda.

and preparations of drugs, diet, "right conduct," medical ethics, and many other aspects of medicine.

School of Surgeons *(Dhanvantari Sampradaya)*

Sushruta wrote the first comprehensive works on surgery. These were later revised by Nagarjuna in the second century AD. The major subjects in his texts were the following:

- Injections
- Preoperative care
- Postoperative care
- Suturing
- Asepsis
- Sterilization
- Operation theaters
- Hospitals

Sushruta described 141 types of instruments and listed 40 types of surgeries and surgical techniques for treating cataracts, hemorrhoids, hernias, and bone problems, for cosmetic and plastic purposes, and for the removal of kidney stones and gallstones.

TABLE 32-1 **Specialties in Ayurveda**

AYURVEDIC NAME	ENGLISH NAME
Shalya Tantra	General surgery
Shalkya	Ophthalmology and otorhinolaryngology
Kaya Chikitsa	Medicine
Bhutvidya	Psychiatry
Kumar-Bhritya	Pediatrics, obstetrics, gynecology
Agada Tantra	Toxicology and jurisprudence
Rasayana	Geriatrics
Vajikaran	Fertility and sterility

Branches of Ayurveda

Ayurveda encompasses eight specialties or branches. They comprise a system developed to prevent and cure disease, as well as achieve and maintain excellent health. Table 32-1 lists the branches.

PHILOSOPHY

Ayurvedic philosophy is based on the Samkhya philosophy of creation. It has influenced major strains of philosophy in both Eastern and Western civilization. The word *Samkhya* is derived from the Sanskrit words *Sat* (truth) and *Khya* (to know). The *Rishi Kapila* (*Rishi* means realized beings or seers of truth) realized the Samkhya philosophy of creation. They perceived the following:

- The close relationship between humans and the universe (that humans are a microcosm, a universe within themselves, whereas the external environment is the macrocosm).
- The source of all existence is cosmic consciousness, manifest as male *(Shiva* or *Purusha)* and female *(Shakti* or *Prakriti)* energy.

Purusha is formless, colorless, and beyond attribute. *Prakriti* has form, color, awareness, and choice. *Prakriti* creates all the forms of the universe and has three attributes *(Gunas): Satva* (essence), *Rajas* (movement), and *Tamas* (inertia). It is also represented by Brahma (the god of creation), *Vishnu* (god of protection), and *Shiva* (god of destruction), which together comprise a cycle active in this universe.

In *Prakriti,* the three attributes are in balance. Whenever this balance is disturbed, they interact to bring about the evolution of the universe, yielding the cosmic vibration of *Aum.* The cosmic intellect (the *Mahad*) manifests itself as ego *(Ahamkar)*, which, through the help of *Satva,* manifests the five senses and five motor organs, which together constitute the "organic universe." Ego further manifests into the five basic elements (space, air, fire, water, and earth), which, under the influence of *Tamas,* create the "inorganic universe."

Satva is a creative potential *(Brahma), Rajas* is a kinetic protective force *(Vishnu),* and *Tamas* is a potentially destructive force *(Mahesh).* These three—*Brahma, Vishnu, and Shiva*—are constantly operating in the universe.

Five Basic Elements and the Universe (Panchbhuta Philosophy)

The *Rishis* perceived that consciousness consists of these five basic elements: ether (space), air, fire, water, and earth. At the beginning of the world, consciousness was without form, existing as the subtle vibration of the cosmic "soundless" sound *Aum.*

TABLE 32-2 **The five elements and the senses**

ELEMENT	SENSE	ORGAN	ACTION	VEHICLE OF ACTION
Ether	Hearing	Ear	Speech	Mouth
Air	Touch	Skin	Holding, giving, receiving	Hand
Fire	Vision	Eye	Walking	Feet
Water	Taste	Tongue	Procreation	Genitals
Earth	Smell	Nose	Excretion	Anus

Within these vibrations appeared the element ether. Ether started to move, creating air. The movement of ether also produced friction and, through friction, generated heat, then fire. From the heat of the fire, ethereal elements dissolved and liquefied into water. Water then solidified to form molecules of earth. Thus, all matter was born from the five elements. These five elements exist in energy forms.

Five Elements and the Senses

The five elements also connect with the five senses: ether—hearing, air—touch, fire—vision, water—taste, and earth—smell, and they are present in certain physiologic functions. Expressing the functions of the sensory organs are five actions (Table 32-2). In this manner, the elements are directly related to humans' abilities both to perceive the external environment in which they live and to respond to it:

- Ether is the medium through which sound travels. The ear is the organ of hearing, expressing its action through the organ of speech, which creates meaningful sound.
- Air is related to skin and the sense of touch. Its organ of action is the hand, which is especially sensitive. The hand performs the actions of holding, giving, and receiving.
- Fire produces light, heat, and color, and is thus related to vision and direction. Its organ is the eye.
- Water relates to the organ of taste. The tongue is also related to the action of the genitals, the penis, and clitoris. In Ayurveda, the penis and clitoris are called the lower tongues. By controlling the upper tongue, one naturally controls the lower tongue.
- The earth element relates to the sense of smell, and the nose is its organ.

PHYSIOLOGY

The five elements manifest within the body as the *Tridosha* (*Dosha* means protective or, when out of balance, disease producing). The *Tridosha* are the three humors, or basic principles, described earlier—*Vat, Pit,* and *Kaph.*

From the bodily combination of ether and air comes the bodily air principle, *Vat Dosha*. Likewise, fire and water combine as *Pit Dosha,* or fire principle, and earth and water produce the *Kaph Dosha,* or water principle.

These three control all biological, psychological, and physiopathologic functions of the body, mind, and consciousness. They produce natural urges and individual tastes in food, flavor, and temperature. They govern the maintenance and destruction of bodily tissue and the elimination of waste products. They also are responsible for psychological phenomena, including the emotions of fear, anger, and greed, as well as the highest order of emotions: understanding, compassion, and love.

BOX 32-1 **Properties of *Dosha***

Vat	***Pit***	***Kaph***
Dry	Oily	Oily
Light	Light	Heavy
Cold	Hot	Cold
Rough	Liquid	Slimy
Subtle	Penetrating	Soft
Mobile	Mobile	Static
Clear		Dense
Dispersing		Slow
Smells sour		

Properties of *Dosha*

Vat, Pit, and *Kaph* control all human biological, psychological, and physiopathologic functions and have subtle properties, as shown in Box 32-1.

The *Doshas* increase by similar properties and are diminished by opposite properties. For example, *Vat* is dry, light, and cold, so any food, medicine, lifestyle, or behavior that increases these qualities increases *Vat* within the body. Conversely, oily, heavy, or hot factors decrease *Vat.*

Functions of *Tridosha*

Each humor has a specific action. *Vat* is the principle of movement and may be called the bodily air principle, as opposed to the environmental air principle. *Vat* is a subtle energy governing all biological movement—breathing, blinking, muscle and joint movement, heartbeat, and all nerve and membrane contractions and expansions. In addition, it controls the psychological functions governing the emotions of fear and anxiety. *Vat* also controls pain, tremors, and spasms. Broadly speaking, the whole nervous system can be labeled as *Vat* function. The large intestine, pelvic cavity, bones, skin, ears, and thighs are the places of *Vat.* Any excess of *Vat* accumulates in these areas.

Pit, or bodily fire, governs digestion, absorption, assimilation, nutrition, temperature, skin color, luster of the eye, intelligence, and understanding. It arouses anger, hate, and jealousy. The small intestine, stomach, blood, sweat glands, fat, eyes, and skin are the places of *Pit;* all metabolism is governed by *Pit.*

Kaph, biological water, is the cement of the body, providing for physical structure. It is responsible for body resistance and biological strength. It lubricates the joints; provides moisture to skin; and promotes wound healing, strength, vigor, and stability. It supports memory, gives energy to the heart and lungs, and maintains immunity. *Kaph* is present within the throat, chest, head, sinuses, nose, mouth, stomach, joints, cytoplasm, plasma, and liquid secretions. Psychologically, *Kaph* governs attachment, greed, longstanding envy, calmness, forgiveness, and love.

A balance of the *Dosha* is necessary for optimal health. Together, they govern all metabolic activities: anabolism *(Kaph),* catabolism *(Vat),* and metabolism *(Pit).*

Individual Psychosomatic Constitutions—*Prakriti*

Prakriti, a Sanskrit word composed of *pra* (before) and *akriti* (creativity), denotes the constitution of each individual as determined at conception. At the time of fertilization, permutations of *Vat, Pit,* and *Kaph* determine the constitution of the new individual,

with maleness or femaleness dominating other traits. These basic traits are also shaped by other important factors, such as diet, lifestyle, behavior, emotions, and seasons.

As illustrated in Box 32-2, up to seven different constitutions can exist depending on the permutation and combination of *Vat, Pit,* and *Kaph. Prakriti* is genetically determined; the basic constitution, the combination of the three humors, remains unchanged throughout an individual's lifetime. The combination can, however, respond to environmental changes.

Life is considered a sacred path in Ayurveda, a ceaseless interaction between the internal *(Tridosha)* environment and the external environment, or the sum of cosmic forces. To counteract external change, an individual may create a balance in the internal forces by altering diet, lifestyle, and behavior. The characteristics of the corresponding psychosomatic constitutions are listed in Table 32-3.

BOX 32-2 The Seven Types of Constitution

- *Vat*
- *Pit*
- *Kaph*
- *Vat-Pit*
- *Pit-Kaph*
- *Kaph-Vat*
- *Vat-Pit-Kaph*

Mental Constitutions

On the mental and astral planes, three *Gunas* (attributes of female energy or *Prakriti*) correspond to the three humors that make up the physical constitution. In the Ayurvedic system, the *Gunas* are *Satva, Rajas,* and *Tamas.* They provide the basis for the distinctions in human temperament and individual differences in psychological and moral dispositions. These attributes are further subdivided, but that is beyond the scope of this chapter.

Satva

This type of mind expresses essence, understanding, purity, clarity, compassion, and love. People of Satvic psyche (*Satva* temperament) have healthy bodies and pure behavior and consciousness. They believe in the existence of God, are religious, and are often holy persons.

Rajas

This type of mind operates on the sensual level. Such persons are interested in business, prosperity, power, prestige, and position. They enjoy wealth, are generally extroverted, and are politically minded.

Tamas

This type is distinguished by its ignorance, inertia, heaviness, and dullness. Tamasic people are lazy, selfish, and destructive by nature. They show little respect to others. All their activities are egocentric. The Satvic person attains self-realization without much effort, whereas those of Rajasic or Tamasic mind have difficulty.

TABLE 32-3 **Psychosomatic constitutions *(Prakriti)***

CHARACTERISTIC	*VAT*	*PIT*	*KAPH*
Body frame	Tall or small, thin, ill-nourished, hard, dry, cold	Medium, many moles, well nourished, pimples, patches of freckles, pigment, tender appearance	Stout, well-nourished, big, oily, greasy, cold, beautiful
Skin	Dry, cracked, tough, broken, brownish, black	Soft, thin, yellow, red, pink	Greasy, soft, yellow, white
Hair on head	Brown, scanty, coarse, curved, wavy, wrinkled	Pinkish, yellow, moderate, soft, baldness, premature graying	Black, plentiful, firm, wavy, curved
Head	Small size	Moderate in size	Big and steady
Eyes	Small, dry, thin, muddy brown, unsteady gaze, not pleasant looking	Thin, yellow, pink coppery, quickly become inflamed, pleasant looking	Big, white, pink, pleasant looking, thick, fixed, greasy
Body weight	Less	Moderate	Heavy
Action of body	Quick unsteady walk, quick actions and movements	Moderate, intelligent actions	Steady walk, slow and dignified
Eliminations	Less, constipated	Copious, watery	Moderate, solid
Strength	Less, tires quickly	Moderate	Strong, hard worker, can withstand strains
Body odor	No smell, less sweating	Heavy sweating, bad smell	Less sweating, pleasant smell
Voice	Feeble, broken, hidden, hoarse, unpleasant	High pitch	Pleasant, deep bass voice, good tone
Speech	Quick, very talkative	Moderate	Slow, definite
Sleep	Less sleep, wakeful at night	Moderate	Sleeps a good deal
Dreams	Moving in sky, action	Cold, flowers, sun, fire, lightning, red, frightful dreams	Ponds, lakes, flowers, swans, beautiful sights
Sex	Less sex capacity, less semen/menses, few children	Less sex capacity, few children	Great sex capacity
Life expectancy	Short	Moderate	Long-lived
Reaction to disease	Quick to get diseases, usually nervous disorders	Moderate, usually inflammations	Good resistance, usually cold and phlegm type
Reaction to drugs	Minimum doses required	Intolerance to drugs	Slow, tolerates at high dose

These three subtle mental energies are responsible for behavior patterns that may be altered and improved through practice and spiritual discipline, such as yoga and meditation.

HEALTH AND DISEASE

Health is defined in Ayurveda as the soundness of body *(Shrira)*, mind *(Manas)*, and soul *(Atma)*. Each part of this tripod of life should receive equal attention to ensure that the individual achieves sound health. Ayurvedic medicine stresses that psychic influences strongly affect the body in health as well as disease, a fact that must also be taken into account in modern therapeutics.

Modern science takes pride in its understanding of physiology but, in doing so, has emphasized fragmentation, isolation, and disunity. Instead of wholeness and interaction, this modern view accepts only physical objects as causes of disease, whereas these objects are merely the agents of disease, able to cause specific symptoms, but only in a susceptible host. Disease is the result of a disruption of the spontaneous flow of nature's intelligence within physiology. When people violate nature's law and cannot adequately rid themselves of the results of this action, then they acquire diseases.

Ayurveda conceives the body as being composed of three principal divisions: three *Doshas* (humors), seven *Dhatus* (tissues), and three *Malas* (excretions).

The three *Doshas* regulate cell functions. *Pit* gives energy and is responsible for cellular, enzymatic, and metabolic functions; *Kaph* helps in synthesizing blocks of cells; and *Vat* controls the other two. A balance of these *Doshas,* good quality tissues (the seven *Dhatus*), and a certain character of excretions are essential for maintaining health.

As explained earlier, an individual is born with a particular *Dosha* predominating in his or her constitution *(Prakriti).* This predominant *Dosha,* quite apart from genetic, age, environment, and dietary factors, may make an individual susceptible to a certain disease. For example, *Pit Prakriti* individuals are more prone to develop a disease syndrome with symptoms similar to a peptic ulcer. This is due to hyperactivity of the *Pit Dosha,* which regulates enzymatic activity. Hyperpepsinogenemic individuals are more susceptible to duodenal ulcer formation.[2]

Ayurveda teaches that the origin of most diseases is found either in an exogenous or endogenous *Dosha* imbalance, or in an inherent or acquired weakness of the tissues. Therefore, a successful treatment or prevention of disease consists of normalizing cellular functions through correcting any *Dosha* imbalance or improving inherent tissue vitality. For example, in the treatment of cancer, the use of agents cytotoxic to the cancer cells is important. However, equally important is potentiation of the immune system and stimulation of the body's own healing mechanisms.

MODES OF THERAPY

Once a diagnosis is made, Ayurveda offers various modes of therapy. The treatment is chosen according to patient constitution, as well as disease process. Modalities include dietary alterations, botanical medicines, minerals, animal products, exercise, yoga, meditation, counseling, and surgery.

Diet

Ayurveda places great emphasis on diet, for both its direct effect on the individual's physiologic state and its influence on the action of medicines. Proper assimilation of dietary constituents is essential for the maintenance of good health. Improper assimilation results in the formation of intermediary products of digestion that have toxic properties and are therefore treated as foreign by the body. Such toxic products are called *Ama* (this leads to the concepts of immune and autoimmune disorders).

Arthritic diseases such as rheumatoid arthritis are attributed to an accumulation of *Ama.* Could these toxic intermediates—macromolecules absorbed transmucosally from the intestine (in nutritionally insignificant amounts)—provoke strong immune reactions? The human gut has a complex system to control the continuous onslaught of antigenic substances derived from food, microorganisms, and toxins.[3] It has been suggested that absorption of such compounds could underlie the pathogenesis of disease in the gut, as well as in distant sites such as the liver and spleen.[4]

Ayurveda stresses prevention of the formation and accumulation of *Ama* through appropriate diet and the use of therapies to improve digestion. It also considers various dietary factors that trigger or eliminate certain diseases.[5] That is why Ayurveda places emphasis on diet according to the patient's psychosomatic constitution *(Prakriti),* time of day *(Dincharya),* and season *(Ritucharya).* For example, a person with the *Pit* psychosomatic constitution should not eat foods that are hot, pungent, or spicy at noon in the summer, since this tends to increase diseases of inflammation.

Ayurveda prescribes specific diets for several psychiatric disorders. Recent research supports this approach. Brain levels of the neurotransmitters 5-hydroxytryptamine, catecholamine, and acetylcholine have been found to be influenced by dietary constituents. Consequently, it has been suggested that normal brain functions and mental disease can be altered by diet.[6] Recent exciting developments include the successful treatment of mental depression with neurotransmitter precursors.[7,8]

Ayurveda also prescribes certain diets *(Pathya)* during drug therapies, since dietary constituents are believed to influence drug action.

Individualization of Medicinal Therapy

Medicinal therapy is highly individualized in Ayurveda.[9] The choice and dose of medicine are influenced not only by disease but by the individual's constitution and the environmental conditions likely to affect that individual's *Doshas.*

For example, *Piper rotudum* (black pepper) and *Zingiber officinale* (ginger), which increase *Pit* (increasing stomach acid and pepsin secretion), are used cautiously in individuals with a *Pit* constitution. Another example is in the treatment of the patient with hypertension. Ayurveda prescribes *Terminalia chebula* for the treatment of hypertensive patients who have *Vat Prakriti,* whereas for the patient with *Pit Prakriti,* one uses *Terminalia arjuna.*

In the *Vimanastrana,* Charak presented an interesting discussion of host- and drug-related factors that help in the determination of the drug and dosage (Box 32-3).

Ayurveda also emphasizes proper timing for the administration of medicines. Considering that chronopharmacology (the study of the timing of drug administration in relation to physiologic function) has only recently been developed as a branch of modern therapeutics, it seems remarkable that such astute observations about the timing of medicaments were made so many centuries ago.

Pharmacy in Ayurveda

In Ayurveda, pharmacy is highly developed. Almost 70 books contain more than 8000 recipes for the preparation of different medicines, most of which are derived from minerals and plants.

BOX 32-3 **Host- and Drug-Related Factors**

Drug Factors

Prakriti	Constitution of the drug
Guna	Properties
Prabhava	Activity (potency)
Desh	Place
Ritu	Season
Grahan	Storage
Nihit	Transport
Sanskar	Refinement
Matra	Dose
Sanyog	Combination
Adhishthan	Ability to reach site of action

Host Factors

Prakriti	Constitution of host
Vayam	Age
Vikriti	Pathologic condition
Sar	System strength
Satamya	Tolerability
Satva	Psychological state
Ahar Shakti	Digestive capacity
Vyayam Shakti	Exercise tolerance
Balam	Strength of host

Many formulations including simple distillates *(Arka),* decoctions *(Kwatha),* tinctures *(Avleha),* powders *(Churna),* pills (*Vati, Goti,* and *Modak*), fermented products *(Asva),* and medicated oils *(Taila and Ghrita)* are available. The oil preparations are particularly useful since they help to target the sites of actions.

Detailed descriptions of the methods are recommended to ensure a medicine is suitable for human use.[10] One pharmaceutic technique, *Samskara* (refinement), is known as *Shudhi* (purification), a process that eliminates the toxicity of some minerals and plants. Another practice is the administration of drugs in combination *(Samyoga)* to reduce toxicity and increase efficacy.

RESEARCH

Considerable modern research has proven the efficacy of Ayurvedic herbal preparations, and research has now moved to elucidating their mechanisms and sites of action.[11] Recent studies demonstrated probable genomic bases for metabolic differences as predicted by *Prakriti*. This genetic variant may provide newer approaches to pharmacogenomics. Extensive studies on *Prakriti* subtypes and genome mapping, especially of other important drug metabolizing enzymes polymorphisms like CYP2C19, CYP2D6, CYP2C9, CYP3A4, TPMT, etc., would be useful to understand a possible *Prakriti* pharmacogenomics relationship to its correlating genotype, *Prakriti,* and drug metabolism.[12]

Curcumin, the active principle of *Curcuma longa,* has been found to exert a powerful anti-inflammatory effect by blocking many inflammatory pathways, reversing insulin resistance, and reversing cancer by repairing defective genes.[13] Further, it has been shown to selectively inhibit platelet prostaglandin production, while sparing vascular endothelial prostaglandin synthesis.

Many plant preparations have been used to strengthen general host resistance. *Rasayna, Jeevaniya,* and *Balya* increase tissue resistance to disease, a concept similar to "prohost therapy" as put forward by Hadden.[14] Prohost therapy claims to augment cellular responses and, consequently, ameliorate disease states.[15]

A very recent paper published in *Phytotherapy Research* in May 2011 found that aqueous extract of *Withania somnifera* root had an ability to inhibit the formation of mature amyloid-β fibrils in vitro. Amyloid plaques in the brain cause Alzheimer's disease. This is an exciting discovery and may help many people from getting Alzheimer's disease.[16] Perhaps most exciting, however, is the current research demonstrating efficacy of Ayurvedic herbal preparations in conditions for which modern medicine has limited or no success. For example, animal studies showed that *Withania somnifera (Ashwagandha)* can reverse the immunosuppression of cyclophosphamide, azathioprine, and prednisolone, and a 50% alcoholic extract of *Phyllanthus emblica* protects the liver from paracetamol.[17,18] Recent human studies found that patients with acne vulgaris demonstrated substantial improvement, with no significant side effects, after using *Sunder Vati* compared with placebo. Interestingly, the study found three other Ayurvedic formulas ineffective. Patients with osteoarthritis experienced substantial, highly significant improvement in pain and disability with no significant side effects (however, the radiologic findings did not improve).[19]

AYURVEDIC AND MODERN MEDICINE

In evaluating Ayurvedic medicine by modern standards, one encounters a number of difficulties. First, there is in nature a wide variation in the quantity of pharmacologically active substances in plants. In addition, many findings are more subjective than objective. The modern scientist has difficulty recognizing subjective experiences because no reliable methodology has been developed to measure and reproduce such experiences. Yet totally objective experience, which completely disregards the subjective, may be wrong and even dangerous.

There is no such thing as complete objectivity. What people claim as such is merely agreement among many minds. Subjective experience is limited. Senses vary in ability, and reality for one is unreality for another. When using the tools of quantitative, technical science to describe biological and living systems phenomena, one soon encounters limits. Artificial distinctions must be imposed to reduce variables and interpret nonlinear events intelligibly.

Science has often confused the map for the actual reality. Take the example of color vision in bees. The eye of a bee is more sensitive to blue, violet, and ultraviolet light, whereas receptors in the human eye more readily detect red, green, and blue wavelengths. Thus, bees are nearly blind to red light, and humans are quite blind to ultraviolet light. These differing characteristics result in members of each species forming a completely different perception of the same object. Color, rather than being a part of the "reality" of a perceived object, is an expression of sensory apparatus, determined by each species' or individual's unique pattern of interneural connections. Even more interesting is the fact that, within the same species, perception may vary considerably.

Ayurvedic philosophy may strike the contemporary reader as unnecessarily complex for the conceptual territory it addresses. However, it is actually quite succinct and relevant to modern life. Its precepts have influenced many systems of healing, including naturopathic medicine, through several paths of its root traditions. It emerged alongside systems known to early Persians and Greeks, as well as the Chinese. Modern medicine is itself a distillation of these same rich traditions. When one compares Ayurvedic concepts with those of preindustrial Europe, much similarity becomes apparent.

SUMMARY

Only some glimpses of Ayurveda are presented here. This ancient system of medicine, developed over centuries, has a consistent and logical framework and gives detailed instructions for the preservation of health and the treatment of disease. Ayurveda faced a setback when modern medicine subjected all knowledge to experimental and statistical verification, which, although useful, is limited by the tools available and the perceptions underlying the questions asked. Now that considerable knowledge of cellular physiology has accumulated and more sensitive modern biomedical research tools exist, we may be able to evaluate the concepts of Ayurveda more effectively.

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CHAPTER 33

Botanical Medicine—A Modern Perspective

Michael T. Murray, ND

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INTRODUCTION

The term herb refers to a plant used for medicinal purposes. Are herbs effective medicinal agents or is their use merely a reflection of folklore, outdated theories, and myth? To the uninformed, herbs are generally thought of as ineffective medicines used before the advent of more effective synthetic drugs. To others, herbs are simply sources of compounds to isolate and then market as drugs. However, to some, herbs and crude plant extracts are effective medicines to be respected and appreciated.

For many people of the world, herbal medicines are the only therapeutic agents available. In the late 1990s, the World Health Organization estimated that about 80% of the world's population relies on herbs for primary health care needs.[1] This widespread use of herbal medicines is not restricted to developing countries, since it has been estimated that 70% of all medical doctors in France and Germany regularly prescribe herbal preparations.

Although herbal medicine has existed since the dawn of time, knowledge of how plants actually affect human physiology remains largely unexplored. Many individuals formulate their view of herbal medicine based on opinion, philosophy, and ideology. This chapter seeks to facilitate an informed view of herbal medicine. The past and future of herbal medicines are discussed. We believe that the continued evolution of the tradition of herbal medicine can only be accomplished within the context of continued scientific investigation.

Throughout the world, but especially in Europe, the United States, Canada, Australia, and Japan, a tremendous renaissance in the use and appreciation of herbal medicine occurred in the latter part of the twentieth century. For example, in the United States, the sale of herbal products skyrocketed from $200 million in 1988 to more than $3.5 billion in 1997 before leveling off in the $4 billion a year range (Table 33-1). Within the European Community annual sales exceeded $7 billion in 1997.[2]

The rebirth of herbal medicine, especially in developed countries, is largely based on a renewed interest by the public and scientific researchers. During the past 20 to 30 years, there has been a huge increase of scientific information concerning plants, crude plant extracts, and various substances from plants as medicinal agents. For example, a PubMed search of the term "herbal medicine" yielded over 1300 hits in 2010. However, the number of studies of botanical medicines is much higher. For example, there were 130 studies published on *Ginkgo biloba* alone in 2010.

THE ROLE OF HERBS IN MODERN PHARMACY

Plants still play a major role in modern pharmacy. For the past 50 years, about 25% of all prescription drugs in the United States and other developed countries have contained active constituents obtained from plants. Digoxin, codeine, colchicine, morphine, vincristine, and yohimbine are some popular examples. Many over-the-counter (OTC) preparations are also composed of plant compounds. Pharmacognosy, the study of natural drugs and their constituents, plays a major role in current drug development. Unfortunately, the standard path of the approval of a drug is a process that typically takes 10 to 18 years at a total cost of roughly $250 million (Table 33-2).

Because a plant cannot be patented, plants are screened for biological activity and then the so-called "active" constituents (compounds) are isolated and typically

TABLE 33-1 **Total Estimated Herb Sales in the United States 1994-2005**

YEAR	$ TOTAL SALES (MILLIONS)	% INCREASE (-DECREASE)
1994	2020	
1995	2470	22.3
1996	2990	21.1
1997	3557	19.0
1998	4002	12.5
1999	4110	2.7
2000	4260	3.7
2001	4397	3.2
2002	4276	−2.8
2003	4178	−2.3
2004	4320	3.4
2005	4410	2.1

Data from Ferrier GKL, Thwaites LA, Rea PR, et al. U.S. consumer herbal and herbal botanical supplement sales. Nutr Business J. 2006. http://www.nutritionbusiness.com.

TABLE 33-2 **Classic Examples of Drugs From Plants With a Correlation to Its Traditional Use**

DRUG	CLINICAL USE	BOTANICAL SOURCE
Atropine	Anticholinergic	*Atropa belladonna*
Caffeine	Central nervous system stimulant	*Cola nitida*
Camphor	Rubefacient	*Cinnamomum camphora*
Cocaine	Local anesthetic	*Erythroxylon coca*
Codeine	Analgesic/antitussive	*Papaver somniferum*
Colchicine	Antigout	*Colchicum autumnale*
Digitoxin	Cardiotonic	*Digitalis purpurea*
Digoxin	Cardiotonic	*Digitalis lanata*
Emetine	Amebicide/emetic	*Cephaelis ipecacuanha*
Ephedrine	Sympathomimetic	*Ephedra sinica*
Gossypol	Male contraceptive	*Gossypium* spp.
Hyoscyamine	Anticholinergic	*Hyoscyamus niger*
Kawain	Tranquilizer	*Piper methysticum*
Methoxsalen	Psoriasis/vitiligo	*Ammi majus*
Morphine	Analgesic	*Papaver somniferum*
Noscapine	Antitussive	*Papaver somniferum*
Physostigmine	Cholinesterase inhibitor	*Physostigma venenosum*
Pilocarpine	Parasympathomimetic	*Pilocarpus jaborandi*
Podophyllotoxin	Topical wart remedy	*Podophyllum peltatum*
Quabain	Cardiotonic	*Strophanthus gratus*
Quinine	Antimalarial	*Cinchona ledgeriana*
Reserpine	Antihypertensive	*Rauwolfia serpentine*
Scopolamine	Sedative	*Datura metel*
Sennosides	Laxative	*Cassia* spp.
Theophylline	Bronchodilator	*Camellia sinensis*
Tubocurarine	Muscle relaxant	*Chondrodendron tomentosum*
Yohimbine	Male erectile dysfunction	*Pausinystalia yohimbe*

Data from De Smet PA. Drugs 1997;54:801-840.

chemically modified to produce unique substances. If the compound is powerful enough, the drug company begins the process to procure Food and Drug Administration (FDA) approval. Of 520 new drugs approved by the FDA or comparable entities in developed countries, 30 came directly from natural product sources and another 173 were either semisynthetic from a natural source or modeled after a naturally occurring compound.[1]

Because of the expense and lack of patent protection, few clinical evaluations were done before 1980 on whole plants or crude plant extracts as medicinal agents per se. A key factor in contributing to more research into herbal medicines after this time was the development in Europe of regulatory policies and practices that made it economically feasible for companies to do research. For example, in Germany, regulations allow herbal products to be marketed with drug claims if they are proven to be safe and effective.[3] Whether the herbal product is available by prescription or OTC is based on its application and safety of use. Herbal products sold in pharmacies are reimbursed by insurance if they are prescribed by a physician.

The proof required by a manufacturer in Germany to illustrate safety and effectiveness for an herbal product is less (and more appropriate) than the proof required by the FDA for drugs in the United States. In Germany, a special commission (Commission E) developed a series of 400 monographs on herbal products similar to the OTC monographs in the United States. A herbal product is viewed as safe and effective if a manufacturer meets the quality requirements of the monograph or produces additional evidence of safety and effectiveness that can include data from existing literature, anecdotal information from practicing physicians, and limited clinical studies. In contrast, in the United States, extracts that are identical to those approved in Germany as drugs are available as "dietary supplements," yet manufacturers are prohibited from making any therapeutic claims for their products. No medicinal claims are allowed for most herbal products in the United States because the FDA requires the same standard of absolute proof as required for new synthetic drugs. Thus far, the FDA has rejected the idea of establishing an independent "expert advisory panel" for the development of monographs similar to Germany's Commission E monographs, as well as other ideas to create a suitable framework for the marketing of herbal products in the United States.

The monograph system in Germany allowed companies to market their products according to the guidelines of Commission E. With the ability to make appropriate claims, many companies achieved success with their products and were enabled to fund the necessary research to gain greater acceptance within mainstream, conventional medicine. The use of St. John's wort extract in the treatment of depression is a perfect case in point to illustrate how Commission E monographs led to significant documentation of the efficacy of plants with a long history of folk use for depression.

When the Commission E monograph for St. John's wort came out in 1984, it identified the constituent hypericin as the active constituent and permitted the medicinal use of the herb (in average doses of 2 to 4 g of herb, or 0.2 to 1 mg total hypericin) for depression, anxiety, or nervous excitement.

Originally, it was thought that hypericin acted as an inhibitor of the enzyme monoamine oxidase, thereby resulting in the increase of central nervous system monoamines such as serotonin and dopamine. However, it was later shown that St. John's wort does not inhibit monoamine oxidase in vivo.[4] The antidepressant activities appear to be related more to serotonin reuptake inhibition as occurs with the drugs Prozac, Paxil, and Zoloft; modulation of neuroendocrine function; downregulation of β-adrenergic receptors; and upregulation of serotonin receptors in the brain areas

that are implicated in depression.[4,5] In addition, it appears that although hypericin is an important marker, other compounds such as flavonoids are also thought to play a major role in the pharmacology of St. John's wort. The key point here is that the further understanding and documentation of clinical effectiveness of St. John's wort extract was largely the direct result of a commercial incentive created by the existence of Commission E.[6]

Science Has Fueled the "Herbal Renaissance"

Improvements in analytic techniques and modern pharmacology have given researchers the tools and understanding necessary to evaluate herbal medicines properly. Improvements in plant cultivation techniques and the quality of herbal extracts (quality control and standardization) have also led to the development of some effective plant medicines. These advances have created a renaissance in the appreciation and use of herbal medicine. It seems that science and medicine have finally advanced to a level where nature can be appreciated rather than discounted. The scientific investigation of plant medicines is replacing some of the mystery and romance of herbalism with a greater understanding of the ways in which herbs work. Thirty years ago it was impossible to determine exactly how herbs promoted their healing effects because analytic science had not advanced to a sufficient level of sophistication. This point is well illustrated by the fact that the main mechanism of action responsible for aspirin's anti-inflammatory effect was not understood until the early 1970s, and its mechanism of action for pain relief has yet to be fully understood.

Because the mechanism of therapeutic action of a particular herb could not be fully elicited, many effective plant medicines were erroneously labeled as possessing no pharmacologic activity. Now, researchers equipped with greater understanding and more sophisticated technology are rediscovering the wonder of plants as medicinal agents. Much of the increased understanding is, interestingly, a result of synthetic drug research.

For example, one of the modern classes of drugs is calcium channel blockers. These agents block the entry of calcium into smooth muscle cells, thereby inhibiting contraction and promoting muscular relaxation. Calcium channel blocking drugs are currently being used in the treatment of high blood pressure, angina, asthma, and other conditions associated with smooth muscle contraction. They represent a highly evolved stage of modern drug pharmacy. After calcium channel drugs became better understood, it was discovered that many herbs contain components that possess calcium channel blocking activity. In most cases, the historical use of these herbs corresponded to their calcium channel blocking activity.

In addition to possessing currently understood pharmacologic activity, many herbs possess pharmacologic actions that are not consistent with modern pharmacologic understanding. For example, often an herb appears to affect homeostatic control mechanisms to aid normalization of many bodily processes. When there is a hyperstate, the herb has a lowering effect, and when there is a hypostate, it has a heightening effect. This action is totally baffling to orthodox pharmacologists, but not to experienced herbalists who have used terms such as alterative, amphoteric, adaptogen, or tonic to describe this effect.

The Advantages of Herbal Medicines

In general, herbal preparations are thought to have three major advantages: lower cost, fewer side effects, and medicinal effects that tend to normalize physiologic function. When used most effectively, the mechanism of action of an herb often corrects the underlying cause of a disorder. In contrast, a synthetic drug is often designed to alleviate the symptom or effect without addressing the underlying cause. Interestingly, research has often shown for many plants that the whole plant or crude extract is much more effective than isolated constituents. In many instances, multiple components produce multiple pharmacologic actions.

Herbal medicine will certainly play a major role in future medicine. As modern medicine gains more knowledge and understanding about health and disease, it is adopting therapies that are more natural and less toxic. Lifestyle modification, stress reduction, exercise, meditation, dietary changes, and many other traditional naturopathic therapies are becoming much more popular in standard medical circles. This illustrates the paradigm shift that is occurring in medicine.

With the continuing advancement in science and technology, there has been a great improvement in the quality of herbal medicines available and in the understanding of their optimal clinical use. Improvements in cultivation techniques coupled with improvements in quality control and standardization of potency will continue to increase the effectiveness of herbal medicines.

THE STUDY OF HERBAL MEDICINE

The study of herbal medicine spans the breadth of pharmacology, the study of the history, source, physical and chemical properties, mechanisms of action, absorption, distribution, biotransformation, excretion, and therapeutic uses of "drugs." In many respects, the pharmacologic investigation of herbal medicine is just beginning. This textbook is replete with examples of herbs whose historical use is being justified by new investigations into its pharmacology.

The History of Herbal Medicine

The history of the use of plants as medicines is full of interesting stories and fascinating facts. The evolution that occurred in herbal medicine over the centuries is only beginning to be recognized as more natural medicines gain acceptance. Interestingly, this acceptance is largely a result of increased scientific investigation.

A trend exists toward using natural substances, including compounds found in the human body, such as interferon, interleukin, insulin, and human growth hormone, as well as foods, food components, herbs, and herbal compounds. More and more researchers are discovering the tremendous healing properties of these natural compounds and their advantages over synthetic medicines and surgery in the treatment of many health conditions. Through these scientific investigations, a trend toward natural medicine is emerging. To better appreciate this evolutionary trend, this section presents some of the historical aspects of herbal medicine. Much of the following is derived from Barbara Griggs' *Green Pharmacy: A History of Herbal Medicine*.[7]

In the Beginning

Plants have been used as medicines since the dawn of animal life. The initial use of plants as medicines by humans is thought to have been a result of "instinctive" dowsing. Animals in the wild still provide evidence that this phenomena occurs. Animals, with a few notable exceptions, eat plants that heal them and avoid plants that do them harm. Presumably humans also possessed this instinct at one time.

As civilizations developed, medicine men and women were responsible for transmitting the information on herbs to their successors. Before the advent of written language, this information was handed down by verbal and experiential means.

Besides instinctive dowsing, it was commonly believed that plants had been signed by the "creator" with some visible or other clue that would indicate its therapeutic use. This concept is commonly referred to as "the doctrine of signatures." Common examples of this doctrine are the following:

- *Panax ginseng* (ginseng): its roots bear a strong resemblance to a human figure, and its general use is as a tonic.
- *Caulophyllum thalictroides* (blue cohosh): its branches are arranged like limbs in spasm, indicating its usefulness in the treatment of muscular spasm.
- *Sanguinaria canadensis* (bloodroot): its roots and sap are a beautiful blood color, corresponding to its traditional use as a "blood purifier."
- *Lobelia inflata* (lobelia): its flowers are shaped like a stomach, corresponding to its emetic qualities.
- *Hydrastis canadensis* (goldenseal): its yellow-green root signifies its use in jaundice as well as infectious processes.

All of these uses have been confirmed by recent research.

Materia Medicas

With the development of written language, materia medicas (books containing prescribing information on herbs) became the vehicle of passing information about the medicinal use of herbs to future herbalists. Materia medicas were recorded in ancient China, Babylon, Egypt, India, Greece, and other parts of the world. From these materia medicas, it is quite obvious that herbal medicines were highly respected therapies in ancient times.

Galen's Influence

No system, rules, or classification of Western herbal materia medicas existed until the first century AD, when Galen, the Greek physician who founded experimental physiology, established his system of rules and classification. Galen's classification was based on Hippocratic medicine (i.e., balance of the four humors: blood, yellow and black bile, and phlegm) and a profound belief in a beneficent nature. Although his system is considered seriously flawed in the light of modern medical knowledge, Galen is historically considered to be the founder of scientific herbalism.

Galen evaluated and classified each plant according to its relation to Hippocratic medical theory. Although based initially in Hippocratic principles, Galen constructed his own elaborate, and rigid, system of medicine. Galen's work also signified the beginning of a clear division between the professional physician and the traditional healer. As only the well educated could understand Galen's system, and even with the best schooling it remained a mystery to many, all challenges to the professional physician were effectively squelched by dogma.

Galen's system dominated European medical thinking for 1500 years. Perhaps if the Roman Empire had continued to flourish, others would have surfaced to develop alternative theories. Instead, Galenical medicine reigned unchallenged throughout the Middle Ages. By the nineteenth century, the "professional" physician, confident in his supposedly superior knowledge, took Galenical philosophy to an extreme probably never imagined by Galen, by the adoption of bloodletting, purging, and administering exotic medicines. This was in direct contrast to the traditional healer's patient use of traditional herbs and tremendous faith in the healing power of nature.

The Black Plague and Syphilis

Although Galenical medicine dominated the Middle Ages, herbal medicine was still deeply entrenched in European culture. The Black Plague of 1348 may have been the beginning of change in medical thought, since conventional medicine was totally useless. As nearly one third of Europeans died during this plague, the public began to lose faith in Galenical medicine. Nearly 150 years later another blow was dealt to Galenical medicine, when syphilis became the major medical problem. Unlike the Black Death, patients with syphilis tended to survive longer, giving physicians more time to experiment with treatments. At this time, perhaps the greatest hoax in the history of medicine began. Mercury became the standard medical treatment for syphilis despite the fact that even Galen thought mercury too poisonous to use.

Syphilis did, however, open the door for the use of some new herbs from the Americas. A French physician, Nicholas Monardes, published a comprehensive account of sarsaparilla and several other "new" drugs in the treatment of syphilis in 1574. Many Europeans at the time believed that syphilis had come to Europe from the West Indies with Columbus's sailors, and because there was a general belief that whatever disease was native to a country might be cured by the medicinal herbs growing in that region, it was only natural for sarsaparilla to become a popular remedy. Because the standard treatment of syphilis was the use of mercury, which often resulted in greater morbidity than did syphilis, sarsaparilla was a welcome alternative. Despite initial excitement, Monardes' sarsaparilla cure eventually lost favor, probably due to other components in the cure; specifically, patients were confined to a warm room for 30 days and for the following 40 days were required to abstain from both wine and sexual intercourse.

Although the public popularity of sarsaparilla waned, it continued to be used in the treatment of syphilis. During military operations in Portugal in 1812, a British Inspector General of Hospitals noted that the Portuguese soldiers suffering from syphilis who used sarsaparilla recovered much faster and more completely than their British counterparts who were treated with mercury.

Sarsaparilla was also used by the Chinese in the treatment of syphilis. Later clinical observations in China would demonstrate, through the use of blood tests, that sarsaparilla is effective in about 90% of cases of acute syphilis and 50% of cases of chronic syphilis.

Although sarsaparilla was clearly more beneficial than mercury in the treatment of syphilis, mercury was the standard medical treatment of choice for more than four and a half centuries. Some historians have stated that "the use of mercury in the treatment of syphilis may have been the most colossal hoax ever perpetrated" in the history of medicine. Mercury represented a new kind of medicine, one formulated and prepared in a laboratory using the new techniques of chemistry. It helped to prepare the way for future synthetic and mineral drugs at the expense of herbal medicines.

Challenges to Galenical Medicine

The 1500s also saw a strong challenge to Galenical medicine from within the traditional circles. Specifically, Paracelsus, an alchemist who believed strongly in the doctrine of signatures, was responsible for founding modern pharmaceutic medicine. Paracelsus is

probably most remembered for the development of laudanum (tincture of opium). After Paracelsus, Galenical preparations and treatments fell greatly out of favor.

In public circles, herbal medicine was regaining some respect as well. In the early 1600s, Culpepper, an English pharmacist, published his book *The English Physician*. Instead of requiring patients to purchase expensive exotic or imported drugs, Culpepper recommended the herbs his clients and readers had growing in their own backyards. Although Culpepper's herbal philosophy is based on astrologic rationalizations, it reinforced a strong English tradition of domestic herbal medicine. This came at a time when professional physicians were beginning to become contemptuous of herbal medicine.

Meanwhile, in the Americas during the 1600 and 1700s, herbs used traditionally by Native Americans were becoming quite popular, especially in the treatment of malaria and scurvy. Herbal medicine continued to gain even greater respect in the late 1700s, as exemplified by English physician Withering's classic description of digitalis. However, mercury, bleeding, and purging were still the "standard" medical treatments, epitomized by George Washington's death from complications incurred during treatment of a sore throat (i.e., he was bled to death).

The Thomsonian and Eclectic Movements

During the early 1800s, standard medicine may have been ready to reconsider traditional herbal remedies, but then came the Thomsonian movement. Samuel Thomson (1769-1843) patented a system of herbal medicine that, in 1839, claimed more than 3 million faithful followers. Although Thomson brought back to medicine the vitalistic Hippocratic idea of vis medicatrix naturae and gained widespread public support for the use of herbal medicine, the Thomsonian movement was probably detrimental to medical reform.

Thomsonians became locked in prejudice and dogma and insisted that all medical knowledge was complete and could be found in Thomson's works. These and other claims roused scorn, indignation, rage, and resentment in the average North American doctor. Frequently based on purging through the use of herbal emetics, Thomson's treatments were often as harsh as the standard treatments of the times (for further discussion, see Chapter 4).

During the 1800s, the eclectic movement attempted to bridge the gaps between standard medical thought, Thomsonianism, and traditional herbal medicines. Rather than attack the existing medical system, the eclectic movement sought to bring about reform by educating physicians about the use of herbal medicines. Several eclectic medical colleges were established and, for a while, it appeared that the eclectic movement was making headway in its attempt to reform the medical system from within.

The movement eventually failed, however. Several factors were probably responsible for this: a split in the ranks, which diluted the movement; harsh measures like mercury, calomel, and bloodletting were finally discarded by the conventional professional physician, due to a decrease in infectious disease as a result of improved sanitation and hygiene; and, perhaps most important, the failure to establish and sustain quality medical schools.

The Flexner report on medical education in 1910 spelled doom for the eclectics; by 1920, seven of the eight schools that had existed before the report closed, with the last school closing in 1938. Meanwhile, the standard medical schools, aided by the Rockefeller Foundation, flourished, promoting the growth of the modern pharmaceutic industry and the current near-monopoly of the medical profession.

The Growth of the Pharmaceutic Industry

Because a plant cannot be patented, little research was done before the latter part of the twentieth century. Instead, pharmaceutic firms and researchers screened plants for biological activity and then the so-called active constituents were isolated and chemically modified to produce unique, patentable compounds. Much to the dismay of the researchers was the discovery that in many instances the isolated constituents were less biologically active than the crude herb. Because the crude herb provided no economic reward to the American pharmaceutic firm, the crude herb or extract never reached the marketplace. In contrast, European policies on herbal medicines made it economically feasible for companies to research and develop phytopharmaceutics. The policies in the United States contributed to the tremendous growth of the pharmaceutic industry and loss of appreciation and respect for herbal medicine.

The herbal industry further compounded the problem by failing to provide quality herbal products or take advantage of technologic advances that allowed for standardization of chemical constituents. The herb that best exemplifies the failure to adopt standardization techniques is digitalis. One batch of crude digitalis might have a low level of active constituents, making the crude herb ineffective, whereas the next batch might be unusually high in active constituents, resulting in toxicity or even death, when standard amounts are used. The lack of standardization made it easier for U.S. pharmaceutic firms to rationalize their economic need to isolate, purify, and chemically modify the active constituents of digitalis so they could market these compounds as drugs. The problem with using the pure active constituent is that the safe dosage range is smaller: digitalis toxicity and death have increased dramatically as a result of purification. Toxicity was less of a factor when using the crude herb because overconsumption of potentially toxic doses resulted in vomiting or diarrhea, thus avoiding the severe heart disturbance and death that now occur with pure digitalis cardiac glycoside drugs.

Fortunately, several European and Asian pharmaceutic firms began specializing in phytopharmaceutics in the latter half of the twentieth century. These companies have played a prominent role in researching, developing, and promoting herbal medicines.

Research is demonstrating that crude extracts often have greater therapeutic benefit than the isolated "active" constituent. This has been long known in other parts of the world, but in this country, isolated plant drugs are still thought of as having the greatest therapeutic effect. This myth is gradually being eroded as our knowledge of herbal medicines increases.

If current standardization techniques had been available earlier in this century, it is possible that many current prescription drugs would be herbal extracts instead of isolated and modified active constituents or synthetic chemicals.

FINAL COMMENTS

Although the future looks extremely promising for herbal medicine, ultimately its growth and continued success will be determined by the following:

- Continued scientific investigation and clinical research
- Adoption by manufacturers of recognized standards of quality
- Governmental regulations that allow meaningful therapeutic claims

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CHAPTER 34

Botanical Medicine—Understanding Herbal Preparations

Michael T. Murray, ND

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INTRODUCTION

The clinical application of botanical medicine involves the use of various herbal preparations. That being the case, it is imperative that practitioners and physicians using herbal medicines understand the differences among the various forms. Commercial herbal preparations are whole fresh and dried herbs, teas, tinctures, fluid extracts, and tablets or capsules. In addition, juices, purified compounds, and specific fractions of plants (e.g., volatile oil preparations) can also be considered herbal medicines. Each form has advantages and disadvantages and varying ways of expressing its medicinal strength. Any form may be an effective medicine as long as it can deliver an effective dosage of active compounds. The following section reviews the major extraction forms, discusses the benefits of standardized botanical extracts, and emphasizes the importance of delivering a clinically effective level of active compounds regardless of the form of the herbal preparation.

Types of Extracts

An extract is a concentrated form of an herb obtained by mixing the crude herb with an appropriate solvent (such as alcohol or water, or both). A major advance in the herb industry has been the improvement in extraction and concentration processes.

When an herbal tea bag is steeped in hot water, it is actually a type of herbal extract known as an infusion. The water is serving as a solvent in removing some of the medicinal properties from the herb. Teas are often better sources of bioavailable compounds than powdered herbs, but are relatively weak in action compared with tinctures, fluid extracts, and solid extracts. These forms are commonly used by the lay public and herbal practitioners for medicinal effects.

Tinctures are typically made using an alcohol and water mixture as the solvent. The herb is soaked in the solvent for a specified amount of time, depending on the herb. This soaking is usually from several hours to days; however, some herbs may be soaked for much longer periods of time. The solution is then pressed out, yielding the tincture.

Fluid extracts are similar to, but more concentrated than, tinctures. Although they are most often made from hydroalcoholic mixtures, other solvents may be used (e.g., vinegar, glycerin, propylene glycol). Commercial fluid extracts are usually made by distilling off some of the alcohol, typically by using methods that do not require elevated temperatures, such as vacuum distillation and counter-current filtration. However, some small manufacturers produce fluid extracts in a similar manner to tinctures via percolation at room temperature.

A solid extract is produced by further concentration of the extract by the mechanisms described earlier for fluid extracts, as well as by other techniques such as thin-layer evaporation. The solvent is completely removed, leaving a viscous extract (soft solid extract) or a dry solid extract depending on the plant, portion of the plant, solvent, and drying process (if any) used. The dry solid extract, if not already in powdered form, can be ground into coarse granules or a fine powder. A solid extract can also be diluted with alcohol and water to form a fluid extract or tincture.

Strengths of Extracts

The potencies or strengths of herbal extracts are generally expressed in two ways. If they contain known active principles, their strengths are commonly expressed in terms of the content of these active principles. Otherwise, the strength is expressed

in terms of their concentration. For example, tinctures are typically made at a 1:5 to 1:10 concentration. This means one part of the herb (in grams) is soaked in five parts solvent (in milliliters of volume), meaning there is five times the amount of solvent (alcohol/water) in a tincture as there is herbal material. Fluid extracts are typically 1:1.

A 4:1 concentration means that one part of the extract is equivalent to, or derived from, four parts of the crude herb. This is the typical concentration of a solid extract. A quantity of 1 g of a 4:1 extract is concentrated from 4 g of crude herb.

Typically, 1 g of a 4:1 solid extract is equivalent to 4 mL of a fluid extract and 20 to 40 mL of a tincture. Some solid extracts are concentrated as high as 100:1, meaning it would take nearly 100 g of crude herb, or 100 mL of a fluid extract, or 1 L of a tincture, to provide an equal amount of herbal material in 1 g of a 100:1 extract.

Determining Quality

Before the 1980s, the quality of the extract produced was often difficult to determine because many of the active principles of the herbs were unknown. However, advances in extraction processes, coupled with improved analytic methods, reduced this problem of quality control.[1,2] The concentration method of expressing the strength of an extract does not accurately measure potency because there may be great variation among manufacturing techniques and raw materials. By using a high-quality herb (i.e., rich in active compounds), it is possible to have a more potent dried herb, tincture, or fluid extract compared with the solid extract that was made from a lower quality herb. Standardization of herbal extracts for key active constituents has been suggested to be the solution to this problem.[3]

Standardized Extracts: The Best Solution

Standardized extracts (also referred to as guaranteed potency extracts) refer to an extract guaranteed to contain a "standardized" level of active compounds or key chemical marker. Stating the content of active compounds or key chemical marker rather than the concentration ratio allows for more accurate dosages to be made. However, the complex composition of an herbal medicine makes it unwise to ignore the other constituents.

The best scenario for determining the quality of an herb is the level of active components or key biological markers, along with taking into consideration the complete chemical profile. Regardless of the herb's form, it should be analyzed to ensure that it contains these components at an acceptable standardized level. More accurate dosages can then be given. This form of standardization has emerged as the preferred method, but it is not without its shortcomings. Chief among them is that assigning too much importance to individual components rather than the entire chemical profile leads to the assumption that controlling for the level of marker compounds is equivalent to controlling the entire pharmacologic effect of the herbal medicine. However, stating the content of active constituents versus drug concentration ratio does allow for more accurate dosages to be based on active constituents and provides the greatest degree of consistency and assurance of quality, especially if attention is also given to the other constituents.

Although referred to in terms of active constituents, it must be kept in mind that these are still whole extracts and not isolated constituents. For example, a *Uva ursi* extract standardized for its arbutin content, say 10%, still contains all of the synergistic factors that enhance the active ingredient's function.

Techniques Used in the Production of Herbal Products

A tremendous range of sophistication exists in processing herbs, from crude herb to highly concentrated standardized extracts. Nonetheless, there are some common stages. Some of the processes in the production of herbal products and the machines that perform these functions are discussed in the following section.[3]

Collection/Harvesting

When plants are collected from their natural habitat, they are said to be "wild-crafted." When they are grown using commercial farming techniques, they are said to be "cultivated." Collection of plants from cultivated sources ensures that the plant collected is the one that is desired. When an herb is wild-crafted, there is a greater chance of picking the wrong herb and of variation in potency. However, some herbal practitioners believe that wild-crafted herbs are inherently superior because growth in their natural habitat produces an herb with constituents and properties more consistent with traditional use. The use of analytic techniques can be employed to guarantee that the plant collected is the one desired and that its concentrations of medicinal constituents are within an acceptable range.

Herbs from all over the world are marketed in the U.S. marketplace. Herb collectors vary from uneducated natives to self-proclaimed "herbalists" to trained botanists.

The mode of harvesting varies from hand labor to sophisticated equipment. The mode is not as important as the time of year. A plant should be harvested when the part of the plant being used contains the highest possible level of active compounds. Again, this is ensured by using analytic techniques.

Drying

After harvesting, most herbs have a moisture content of 60% to 80% and cannot be stored without drying. Otherwise, important compounds could break down or microorganisms could contaminate the material, or both. As many of the desired compounds are heat labile, the majority of herbs require relatively mild conditions for drying. Commercially, most plants are dried within a temperature range of 100°F to 140°F. During drying, the plant constituents must not be damaged or suffer losses that would prevent them from conforming to accepted standards. With proper drying, the herb's moisture content is reduced to less than 14%.

Garbling

Garbling refers to separation of the portion of the plant to be used from other parts of the plant, dirt, and other extraneous matter. This step is often done during collection. Although there are machines that perform garbling, garbling is usually performed by hand.

Grinding

Grinding or mincing an herb means mechanically breaking down either leaves, roots, seeds, or other parts of a plant into small pieces ranging from larger course fragments to fine powder. Grinding is employed in the production of crude herbal products, as well as in the initial phases of extracts.

Often the material must be pre-chopped or minced before feeding it into a grinder. In the process of grinding, a number of machines can be used, but the most widely used is the hammer mill. These machines are simple in design. The hammers, arranged radially, follow the rotation of the shaft to which they are attached, breaking up the material that is fed into the machine from above. On the walls of the chamber is a grid, which determines the size of

the material that is passed through it. Other types of grinders include knife mills and teeth mills.

Extraction

The process of extraction is used in making tinctures, fluid extracts, and solid extracts. Extraction in the context of this textbook refers to separating, by physical or chemical means, the desired material from a plant with the aid of a solvent. In the U.S. health food industry, most extracts use alcohol and water mixtures as solvents to remove soluble compounds from the herb. The exceptions are liposterolic extracts, which are produced either through the use of lipophilic solvents or with the aid of hypercritical carbon dioxide (carbon dioxide gas compressed to a liquid by high pressures).

Most extracts that are produced by small manufacturers use maceration procedures. The simplest process consists of soaking the herb in the alcohol/water solution for a period of time and then filtering it. For many botanicals, this process yields a lower quantity of active constituents at a higher price because of the cost of the solvent. Because tinctures are 1:5 concentrates, 80% of the bottle is alcohol and water and only 20% is herbal material. In essence, the cost of the alcohol is a major portion of the retail price of tinctures.

Larger manufacturers use more elaborate techniques to ensure that the herb is fully extracted and the solvent is reused. For example, counter-current extraction is often used. In this process, the herb enters the column of a large percolator composed of several columns. The material to be extracted is pumped through the different columns at a specific temperature and flow speed, where it continuously mixes with solvent. The extract-rich solvent then passes into another column, while fresh solvent once again comes into contact with herbal material as it is passed into a new chamber. In this process, complete extraction of health-promoting compounds can be performed. The extract-rich solvent is then concentrated by the following techniques.

Concentration

After extraction of the herb, the resulting solutions can be concentrated into fluid extracts or solid extracts. In large manufacturing operations, techniques and machines such as thin-layer evaporators are used to ensure that the extracted plant components are not damaged. These machines work by evaporating the solvent and leaving the plant compounds. The solvent vapors pass into a condenser whereby they return to a liquid for reuse. The result is separation of the extracted materials from the solvent so that the final product is a pure extract, and the solvent can be used again and again.

Drying of Extracts

Many practitioners prefer the extract dried to a solid form because it is more chemically stable and lower in cost (alcohol is often more expensive than the herb). In addition, tinctures, fluid, and soft extracts can more easily be contaminated by bacteria and other microorganisms. Liquid forms of extracts also promote reactions that eventually break down some active constituents. A number of drying techniques are employed, including freeze-drying and spray drying (atomization). The result is a dried powdered extract that can then be put into capsules or tablets.

Excipients

The same excipients used in the manufacture of drug preparations and vitamin and mineral supplements are often used in the production of tablets and capsules containing herbs or herbal extracts. Many manufacturers provide a list of excipients contained in their products.

ANALYTIC METHODS

Improvements in analytic methods have definitely led to improvements in harvesting schedules, cultivation techniques, storage, stability and concentration of active compounds, and product purity. All of these gains have resulted in tremendous improvements in the quality of currently available herbal preparations.

Methods currently used in evaluating herbs and their extracts include the following:

- Organoleptic
- Microscopic Evaluation
- Physical/Chemical Analysis
- Chromatography
- Biological Analysis

Organoleptic

Organoleptic means the "impression of the organs." Organoleptic analysis involves the application of sight, smell, taste, touch, and occasionally even sound to identify the plant. Typically, the initial sight of the plant or extract is so specific it is easily recognized. If this is not enough, perhaps the plant or extract has a characteristic odor or taste. Organoleptic analysis represents the simplest, yet the most human, form of analysis.

Microscopic Evaluation

Microscopic evaluation is indispensable in the initial identification of herbs, as well as in identifying small fragments of crude or powdered herbs. It is also important in the detection of contaminants and adulterants (e.g., insects, animal feces, mold, fungi). Every plant possesses a characteristic tissue structure, which can be demonstrated through study of tissue arrangement, cell walls, and configuration when properly mounted in stain reagents and media.

Physical/Chemical Analysis

In crude plant evaluation, physical methods are often used to determine the solubility, specific gravity, melting point, water content, degree of fiber elasticity, and other physical characteristics. Various chemical/physical methods are also used to determine the percentage of active principles, alkaloids, flavonoids, enzymes, vitamins, essential oils, fats, carbohydrates, protein, ash, acid-insoluble ash, or crude fiber present.

Chromatography

The most sophisticated analytic processes involve more highly technologic assays to determine quality. Advanced techniques such as thin-layer chromatography, high-pressure liquid chromatography, capillary electrophoresis, and nuclear magnetic resonance are used to precisely separate, identify, and quantify molecules. The readings from these machines provide a chemical "fingerprint" as to the nature of chemicals contained in the plant or extract.[4] These techniques are invaluable in the effort to identify herbs, as well as to standardize extracts.

Biological Analysis

The plant or extract can also be evaluated by various biological methods, mostly in vitro or animal tests, to determine pharmacologic activity, potency, and toxicity.

QUALITY CONTROL IN HERBAL PRODUCTS

Quality control refers to processes involved in maintaining the quality or validity of a product. Regardless of the form of herbal preparation, some degree of quality control should exist. Without quality control, there is no assurance that the herb contained in the bottle is the same as what is stated on the outside. One of the key solutions to the quality control problem that exists in the United States is for manufacturers and suppliers of herbal products to adhere to quality control standards and good manufacturing practices. With improvements in the identification of plants by laboratory analysis, consumers should at least be guaranteed that the right plant is being used. Consumers, health food stores, pharmacists, herbalists, and physicians who use or sell herbal products should ask for information from the suppliers of herbal products on their quality control process. What do they do to guarantee the validity of their product? As more consumers, retailers, and professionals begin demanding quality control from the suppliers, manufacturers will use more quality control processes.

Currently, only a few manufacturers adhere to complete quality control and good manufacturing practices. Companies supplying standardized extracts currently offer the greatest degree of quality control; hence, these products typically offer the highest quality. The production of standardized extracts seeking registration in Europe may serve as a model for quality control processes for all forms of herbal preparations (Box 34-1). In general, it is believed that if the active components of a particular herb are known, whatever the form of the herb product, the herb should be analyzed to ensure that it contains these components at a medicinally appropriate level. More accurate dosages can then be given. Products should also be subjected to bacteriologic counts and be free of contaminants.

The Issue of "Phytoequivalence"

It is often difficult to translate the effectiveness of a particular form of an herbal product to another form. For example, how many milk thistle *(Silybum marianum)* seeds are required to produce the same effects as those demonstrated in clinical studies conducted on milk thistle extracts standardized to contain 70% silymarin? Or does an extract of St. John's wort that is standardized to contain 0.3% hypericin and 3% to 5% hyperforin, but whose remaining chemical profile is substantially different from the clinically proven St. John's wort, produce the same benefits? The real answers to these questions require investigations into phytoequivalence and pharmacokinetics.

The concept of phytoequivalence dictates that if a particular extract demonstrates certain clinical results, a second extract can only be considered as being equivalent if it possesses the same chemical profile as the first extract. This definition of phytoequivalence requires that not just the level of marker compounds or key active constituents, or both, be the same, but that the extracts be identical in the complete spectrum and quantity of all constituents. However, assuring identical chemical equivalence may not assure true therapeutic equivalence if pharmacokinetic factors are not taken into consideration regarding how the herbal medicine is delivered. True phytoequivalence may not be related to having identical extracts but rather to being able to produce the same pharmacokinetic pattern.

BOX 34-1 List of Quality Control Steps Necessary for the Registration of Plant-Based Drug Formulation

1. Selection of suitable plant material
2. Botanical investigation using organoleptic and microscopic techniques
3. Chemical analysis using appropriate laboratory equipment
4. Screening for biological activity
5. Analysis of active fractions of crude extracts
6. Isolation of active principles
7. Determination of chemical structure of active principles
8. Comparison with compounds of similar structure
9. Analytic method developed for formulation
10. Detailed pharmacologic evaluation
11. Studies performed to determine activity and toxicity of formulation
12. Studies on absorption, distribution, and elimination of herbal compounds
13. Clinical trials performed to determine activity in humans

Standardized Extracts Versus Tinctures

Several misconceptions regarding standardized extracts need to be addressed. One is that standardizing an extract results in the loss of important compounds. This is simply not true for the vast majority of standardized extracts. Chemical analysis of standardized extracts and tinctures, whether it be thin-layer chromatography or high-pressure liquid chromatography, has clearly demonstrated that standardized extracts are not only higher in active compounds but also have a broader range of chemical constituents due to more effective extraction.

Another common misconception is that they are more expensive than alcohol-based tinctures and fluid extracts. Calculations based on the cost of delivery of an effective dosage show that the standardized extract is significantly more cost effective. This is because, as noted earlier, there is less of the herb in tinctures and fluid extracts, resulting in consumers paying extra for alcohol, the bottle, and the cost of shipping.

FINAL COMMENTS

The effectiveness of any herb or herbal product from a pharmacologic perspective is dependent on providing an effective dosage of active compounds. Regardless of the form of the herbal preparation, clinical effectiveness requires delivery of an active dosage. At this time, standardization or accurate analysis of the content of active constituents or key biological markers is the only real assurance of the delivery of an effective dosage.

This view should not be controversial. Unfortunately, controversy arises from the fact that, from a pharmacologic perspective, it is unlikely that the dosage schedules historically recommended for most herbal tinctures are sufficient to produce significant pharmacologic effects. Although tinctures of such potentially toxic herbs as Gelsemium, aconite, belladonna, and digitalis often produce a pharmacologic effect when given at low dosages, for most common medicinal herbs, it is difficult to produce an adequate and cost-effective response when the herb is administered in tincture form.

The administration of small dosages of herbs in tincture form is an offshoot of the homeopathic and eclectic use of "mother tinctures" and "specific medicines." The effectiveness of these preparations and their ability to exert pharmacologic effects have not been proved for all but a few botanicals.

The systems of herbal medicine that have been proved to a large extent are based on delivering much higher levels of herbal

compounds than those easily obtained via the use of tinctures. Specifically, we are referring to the use of highly concentrated standardized extracts from Europe and the use of herbal preparations in Traditional Chinese Medicine and Ayurveda. In Traditional Chinese Medicine, the typical daily dose of prescribed crude herbal material is approximately 20 g. This high level of dosage is in stark contrast to a much smaller average amount of the herbal material recommended in the *British Herbal Pharmacopoeia* of 2 to 4 mL of a 1:5 tincture, which provides less than 1 g of herbal material. This difference in dosage may explain the differences in popularity of herbal medicine in China, Japan, India, and Germany compared with its relative obscurity in England, as well as in the United States before the previous decade. The key point is that herbal medicine is not going to be popular if it is not effective. It can be argued that the greater the effectiveness, the greater the popularity.

The tremendous growth noted in the United States since the mid-1980s is, in our opinion, the result of the influx of high-quality standardized extracts into the marketplace. Developments in cultivation, extraction, and concentration processes led to the successful commercial development of these herbal products. Better clinical results were achieved with these herbal medicines because they were able to deliver an effective dose of active constituents.

Although the future looks extremely promising for herbal medicine, ultimately its growth and continued success will be determined by the following:

- Continued scientific investigation and clinical research
- Adoption by manufacturers of recognized standards of quality
- Governmental regulations that allow meaningful therapeutic claims

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CHAPTER 35

Environmental Medicine

Walter J. Crinnion, BS, ND

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ENVIRONMENTAL TOXIC LOAD

The twentieth century, with its promise of "Better Living Through Chemistry," brought us a host of chemical toxicant-related illnesses (referred to here as "environmental illnesses"). We are experiencing the new medical diagnoses of sick (closed) building syndrome[1,2] and multiple chemical sensitivity,[3-5] both of which are known to be related to overexposure to environmental contaminants. The rates of asthma, allergy, autism, attention deficit hyperactivity disorder, and childhood brain tumors, obesity, and diabetes are all skyrocketing. All of these have been linked to the growing environmental burden that is carried by all persons. The primary physiologic action of the major pesticide classes disrupts neurologic function.[6] The primary physiologic action of solvents is neurotoxicity[7] as well. In addition to being neurotoxic, these compounds are profoundly immunotoxic[8-10]and are often toxic to the endocrine system as well.[11-13] The adverse health effects are not limited to those systems as these compounds can also cause a variety of dermatologic, gastrointestinal, genitourinary, respiratory, musculoskeletal, and cardiologic[13-15] problems. A great many of the adverse effects of these environmental toxins appear to be secondary to their mitochondrial damaging capacity.

The Toxic Burden

In an effort to identify what the full burden of environmental chemicals in the U.S. population is, the Centers for Disease Control (CDC) has been performing an ongoing assessment of the levels of environmental chemicals in the U.S. population. This ongoing study utilizes laboratory samples from persons involved in the National Health and Nutrition Examination Survey from the years 1999 to 2000, 2001 to 2002, and 2003 to 2004 (each representing about 2400 persons). In the First National Report on Human Exposure to Environmental Chemicals, 27 different compounds were measured.[16] They tested for the presence of 13 different heavy metals, cotinine, six different organophosphorus pesticide (OP) metabolites, and seven phthalates and their metabolites. Nine of the heavy metals (including lead and mercury), three of the organophosphorus metabolites, and three of the phthalate metabolites appeared fairly ubiquitously. The second report was published 2 years later and expanded its scope of measurement by an additional 89 compounds for a total of 116 chemicals for the years 1999 and 2000.[17] The second report included measurements of dioxins, furans, polycyclic aromatic hydrocarbons (PAH), herbicides, carbamate pesticides, certain organophosphate pesticides (including chlorpyrifos), phytoestrogens, and organochlorine pesticides. Of the 14 PAHs measured (all from combustion) five were found ubiquitously. In the third report (2005), pyrethroid insecticides were added to the list.[18]

In the fourth report, 75 new compounds were measured, bringing the grand total of measured xenobiotics to 212.[19] This report included blood and urinary levels of eight different forms of arsenic along with several aromatic solvents (a total of 30 different compounds) for the first time. This was also the first of the reports that gave values for mercury in adults rather than juveniles and showed that the majority of mercury in the blood is organic rather than elemental. Acrylamides, trihalomethanes (from water disinfection), bisphenol A, phthalates, triclosan, polybrominated diphenyl ethers (flame retardants), benzophenone from sunblock, perfluorocarbons from nonstick coatings, and a host of other xenobiotics were found in the majority

of persons tested in the fourth report. A review of the pertinent findings of the fourth report is available online.[20]

The Environmental Working Group (www.ewg.org) has funded and published two studies that specifically tested adults and newborns in the United States for xenobiotic burden. They originally tested 9 adults for the presence of 210 environmental toxins.[21] These nine adults had an average of 91 of the 210 toxic compounds. Because these compounds can also be passed from mother to child, the EWG did a study to examine how many toxins were passed to babies. The EWG newborn study tested for 423 toxic chemicals in the cord blood of 10 infants born in U.S. hospitals in the year 2004.[22] A total of 287 toxic compounds were found in the samples of the cord blood, with an average of 200 per child. One hundred one of these toxic compounds were found in all of the samples, with a range of total chemicals from a low of 154 compounds per child to a high of 231.

These studies, and hundreds more that have been published in the medical and scientific journals, have shown that we are all burdened with numerous toxic compounds. Examples include the fat-soluble polychlorinated biphenyls (PCBs), chlorinated pesticides (dichlorodiphenyltrichloroethane [DDT], etc.), dioxins and furans, plastics, heavy metals, OPs, aromatic hydrocarbons from tailpipes and cigarettes, flame retardants, napthalenes, and perfluorocarbons. It is no longer a question of if we are all burdened with toxic compounds, but rather if this burden is a causative factor in our health complaints and an obstacle to cure.

Sources of Environmental Toxins

In the previous section, the EWG newborn study[22] highlighted the fact that mothers unwittingly pass fat-soluble toxins to their child during gestation. After birth, the toxic exposures primarily come from the air in our homes and the food that we consume. The U.S. Environmental Protection Agency did a number of total exposure assessment methodology studies in the 1980s, which showed that indoor air contains higher levels of environmental chemicals than outdoor air (even in towns with multiple chemical plants).[23] The majority of compounds found in the indoor air were solvents that came from smoking, dry cleaned clothes, home furnishings, and home cleaning agents. Pesticide use in the home and garden are also contributing factors to the burden of pollutants in indoor air and dust.[24,25]

Food is the other route through which the majority of our xenobiotic load is delivered. The U.S. Food and Drug Administration (FDA) has an ongoing total diet survey that measures a set list of foods for a variety of environmental contaminants, including heavy metals and plasticizer compounds.[26,27] The U.S. Department of Agriculture (USDA) has also been doing an ongoing measurement of pesticide residues on the most commonly consumed fruits and vegetables.[28] The data published in this USDA report form the basis for the "dirty dozen" list of the most toxic fruits and vegetables, which are published on the web by the EWG.[29] This listing gives the consumer information on how to avoid their greatest exposures to OPs.

Plasticizers contaminate food from simple contact with plastic food wrap. The movement of plastics from the wrapping to the food increases with the length of time they are in contact with each other, the fat content of the food, and whether or not heat is involved. Microwaving foods in plastic wrap increases migration, depending upon how closely the food is in contact with the wrapping.[30] Levels of plasticizers are high in store-wrapped meat, poultry, fish, and cheese, with cheese having the highest level of plasticizers. Contrary to a current internet myth, freezing food in plastic containers does not increase plastic levels in the food. Plastic levels in unheated plastic-wrapped foods only increased in those foods after they were heated.[31] Our exposure to some plasticizers, however, comes primarily from fragrances and other personal care products.[32]

Butter has been used as a sampling agent to assess the regional and global distribution of PCBs and other persistent organic pollutants around the globe. When butter was sampled for these compounds from around the world, the highest levels of PCBs were found in butter from Europe and North America.[33] For individuals living in North America, the greatest source of PCB exposure came from butter and fish.[34] However, by far, the single greatest source of PCBs and other "halogenated" persistent toxins in food is farmed Atlantic salmon from grocery stores and restaurants. A study done by the Food Safety Authority of Ireland found that farmed salmon had an average of four times the amount of PCBs and dioxins as wild salmon.[34a] Another study revealed that these farmed salmon had PCB levels over five times higher than those found in a sampling of wild salmon.[35]

These studies were done on relatively small numbers of fish, but had consistent findings. Their findings were confirmed in a subsequent study done on over 700 salmon, totaling approximately two metric tons of farmed and wild salmon from around the globe.[36] Thirteen persistent chlorinated chemical pollutants, including the flame retardant polybrominated diphenyl ether, were found in significantly higher levels in farmed salmon than in wild salmon.

HEALTH EFFECTS OF ENVIRONMENTAL TOXINS

Numerous studies have been published on the adverse health effects of individual xenobiotics. Although the areas of impact cover all the systems in the body, this chapter focuses on the documented immunotoxic, neurotoxic, and endocrinotoxic effects of these chemicals.

Immunotoxicity

Of the three major systems affected by xenobiotic burden (immune, neurologic, and endocrine), the signs and symptoms of immunotoxicity are very often the first to occur in a patient's history. This often begins with the appearance of allergies (including adverse food reactions), after which chemical sensitivity begins. Chronic infections (due to cell-mediated immune dysfunction) and autoimmunity can also be present.[8,9,37] Rarely will a single individual manifest all of these, but clinicians are well advised to be vigilant in looking for such a constellation.

Cell-Mediated Immune Dysfunction

Unfortunately, many of the xenobiotics that have been identified inside all of us are very potent suppressors of cell-mediated immune responses. Dichlorodiphenyldichloroethylene (DDE) (the main metabolite of DDT) causes apoptosis of peripheral blood mononuclear cells, resulting in fewer macrophages roaming the body to phagocytize invading pathogens and trigger an immune response.[38,39] Persons with the highest levels of DDE in their blood also showed reduced mitogen-induced lymphocyte response to concanavalin A.[40] Individuals with this commonly found lipophilic toxin could easily have compromised cellular immune responses. Mercury, another commonly found xenobiotic, also increases apoptosis of both monocytes and lymphocytes and reduces phagocytic ability of the monocytes. It has been demonstrated that workers occupationally exposed to mercury

vapor exhibited diminished capacity to produce both tumor-necrosis factor-α and interleukin-1.[41]

The chemicals produced by combustion, PAHs, have been shown to have similar depressing effects on the immune system, including decreased T-cell dependent antibody response, decreased splenic activity, diminished T-cell effector functions, suppression of T-cell cytotoxic induction, and lower natural killer cell activity.[42] The OPs, which are not as biologically persistent as chlorinated pesticides, are also toxic to the immune system. They have been found to cause decreased percentages of CD4 and CD5 cells, increased number and percentages of CD26 cells, increased incidence of atopy and antibiotic sensitivity, and high rates of autoimmunity. This elevation in autoimmunity is reflected by high levels of antibodies to smooth muscle, parietal cells, brush border, thyroid, myelin, and elevated antinuclear antibody (ANA).[43]

Allergy and Asthma

Increased rates of asthma and allergy have been clearly linked to outdoor air pollution.[44] A day or two after ambient ozone levels spike, persons with asthma have exacerbations of their breathing problems.[45] Hikers who encounter elevated levels of ozone also experience reduced lung function. With each additional 50 ppb of ambient ozone levels, hikers experience a 2.6% decline in forced expiratory volume and a 2.2% decline in forced vital capacity.[46] When persons with asthma and allergies encounter diesel exhaust particles, their allergic problems increase.[47] Even those individuals without a history of allergies can become allergic when exposed to diesel emissions at the same time as an allergen. Herbicide and pesticide exposures,[48] as well as exposure to phthalates (plasticizers) in house dust have also been associated with increased risk for asthma.[49]

Autoimmunity

The development of autoimmunity has been linked with chemical exposure as well. The notion of chemically-induced autoimmune states is, of course, not new because many chemicals are known to induce the onset of systemic lupus erythematosus. Some chemicals, like formaldehyde and other volatile organic compounds, are thought to induce tissue-specific autoimmune reactions by acting as haptens. These low molecular weight molecules bind to various tissues in the body, making a new antigenic combination. The immune system then makes an antibody to this new combination that can attack the parent tissue with or without the chemicals being present. Chemically exposed individuals will often present with elevated antibodies to certain body tissues, including antimyelin, antiparietal, anti-brush border, and antismooth muscle.[50] A study of 298 patients with exposure to industrial chemicals revealed several immunologic abnormalities, including autoantibodies against smooth muscle (odds ratio [OR] 3.99), parietal cells (OR 9.7), and brush border cells in the small intestine (OR 14.45), the thyroid, and myelin sheathing.[51]

Autoimmune hypothyroidism is becoming a much more commonly seen problem in physicians' offices and can be secondary to exposures beyond just OPs.[52] The presence of elevated levels of antinuclear antibodies has also been associated with pesticide exposures other than organophosphates.[53]

A number of investigators have reported that mercurials are also capable of immune activation, leading to autoimmunity while simultaneously reducing the cellular immune response leading to increased infection,[54-57] which is the classic appearance of immunotoxicity.[58] In genetically susceptible mice, the presence of mercury dramatically increased their autoimmune response with increased antifibrillarin antibodies.[59]

BOX 35-1 **Neurotoxicity Presentations**

Organophosphates
- Poor cognition
- Poor attention
- Depression
- Fatigue
- Headache
- Tremors
- Paresthesia
- Slower reaction time

Chronic Low-Level Chlorinated Pesticides
- Poor cognition
- Short-term memory loss
- Balance problems
- Depression
- Fatigue

Solvents
- Poor cognition
- Short-term memory loss
- Depression
- Irritability
- Fatigue
- Headaches

Neurotoxicity

The neurologic system is also a frequent target for xenobiotic compounds. Some patients will present primarily with neurotoxicity symptoms, whereas others may exhibit immunotoxicity signs and symptoms first. The most common neurotoxicity symptoms include reduced cognitive functioning (often referred to by the patient as "brain fog" or "crooked brain"), headache, memory problems, and mood disorders. Tremors, balance problems, and anxiety can also be present (Box 35-1). Although there are indications that xenobiotics may play a role in certain neurologic illnesses, Parkinsonism is the illness that shows the most association.

The nervous system is a unique target for toxic agents in several ways:

1. The adult neuron does not divide and, therefore, replacement of lost neurons is not possible. Nerve cells killed by toxins cannot regenerate.
2. The blood–brain barrier does not block nonpolar substances or items that are actively transported.
3. Because the normal function of the nervous system requires the action of a complex integrated network, damage to even a small portion of the nervous system sometimes can result in marked effects on function.
4. Neurons are dependent on glucose and oxygen, and some cell bodies exist at borderline levels of oxygen. If high energy demands are placed on the system and delivery of oxygen is reduced, then cell death may occur.
5. Because of high lipid content (myelin), there is an accumulation and storage of lipophylic xenobiotics.
6. Neurons have high surface areas and, therefore, increased exposure to toxins.

Unfortunately a great many of the common xenobiotic toxics in our bodies are potent neurotoxins. All of the major classes of pesticides kill pests by virtue of their neurotoxic actions. Chlorinated pesticides and pyrethroids disrupt the ion flow along the axon, whereas organophosphates (which came out of nerve gas research in Germany between the first and second world wars[60]) and carbamates are potent acetylcholinesterase inhibitors (resulting in excessive acetylcholine levels in the synaptic clefts). Solvents, some of which were originally used as anesthetics, dampen the propagation and transmission of electrical impulses along the nerve axons. All of these agents produce various forms of toxic encephalopathy (acute or chronic, selective, or diffuse toxic encephalopathies). Many environmentally ill patients present to their physicians with chief complaints that fit this diagnostic category.

Pesticide Neurotoxicity

Organophosphates. The average clinician will rarely see an individual with acute organophosphate poisoning. Instead, they will see persons presenting with depression, headache, fatigue, cognitive issues, and other problems that could tend to be attributed to other issues of aging. The following OP worker studies highlight these problems.

Greenhouse workers who were exposed to OPs exhibited higher incidences of depression, headache, tremors, and paresthesias.[61] Polish female greenhouse workers exposed to OPs exhibited longer reaction time and reduced motor steadiness than unexposed workers. They also reported increased tension, depression, and fatigue more than controls reported.[62] Dutch farmers and gardeners who used OPs frequently had much higher risk of developing mild cognitive dysfunction than others.[63] Farmers repeatedly exposed to OPs from sheep dip showed much greater vulnerability to psychiatric disorders than controls (quarry workers). They also performed worse than controls on cognitive testing that assessed attention span and how fast they processed information.[64] None of the persons in any of these studies fit the definition of acute OP toxicity and none had dramatic reductions of acetylcholinesterase.

Neurologic problems from OP exposure can also persist. A study of persons previously poisoned by OPs revealed many abnormalities, including memory, abstraction, intellectual functioning, mood, and motor reflexes. They also had greater distress and complaints of disability.[65] A different study of OP workers also revealed diminished memory, learning, and vigilance, but also found diminished plantar and ankle reflexes.[66] The authors noted that the persons with these problems had similar acetylcholine levels as those who did not exhibit these differences. Abnormal deep tendon reflexes were found, along with diminished coordination and muscle strength in Ecuadorian persons exposed to OPs.[67]

Chlorinated Pesticides. Because the use of chlorinated pesticides has been banned in the United States since the 1980s, the symptomatic picture of acute poisoning with them will not be presented. Instead, we find a picture of generalized neurologic dysfunction very similar to what was just presented for OPs.

Early controlled trials of airborne exposure to low levels of DDT revealed that exposed subjects would experience neurologic symptoms, including dimming of vision, a drawing sensation at the base of the nose or behind the eyes, a sense of fullness deep inside the skull, headache, slowness of thought, inability to concentrate, and short-term memory loss.[68] Various muscle symptoms also occurred, including weakness, fatigue, dysphagia, and ataxia. Demonstrable reductions in electromyographic readings were found after nasal exposure to DDT that might account for such symptoms.[69]

A study that compared retired malaria control workers with a reference group of retired persons who did not handle DDT revealed that the exposed group had significantly poorer performance on cognitive, sensory, and motor testing. They did particularly poorly on the cognitive testing (verbal attention, visuomotor speed, and sequencing) and reported significantly more psychiatric symptoms than controls reported.[70]

Neurologic effects of chlordane exposure were studied in a group of persons who lived in an apartment complex where chlordane was used. Seven years after the application occurred, residents and former residents of the complex were assessed. Significant changes were found in the exposed persons, including reduced reaction time, balance dysfunction (shown by increased sway speed), reduction in cognitive function, perceptual motor speed, and immediate and delayed verbal recall. They also had worse scores for mood, including increased tension, depression, anger, and fatigue.[71]

Solvents. Chronic toxic encephalopathy (CTE) from solvent exposure will often gradually improve in 50% of cases with elimination of solvent exposure (Box 35-2). However, 50% will not improve from mere avoidance in the time frame of 6 to 42 months after initial assessment. It is interesting to note that in one study persons on antidepressants were nearly four times more likely to have persistent CTE than those not on the medications.[72] Although the study failed to list which antidepressants were used, many of the antidepressant medications were known to be inhibitors of the CYP system in the liver. Workers with a genetic polymorphism affecting glutathione production had a dramatically increased risk for the development of CTE.[73] It is therefore possible that the reason for such poor recovery from CTE after leaving the main source of solvent exposure is the rate at which the liver can clear these compounds from the circulation. In persons with CTE, brain atrophy was noted in over 50% of them using computed tomographic scan.[74]

Toluene, an aromatic solvent that is commonly present in glues and paints, leads to a very classic presentation of CTE. In one study with toluene-exposed printers, the following symptoms were found: fatigue 80%, impaired memory 60%, impaired concentration 40%, irritability 37%, headaches 30%, mood lability 27%, and depression 20%.

Shipyard painters were found to have significantly higher scores for neurotic behaviors than controls reported.[75] They were also found to have significantly greater problems with short-term memory, concentration, fatigue, dizziness, and insomnia. They also noted more trouble with a feeling of pressure in the chest and perspiration without work. One of the questions most frequently answered affirmatively by the group (in significantly higher levels than controls) was, "Do you often have to go back to check things that you have done, such as turned off the stove, locked the door, etc?"[76]

Female workers exposed to toluene showed significantly more problems with manual dexterity, visual scanning, and verbal memory.[77] The authors of this study noted that the workers who exhibited these changes on neurobehavioral testing showed absolutely no clinical signs of toxicity!

Heavy Metal Neurotoxicity

Lead. Lead is a well-recognized neurotoxin leading to multiple problems in children, including reduced IQ scores,[78] and attention[79] and behavioral problems. Parents of children with lead burdens report that their children have more somatic complaints and delinquent, aggressive, internalizing, and externalizing behavior. Their teachers report that the children have more problems with anxious/depressed behavior, social problems, attention problems, and delinquent, aggressive, internalizing, and

BOX 35-2 Chronic Toxic Encephalopathy (CTE): Designations of Solvent-Induced Neurotoxicity

1. Affective syndrome: neuropsychiatric symptoms, no signs of impairment, reversible.
2. Mild chronic toxic encephalopathy: neuropsychiatric symptoms, proven impairments, uncertain reversibility.
3. Severe chronic toxic encephalopathy: more severe neuropsychiatric symptoms, more pronounced impairments, usually irreversible.

Data from World Health Organization meeting on Organic Solvents, Copenhagen, Denmark, 1985.

externalizing behavior.[80] In Yugoslavian children, specific intelligence testing revealed that lead was most damaging to perceptual–motor aspects of intelligence rather than language-related aspects.[81] Lead exposure in children may also be a factor in pervasive developmental disorders, including autism.[82] A number of studies have also clearly linked lead burden in children and attention deficit hyperactivity disorder.[83-85]

When persons who were lead exposed in childhood were studied 20 years later, neurologic deficits were still found. In this group, significant adverse central and peripheral neurologic effects were present. Peripheral nerve function was altered, as were measures of coordination, reaction time, dexterity, learning, and mood.[86] As persons with lead exposure grew older, their memory capacity continued to decline, at rates faster than aging could account for.[87]

Lead workers have consistently shown neuropsychologic problems at levels significantly higher than those of controls. These problems include visuospatial, visuomotor, comprehension, and symptoms of depression, insomnia, fatigue,[88,89] and postural sway.[90,91] When bone lead burden was measured in older individuals, none of whom had industrial exposures to lead, a clear association was correlated with mental function. As the total bone lead (measured by fluoroscopy of the tibia) increased, cognitive function decreased in a group of older individuals from Baltimore.[92]

Recently, lead burden has been associated with increased risk for the development of Parkinsonism.[93]

Mercury-Induced Neurotoxicity

Mercury in both organic and inorganic forms is neurotoxic. Methylmercury accumulates in the brain and is associated with mitochondria, endoplasmic reticulum, Golgi complex, nuclear envelopes, and lysosomes. In nerve fibers, methylmercury is localized primarily in myelin sheaths, where it leads to demyelination.[94] Mercury is also known to inhibit the uptake of dopamine,[95] serotonin,[96] and norepinephrine[97] at synaptic sites. Mercury apparently has a higher binding affinity for serotonin-binding sites.

The widespread pollution of Minamata Bay, Japan, by methylmercury in the 1950s provided researchers with a clear picture of methylmercury-induced neurotoxicity. Known as Minamata Disease, the neurotoxic signs included ataxia, speech impairment, constriction of visual fields, hypoesthesia, dysarthria, hearing impairment, and sensory disturbances. These neurologic problems persisted and were found in other areas of Japan as the mercury contamination spread through fish consumption.[98] Follow-up studies in the Minamata area almost 40 years after the spill and almost 30 years since a fishing ban was enacted for the area showed the persistence of mercury neurotoxicity. Residents in fishing villages in the area in 1995 reported significantly higher prevalences than "town resident controls" in males for the following complaints: stiffness, dysesthesia, hand tremor, dizziness, loss of pain sensation, cramping, atrophy of the upper arm musculature, arthralgia, insomnia, and lumbago. Female residents of the fishing villages had significantly higher incidents of complaints of leg tremor, tinnitus, loss of touch sensation, leg muscular atrophy, and muscular weakness.[99]

In the Amazon, children exposed to methylmercury from local gold mining have also been studied for the neurotoxic effect of methylmercury. In the villages studied, more than 80% of the children had hair mercury levels above 10 mcg/g (a level above which adverse effects on brain development are likely to occur). Neuropsychological tests of motor function, attention, and visuospatial performance in these children showed decrements associated with hair mercury concentrations.[100] Patients in an internal medicine practice in San Francisco who consumed large fish regularly and had mercury blood levels above 5 mcg/L presented most commonly with fatigue, hair loss, trouble thinking, memory loss, muscle aches, and headaches.[101] One peculiar symptom in this group was a metallic taste in the mouth.

Mental health symptoms are also quite common with mercury toxicity. Evidence linking mercury exposure to psychological disorders has been accumulating for the last 60 years. The recognized psychological symptoms of mercury include irritability, excitability, temper outburst, quarreling, fearfulness, restlessness, depression and, in some cases, insomnia. In a study of individuals with amalgam filling who had them removed, the majority noted psychological improvements. The greatest improvements were found in anger outbursts, depression, irritability, and fatigue.[102] None of these manifestations were too surprising when related to the effect of mercury on reducing the serotonin effect. The association of mercury to depression has stimulated some interesting questions as to whether mercury toxicity was to blame for Sir Isaac Newton's health problems of 1692 to 1693.[103]

Endocrine Toxicity

The most common presentations of toxic damage to the endocrine system are:

1. Sleep disturbances or changes in energy level or mood.
2. Alterations in weight, appetite, and bowel function.
3. Sexual interest and function change; in females, any menstrual change.
4. Changes in temperature perception, sweating, or flushing.
5. Alteration of hair growth and skin texture.

The most common endocrine diagnoses associated with xenobiotic burden include:

1. Infertility
2. Hypothyroidism
3. Adult-onset diabetes and obesity

Infertility

Pesticides, solvents, aromatic hydrocarbons, heavy metals, and chemical dusts have been associated with both male and female infertility.[104]

Herbicides and Organophosphate Pesticides. A study of Ontario farmers showed an association of female pesticide use with fecundity,[105] and the relative risk of being infertile from pesticide exposure was 3.8. Five compounds reduced females' fecundity rates 24% to 49%: Dicamba (0.51), glyphosate (0.61), 2,4-D (0.71), organophosphates (0.75), and thiocarbamates (0.76). Glyphosate is commonly known as "Roundup" and is highly advertised in print and on TV for its safety, yet was clearly associated with infertility in this study. In a study of Spanish greenhouse sprayers exposed to OPs, higher spontaneous abortion rates were found, along with higher rates of depression and headaches.[106] Although these health problems were clearly evident, no significant decrease in erythrocyte acetylcholinesterase was found. This reproduced other studies showing apparent adverse organophosphate health effects without the expected serum finding indicating an acute OP toxicity. A study in California farming counties showed a clear association with pesticide spraying and fetal death due to congenital anomalies.[107] In this study, when an OP or carbamate pesticide was sprayed in one of eight adjacent square miles of women's residences during the third to eighth week of pregnancy, the OR of fetal death was 1.4. When the spraying occurred within one square mile of a residence, the OR increased to 2.2.

Chlorinated Pesticides and Polychlorinated Biphenyls. Chlorinated compounds were studied in a German clinic for association with reproductive difficulties.[108] Hexachlorocyclohexane (HCH) serum levels were significantly associated with miscarriage history and uterine fibroid presence. Higher HCH and PCB levels were also noted more frequently in women with antithyroid and antinuclear antibodies. PCB exposure and elevated antithyroid antibodies have also been reported elsewhere.[109] PCB serum levels were significantly associated with endometriosis and increasing DDT levels with reduced conception. Pentachlorophenol (PCP) levels were also found to be associated with increased miscarriage rates and levels of ANA.

A noncontrolled study in Canada looked for the presence of certain xenobiotics in the serum and follicular fluid from infertile females and seminal plasma from their male partners.[110] These eighteen couples all attended an in vitro fertilization program in hopes of becoming parents. They found DDE, mirex, HCH, trichlorobenzene, and three different PCBs in more than 50% of all follicular fluid samples. Four different PCBs, DDE, and endosulfan were also found in over 50% of all serum samples. DDE was the most frequently found contaminant, had the highest residue, and was negatively associated with fertilization. Of the couples tested, those who failed to achieve pregnancy with in vitro fertilization methods generally had higher toxic levels than successful couples. It is unfortunate that these authors did not get a matched control group of fertile couples to compare the toxic burden.

In the same Canadian study, women with higher DDE levels had greater trouble conceiving. This finding was also noted in the previously mentioned German study and was recently redocumented as a generational effect as well in a group of women from Oakland, California.[111] In this study, serum levels of DDT/DDE were measured from maternal samples at the time of birth. The time it took these daughters to conceive were then followed for 28 to 31 years. Differing generational effects were found for both DDT and DDE. Maternal levels of DDT were associated with reduced fecundity (32% less) in their daughters, whereas DDE levels were associated with increased fecundity (16% greater).

Solvents. Occupational solvent exposure has been associated with infertility (OR 1.76) and tubal-factor infertility (OR 1.95).[21] Reduced fecundity has also been shown in female toluene workers (fecundity rate [FR] 0.47)[112] and in laboratory workers exposed to organic solvents (FR 0.79).[113] Toluene was also associated with a reduction in luteal phase luteinizing hormone in both males and females.[114] In laboratory workers, the greatest reduction of fertility was found in association with acetone exposure (FR 0.72). Chronic benzene exposure was associated with abnormally long menstrual cycles.[115] Wives of men who worked around organic solvents also showed decreased fecundity (FR 0.36).[116] A study in Chinese female chemical plant workers revealed an increased risk (OR 2.9) for spontaneous abortions.[117] Of the myriad of petrochemicals they were exposed to, benzene (OR 2.5), gasoline (OR 1.8), and hydrogen sulfide (OR 2.3) all showed independent significant association with miscarriages. A study in pharmaceutic factory workers also showed increased spontaneous abortion risk from multiple solvent exposures.[118] The risk increased as the number of solvents used increased, with the greatest risk found in those who were exposed to four or more solvents. In pharmacy assistants, an increased risk was found for stillbirths and perinatal death for those with solvent exposure.[119] A National Institute Occupational Safety and Health study of forest service workers exposed to two different paints used to mark trees revealed a 177% and a 181% increased risk of miscarriage over workers who were not exposed to these paints.[120] Those forest workers who were exposed to herbicides had an 82% increase in their risk as well. A single case of first-trimester maternal exposure to the solvent *N*-methyl-2-pyrrolidone, resulting in fetal death in week 31 of gestation, was also reported in the literature.[121]

Hypothyroidism

PCBs have been closely studied for their possible adverse effects on thyroid hormonal status and function. Both PCBs and thyroxine are made of two connected benzene rings with attached halogens; PCBs having chlorine molecules and thyroxine with iodine. Interestingly, the common human contaminant bisphenol-A is also structurally similar, with two bromine molecules on each of the rings. PCBs have demonstrated in vitro activity in binding transthyretin, a transport protein mechanism for thyroxine.[122] This effect of blocking the transport of thyroxine via this molecule (which does not affect thyroxine-binding globulin) is also found with dioxins and furans. They also appear to adversely affect the thyroid hormone metabolizing enzymes (uridine-diphosphate-glucuronyl transferases, iodothyronine deiodinases, and sulfotransferases) found in the liver and brain.[123]

Elevated antithyroid antibodies, both antiperoxidase and antithyroglobulin, were found in workers in a PCB manufacturing plant.[109] This is reflective of the earlier noted study,[108] in which PCBs and HCH were frequently found in infertile German women with antithyroid and antinuclear antibodies. Surprisingly, no difference was found in the levels of T4 and thyroid stimulating hormone (TSH) in these 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) workers than in the control group. One of the limitations in this and other studies looking at the effect of toxins on thyroid function is the use of TSH normal ranges. Only TSH levels that are above the upper limit of normal, showing a gross hypothyroidism, would be considered an abnormal finding. Many alternative clinicians have found that TSH levels between 3 and 5, within laboratory normal ranges, typically indicate subclinical hypothyroidism. The use of the term subclinical here can be misleading, because the individuals in questions typically present with symptoms of hypothyroidism and note dramatic symptomatic improvement with proper thyroid hormone replacement. At least some of the workers in this study with elevated antithyroid antibodies would certainly be expected to eventually have elevated TSH and reduced T3 or T4 levels and would have found symptomatic improvement with replacement of these hormones.

A recent study in Sweden examined women who were exposed to PCBs from consuming at least two meals of fish from the Baltic Sea each month. Their PCB serum levels were measured along with their FT3, TT3, FT4, and TT4 levels, which revealed a significant inverse correlation between PCB levels and TT3 and an insignificant inverse correlation with TT4.[124] German children showed a significant positive correlation between PCB serum levels and elevation of TSH.[126] They also showed a significant inverse correlation between serum PCB levels and FT4, as one would expect to find with increasing TSH levels.

Chlorinated pesticides have also been associated with hypothyroidism. A study of Indian women looked for any association between DDT and dieldrin in women with elevated TSH and depleted T4. DDT was found to be higher in all of the hypothyroid women, though not significantly, but dieldrin was significantly associated with low T4 levels.[125] As mentioned previously, pesticide applicators had elevated TSH levels during the seasons in

which they sprayed most (summer to fall). These applicators used both OPs and fungicides.

Adult-Onset Diabetes

The incidence of adult-onset diabetes has risen in the last decade at rates much higher than previously recorded.[127,128] Although there is clear association with a variety of lifestyle choices to the risk of diabetes, new information is also pointing to a xenobiotic link.[129] Arsenic, naturally present in groundwater throughout the world, has been associated with the development of diabetes.[129,130] Arsenic is present in some of the following foods: shellfish, chicken, and rice, and is high in cigarette smoke. The presence of chlorinated pesticides and dioxins have also been linked to the development of diabetes.[131] In this study, the OR for developing diabetes was 2.5 for those with the lowest levels of PCB 153 in their blood and was 6.8 for those with the highest levels. The chlordanes trans-nonachlor and oxychlordane had ORs of 2.7 (each) for those with the lowest blood levels of these termiticide residues, and ORs 11.8 and 6.5, respectively, for those with the highest blood levels present. When the sum of all six bioaccumulative toxins were combined, the odds of developing diabetes went from a low of 14-fold to a high of 37.7-fold for those with the greatest fat-soluble burden. Studies examining other persistent pollutants have also revealed greater diabetes risk.[132]

DIAGNOSTIC METHODS

A comprehensive history is the cornerstone of detecting xenobiotic-induced health problems. While taking a history, special attention should be paid to both occupational and nonoccupational chemical exposures. Occupational exposures are usually the easiest to document, and should always be followed up with a request for the Material Safety Data Sheet on each chemical from the employer. Nonoccupational exposures are harder to document, but in a family practice are often found to be the main culprit. Specific questions should be asked about the history of residences: where the patient lived, how new the structure is, age of carpeting, time of remodel, type of heating, use of indoor or outdoor pesticides, attached garage, etc. Once the history of residential exposure is garnered and compared with the chronologic symptom history, the answer may become quite clear.

However, because of the ubiquitous nature of the chemicals in question, a history may not always give a clear picture of exposure. Other laboratory tests may be helpful in these cases. A standard complete blood count and general blood chemistry test is usually nonremarkable in cases of chronic low level exposures (although the author often finds leukopenia present in his population of toxic patients). In his patient population, the author rarely finds elevated levels of liver enzymes, even when solvents and pesticides are present in the serum. This has also been reported in the literature with persons occupationally exposed to solvents.[133]

Serum tests for the presence of the most common, and most harmful, chlorinated pesticides, PCBs and solvents can prove invaluable. The publication of the CDC's National Reports has revitalized this area of laboratory medicine, because it provides national reference values for many of these compounds for the clinician. Before the publication of these data, the clinician had to rely on industrial-derived reference values or reference values from the pool of information that the laboratory itself had derived from its clients. For the biologically persistent PCBs and chlorinated pesticides, the CDC gives levels both in parts per billion and as lipid-adjusted (nanogram per gram lipid) values. These fat-soluble toxins are released from adipose tissue along with triglycerides and cholesterol.[134] Previously published research actually found that quantifying the fat-soluble xenobiotics according to the amount of lipids in the blood corresponded excellently with the amount of xenobiotics present in adipose biopsies of the same person.[135] Using the lipid adjusted values as a glimpse of the adipose burden of these compounds also allows the clinician to monitor the effectiveness of their depuration treatments. Follow-up testing would allow one to see if the body burden was decreasing.

Utilizing the CDC information that gives the 50th, 75th, 90th, and 95th percentiles for these toxins can also help the clinician to identify when the chlorinated pesticides or PCBs are from current exposure, rather than just being released from body stores. First, the clinician needs to find out the relation of the patients' parts per billion and nanogram per gram lipid values to the values given by the CDC. For example: the parts per billion value is very close to the 50th percentile, whereas the nanogram per gram lipid value appears to be somewhere between the 50th and the 75th percentiles. In any case where the serum level (parts per billion) appears to be in relation to CDC values that are less than or equal to that of the nanogram per gram lipid, it would indicate that the amount in the blood originated entirely from the adipose stores. If the level in the serum (parts per billion) was higher—around the value given for the 75th percentile—whereas the nanogram per gram lipid was below the CDC 50th percentile, then one could safely interpret that the patient had a current exposure to this toxin.

OP presence can be assessed by testing the urine for metabolites. Similar testing can be done for phthalate (plasticizers) metabolites, bisphenol A, and parabens. The presence of any of these metabolites in the urine would mean that the person was exposed to these compounds in the week before taking the urine sample. These tests can be highly useful in helping persons to attain a diet and lifestyle that are free from several serious toxic families.

Heavy metals can be measured in the hair, blood, urine, and stool. Blood levels are mostly indicative of current exposure levels and are still considered by many physicians to be the only valid method of heavy metal assessment. Unfortunately, the blood reference values for heavy metals are typically based upon industrial medicine standards for toxicity in the workplace. Fortunately, the CDC national reports again provide the national normal ranges for most of the heavy metals in blood and in urine (given as microgram per liter and microgram per gram creatinine). Utilizing both pre- and post-challenge urine tests for heavy metals can reveal if the patient is currently exposed and provide information on the appropriateness of the chosen heavy metal "chelating" agent.[136] When used with an oral chelating agent, doing a pre- and post-challenge test can also reveal information about the absorptive ability of the person (or lack thereof).[137]

TREATMENT METHODS

The basics of effective treatment for chemically-induced illnesses are avoidance of further exposures, supplementation to support chemical elimination and antioxidant protection mechanisms, and reduction of the body burden of xenobiotics.

1. **Avoidance of further chemical exposure.** This should not be overlooked, although it is often the most difficult step for compliance. In cases of multiple chemical sensitivity, this step is indispensable. By simply having a chemically-safe dwelling, many persons with chemical sensitivity begin to improve.[138] Compounds to be avoided include solvents, paints, exhaust fumes, perfumes, hair sprays, new furniture, carpeting, cabinetry, plastics, gas or oil heat, etc. Because the home is the environment

that is most in one's control, the home must be made a "safe oasis." If there are building materials that are off-gassing chemicals and these materials cannot be removed, they should be sealed. There are a number of good books available to help with these issues.*

The single greatest source of solvent exposure in the home comes from smoking inside, which also provides combustion by-products, cancer-causing chemicals, and heavy metals. After smoking, the next greatest sources are carpeting, new cabinetry, and new painting. Cleaning supplies, including tile cleaners, perfumes, air fresheners, and the presence of dry-cleaned clothing complete the rest of the top indoor polluters. Exposure to all of these can be reduced with simple lifestyle choices such as:

- Do not wear shoes indoors.
- Replace your furnace filters every 6 weeks with high quality pleated filters (rated Minimum Efficiency Reporting Value [MERV] 7-9).
- Air out dry cleaned clothing in the garage or car trunk for a week before bringing it into the house.
- Do not smoke indoors.
- Consider replacing your carpet with tile or stone flooring.
- Use nonscented laundry detergent and fabric softener.
- Consider getting an air purifier that has both charcoal and HEPA filters—(for example, IQAir and Blue Air). Make sure you get one with enough cubic feet of air purified each minute to clear the air in your bedroom at least once every 30 minutes.

In addition to avoiding environmental chemicals, any foods that cause adverse reactions should be avoided (see Chapter 15 on Food Allergies). Organic foods should be used wherever possible, as well as purified water. Avoiding the "dirty dozen" fruits and vegetables (www.foodnews.org), along with all farmed salmon, high mercury fish, and nonorganic dairy products will significantly reduce toxin exposures by food.

2. **Dietary support.** The best macro-diet choice (in addition to organic foods) is to consume a diet with high protein, low carbohydrate, and low fat. Such a diet helps Phase 1 biotransformation significantly.

Metabolism of toxic chemicals and drugs has been shown to be impaired by protein deprivation. Increased toxicity of chemical compounds and drugs has been reported with protein deficiency. Protein deficiency decreases the activity of liver mixed function oxidase (MFO) systems, which increases the half-life of numerous toxic chemicals and drugs and potentiates drug action and toxicity. The quantity and quality of protein in the diet alters both Phase 1 and Phase 2 reactions in drug metabolism (a gelatin diet induces very low MFO activity). The toxicity of organochlorinated compounds (OCCs), acetylcholinesterase inhibitors, herbicides, and fungicides have all been shown to be increased several-fold by protein deficiency. Reduced clearance of antipyrine and increased half-life of antipyrine have been found in Asian vegetarians with low dietary protein intake. This was not found in white vegetarians with adequate protein intake.

Although protein deficiency clearly reduces the ability of the body to adequately metabolize chemicals,[139] the opposite also appears to be true. Isocalorically increasing the ratio of dietary protein to carbohydrate ratio in well-nourished volunteers was shown to enhance clearance of antipyrine and theophylline. Although it was not clear if the effect of the protein was due to the amino acid content alone, it was known that methionine and cysteine deficiency led to reduction of intestinal and hepatic MFO enzyme activity. Hepatic MFO activity can also be suppressed by folic and choline deficiency. Low methionine intake also impacts selenium metabolism by making less selenium available for glutathione-peroxidase biosynthesis. High sugar intake is also known to reduce the clearance of certain chemicals from the liver.

Rice bran fiber (RBF), which can be found in a diet high in brown rice or using RBF as a fiber supplement, has been shown to have a high binding ability with PCBs and other toxins, including the combustion by-product benzo(a)pyrene in a laboratory setting.[140] When measured against other fibers, RBF demonstrated the ability to dramatically reduce the reabsorption (termed "hepatic recycling") of PCBs from the intestines in animals.[141] Hepatic recycling occurs after the liver dumps some of these toxins into the intestines with bile, but when these compounds make it to the small intestine, they are reabsorbed into the bloodstream and sent back to the liver. This recycling pattern is the main reason why such a minute amount of these toxins actually make it out of the body. Although RBF helps to break this recycling and gets more toxins to leave, wheat bran showed absolutely no benefit in this regard.[142] A study using either spinach fiber or RBF in animals that had been exposed to PCBs showed that RBF increased fecal PCB excretion 6.6 times and spinach fiber 4.1 times.[143] Another animal study showed that a 10% RBF diet increased the excretion of toxic furans 4.5 times that of placebo.[144] A few studies were done on a fermented RBF product that is available as a food item in Japan. PCB-burdened patients who consumed 7 to 10 grams of it three times daily (after each meal) for a year had twice the amount of dioxin excretion as their counterparts who did not consume that much fiber.[145]

Chlorophyll has long been thought of as a blood purifier and recent studies have documented its effectiveness at helping to clear persistent chemical pollutants from the body. As previously mentioned, both spinach fiber and matcha green tea increased the excretion of chlorinated persistent pollutants. Both of these compounds have chlorophyll, which may be a part of their effectiveness. The seaweed nori, which also contains chlorophyll, was tested in rats to measure its power at helping to clear dioxins. Rats fed a diet of 10% nori had an increase in fecal excretion of two different dioxins at levels 5.5 and 6.0 times more than the control group.[146] Chlorella, long a popular "detoxification" agent was also tried with dioxin-contaminated rats. The group of rats given chlorella had increased dioxin excretion that varied from 30% to over 300% higher than the control group.[147] Postulating that it was the chlorophyll content of the chlorella that was the active ingredient, this group of researchers then set out to measure that hypothesis.

The effectiveness of chlorophyll alone on the excretion of dioxins and furans from rats was quickly established. The higher the content of chlorophyll in the diet, the greater the excretion of these fat-soluble persistent toxins in the feces. The ranges of chlorophyll went from a low of 0.1% to a high of 0.5% in the diet. A diet with 0.1% chlorophyll is roughly equivalent to consuming 10% of your diet as spinach or 20% as seaweed. In the 0.1% group, the fecal excretion of the various toxins ranged from 40% to 80% greater than the control group. At the end of the study, all of the animals that were given chlorophyll had a lower total body burden of these persistent toxins than their counterparts.[148]

Because chlorophyll turned out to be the active agent in binding some of these toxic pollutants and increasing their levels in the stool, the next step was to check how well chlorophyll-containing

*Three good books on this subject are *Less Toxic Living* by Carolyn P. Gorman, available from Environmental Health Center-Dallas (214) 368-4132; *Success in the Clean Bedroom* by Natalie Golos, Pinnacle Publishers, Rochester, NY; and *Your Home, Your Health, Your Well-Being* by David Rousseau, published by Hartley and Marks, Vancouver, BC, Canada.

vegetables did in lowering toxic burden. In this study, rats were fed either a diet with or without 10% vegetables. As with the previous study, the higher the level of chlorophyll in the vegetables, the higher the rate of excretion of the toxins.[149] The vegetables with the smallest increase in fecal dioxin excretion (60% to 300% increase) were Chinese cabbage, broccoli, onion, Welsh onion, cabbage, and celery. The vegetables with the next highest dioxin excretion (330 to 480% increase) were kale, Chinese chive, Shungiku, Chingensai, green lettuce, and sweet peppers. The group that topped the charts with an increased dioxin excretion of 760% to 1160% were: Komatsuna, mitsuba, spinach, and perilla. So, here again we have spinach topping the charts. However, because spinach is 1 of the top 12 most toxic vegetables, one would need to find organic spinach or use some other form of chlorophyll. The same can be said for seaweeds' toxin mobilizing ability, which has been previously discussed. Seaweeds have been found to be highly contaminated with heavy metals and, therefore, are not a good addition to diet or health plans.

3. **Nutritional supplementation.** In cases of toxic overload, supplementation can be tricky, as some persons with severe chemical reactivity can react to many of the nutrients that are normally needed. In his four-volume treatise on *Chemical Sensitivity*, Rea stated that his chemically burdened patients were typically deficient in magnesium, selenium, and Vitamin B_6 (whether or not they were taking oral supplements of these).[5] Supplementation with high levels of antioxidants is typically recommended because all of these xenobiotics have been shown to cause oxidative damage.
4. **Depuration (cleansing).** The removal of impurities from the body is known as depuration. This is the preferred term for cleansing xenobiotics from the body. Besides all of the literature about the use of RBF and chlorophyll for depuration, two additional methods have been discussed in the scientific literature: fasting and sauna.

Most of the published literature is from one of the Health Med clinics associated with the Church of Scientology, which performs the "Hubbard Purification Rundown." This protocol utilizes exercise, high temperature saunas, increasing doses of niacin, and electrolyte replacement. They published studies showing the benefit of this protocol for reducing levels of PCBs, polybrominated biphenyls (PBBs), and hexachlorobenzenes.[150-152] Their studies, along with unpublished information from Environmental Health Center, Dallas (EHC-D), with William Rea, MD, showed that sauna therapy reduces xenobiotic levels in treated individuals.

The only published treatment besides sauna therapy that has shown benefit in treating poisoned individuals is fasting. This has been documented in a single study that examined individuals poisoned by PBB contaminated rice bran cooking oil in Taiwan.[153] Although fasting reduced their symptoms, it increased the level of circulating xenobiotics in their serum. Presumably the elevation of circulating toxins was due to the increased rate of lipolysis in fasting individuals. Thus, the fat soluble PBBs were released from storage into the bloodstream in higher than normal rates. At that point it, would have been up to the liver to clear these out of the serum or they would have been redeposited into the adipose tissue. More research is obviously needed on the role of fasting in the treatment of environmental overload.

A comprehensive naturopathic protocol for treating environmentally poisoned individuals was developed by the author and has been in use for over 10 years. An outcome study on persons who underwent this protocol for a variety of chemically-induced ills revealed it to be surprisingly effective. Of all the various problems treated with the depuration protocol, 83% of the participants rated their results as good or great. The two conditions in which 100% of the participants reported great results were asthma (n = 3), and addiction recovery (n = 1). There were several problem (chief complaint) categories in which 100% of the participants rated their results as moderate/good or great. Those categories were autoimmune, dermatologic, and gastrointestinal, and/or liver. The categories with the next highest ratings of moderate/good and great were fatigue with 92% improvement, allergies with 85%, and chemical sensitivities with 84% improvement.[154]

The Crinnion Depuration Protocol

The Crinnion Depuration Protocol consists of the following components:

1. **Daily exercise.** Exercise usually consists of using an exercycle, rebounder, or brisk walking to begin lipolysis and diaphoresis.
2. **Thermal chambers**. Up to 36 minute "sauna" sessions are done with temperatures at a range of 120°F to 135°F with cool-down periods in between. Glass bottled spring water is given along with electrolyte replacement. Although the Hubbard clinics use higher temperatures, we found that individuals will put out more toxins (as evidenced by stronger chemical odors), and will have less adverse symptoms when lower temperatures are used. The thermal chambers will increase the rate of lipolysis in the adipose tissue throughout the body. When this occurs, the lipophilic xenobiotics will be released into the bloodstream. Those compounds in the subcutaneous fat pads will be mobilized through sweat as well as into the blood.
3. **Constitutional hydrotherapy.** This uses alternating hot and cold towels with sine wave stimulation as done by Drs. O.G. Carrol and Harold Dick. This therapy has been used for decades to stimulate the body's own self-healing activity. We found that it also increased the amount of toxin-laden bile dumped from the liver into the intestines. Also assisting the choleretic and cholagogue action on the liver is an herbal capsule taken daily consisting of *Chelidonium*, *Chionanthus*, *Taraxacum*, *Arctium lappa*, *Silybum mar.*, and *Urtica dioca*.
4. **Colonic irrigation.** Gravity fed machines are used to gently introduce triple-filtered water into the large intestines, providing an avenue for toxic bile to rapidly leave the body. Individuals will routinely have "liver dumps" of bile that range in color from yellow to red, with occasional gray or brown. The color of bile normally ranges from green to yellow to orange to red depending upon the amount of time of exposure to bacterial action in the bowel. However, in this situation we believe that it is dumped from the liver and rapidly passed through the small intestines, similar to what is seen in "gastric dumping" syndrome. We are therefore unable to account for the differences in color of this effluent. In some patients with heavy agricultural exposure, we have seen higher amounts of fluorescent yellow bile. Hence, the color of the bile may be more attributable to the chemical compounds in the bile than the bacterial action upon the bile. We have documented that chlorinated pesticides are present in the effluent, which we refer to as "bile dumps."
5. **Constitutional homeopathy.** This has been used primarily as a stand-alone treatment with the use of any other supplemental and treatments prohibited. However, we have found it to be a valuable component of this protocol and completely compatible with all the other treatment methods involved. It appears most beneficial in those individuals who need a boost for their vital force to get them moving toward healing, and for those who are stuck in emotional issues that they have not been willing to look at.

6. **Body therapies (massage, Shiatsu, craniosacral, visceral, chiropractic).** These are done as needed for the individual to treat specific musculoskeletal problems and to assist in mobilizing toxins that are stored in the tissues.
7. **Counseling.** Mental and emotional toxins are as big a problem as physical and/or chemical toxins. When people are exposed to powerful emotional toxins (abuse, etc.) that they have no outlet for handling, they end up "stuffing" the emotional toxins. When this emotional stuffing occurs, any physical toxins that they are exposed to at that time are also stuffed (stored) rather than being eliminated. Because of this, when they start to mobilize the physical toxins, the old emotional issues will come back into consciousness. When individuals choose to again suppress the emotional issues (rather than facing them), their physical cleansing will also stop. This is evidenced by the observations that they will stop sweating in the thermal chambers, stop heating the cold towels in the hydrotherapy, and stop having good liver releases in the colonic therapy. When the emotional "toxins" are faced and released, then these cleansing parameters are returned to former levels. Assisting all of the individuals going through this depuration protocol with their emotional issues helps them to cleanse physically.

This protocol is run on a daily basis that usually lasts between 4 and 8 weeks (5 sessions weekly). This protocol begins the depuration process, which then must be continued once the individual returns home. Most individuals will need to continue regular cleansing (use of home saunas, hydrotherapy, and colontherapy) for at least 12 months after completing their intensive in-office cleansing. When testing for serum levels of chlorinated pesticides, PCBs, and solvents is repeated along with immune parameters after 12 months, improvements are routinely seen. In addition to symptomatic relief, improvements in the laboratory reports (decrease in serum xenobiotics and reduction in autoantibodies, etc.) is clearly evident.

SUMMARY

Environmental chemicals are ubiquitous in our environment and in our bodies. Damage by these xenobiotics can be found in virtually every cell, tissue, and organ system in the human body. However, the main targets appear to be the immune, neurologic, and hormonal systems. Many of the chronic health problems caused by toxins in these systems often present as classic problems that are considered to be the result of aging. Classic immunotoxicity manifestations include the development of allergies and asthma, chemical reactivity, chronic infections, and autoimmunity. Neurotoxicity typically presents with decreased cognition, headache, fatigue, short-term memory loss, and mood disorders. Endocrine toxicity can result in hypothyroidism, obesity, infertility, and diabetes.

Exposure to many of the ubiquitous xenobiotic toxicants can be easily eliminated by simple lifestyle choices (Box 35-3), although the burden of fat-stored pollutants can be reduced by depuration techniques that often can be handled through dietary changes. The diagnosis of xenobiotic-induced damage can be elucidated by a comprehensive history, along with evidence of serum toxin levels and toxin-induced immune system damage.

BOX 35-3 Treatment

Avoiding toxic exposures is mostly in one's control

Diet and home air:

1. Avoid the 12 most toxic fruits and vegetables (peaches, apples, bell peppers, celery, blueberries, kale, nectarines, strawberries, cherries, pears, imported grapes, spinach, lettuce, potatoes); use organic varieties of these instead.
2. Freely eat all of the 15 least toxic fruits and vegetables (onions, avocado, sweet corn, pineapples, mango, asparagus, sweet peas, kiwi fruit, cabbage, eggplant, cantaloupe, watermelon, grapefruit, sweet potato, honeydew melon).
3. Do not eat any farmed or Atlantic salmon
4. Freely eat Alaskan salmon (available fresh only from June until October); canned and frozen Alaskan Salmon available year round.
 a. Alaskan/Pacific salmon will always be labeled as King (Chinook), Red (Sockeye), or Silver (Coho) Salmon. If that distinction is not given, it is farmed salmon being passed off as Alaskan.
5. Avoid the fish with the highest mercury content (shark, swordfish, king mackerel, tuna, orange roughy, marlin, Chilean bass, lobster, halibut, snapper).
6. Freely eat the fish with the lowest mercury content (clam, Ocean perch, Alaskan salmon, tilapia, flounder, sole, catfish).
7. Avoid all sugar—sugar reduces the ability of the liver to clear toxic compounds out of the bloodstream.
8. Begin to reduce the toxicity of the air inside the home:
 a. Don't wear shoes indoors.
 b. Replace the furnace filters every 6 weeks with high quality pleated filters (rated MERV 7-9).
 c. Air out dry-cleaned clothing in the garage or car trunk for a week before bringing them into the house.
 d. Do not smoke indoors.
 e. Consider replacing the carpet with tile or stone flooring.
 f. Use nonscented laundry detergent and Bounce.
 g. Consider getting an air purifier—the best are IQAir and Blue Air. Make sure you get one with enough cubic feet of air purified each minute to clear the air in your bedroom at least once every 30 minutes.
 h. Follow the directions for step-by-step reduction of indoor air pollution sources in *Clean, Green and Lean* (Wiley, Publisher)

Dietary things to do:

1. Consume broccoli and the other members of the brassica family daily.
2. Consume green tea daily.
3. Increase levels of green foods (green leafy veggies) daily.
4. Consume brown rice daily, or take a rice-fiber supplement.

Basic supplementation:

1. Multivitamin/multimineral—take a quality product daily
2. Vitamin C—begin with 3000 mg/day, for cases of high toxicity, a total of at least 9000 mg/day may be needed (unless this causes diarrhea).
3. *N*-acetyl cysteine—1500 to 1800 mg/day. This nutrient helps to increase the amount of glutathione in the body.
4. Magnesium citrate—1 capsule (140 mg) up to three times daily.
5. A good probiotic—1/day.
6. Rice bran fiber—1 tablespoon in water or juice after each meal.
7. Whey protein powder—2 scoops daily in water or organic juice—high quality whey protein will help boost glutathione level and increase the ability of the liver to clear toxins out of the blood.

Cleansing:

1. Begin doing colonic irrigations. This is the best way to reduce the total toxic burden. It works best to do five colonics in the first 2 weeks, which will typically reduce the circulating toxic load enough for both the patient and the clinician to notice the difference.

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CHAPTER 36

The Exercise Prescription

Jade Teta, ND, CSCS, and Keoni Teta, ND, LAc, CSCS

INTRODUCTION

Movement has been inextricably linked to health, well-being, and survival throughout human existence. It served as the means to procure food and was the key tool in protecting ourselves in times of danger. The ability to fight, flee, migrate, and forage was at the very core of life. Today, movement is no longer required for survival, and food is easily available with little need to expend energy. Yet the ancient connection between movement and metabolism remains permanently imprinted into our physiologic function. Combating the diseases of the modern day is impossible without restoring movement as a permanent way of life.

Because a full discussion of movement and exercise physiology is beyond the scope of this chapter, this chapter will instead focus on movement as medicine for the most common diseases, with special focus on the overlapping mechanisms that account for exercise's beneficial impact. A strong emphasis will be given to newer understandings of exercise physiology and metabolism and how this information relates to the practice of medicine as well as the historical human condition.

The obesity epidemic, by most estimates, is the greatest health challenge of this century. It already represents one of the largest modifiable risk factors for increased morbidity and mortality, with close to 66% of the U.S. population overweight or obese.[1,2] Because of the huge challenges obesity represents, and the powerful role exercise can play, this chapter will be framed in the context of weight management. Other related health issues, such as exercise approaches for inflammation, cardiovascular disease, cancer, mood, and the brain, will also be discussed.

EXERCISE IN HISTORICAL CONTEXT

Human movement patterns have always necessitated multiple parameters of fitness. Understanding these historical movement patterns provides guiding context in which to view exercise. Although research in exercise is essential to understand, without a guiding context it can be difficult to provide appropriate exercise prescription. Viewing movement through the lens of human evolution, we believe, provides the frame of reference necessary to understand how to use movement as medicine.

Longer duration lower intensity exercise made up the majority of early human activity.[3-5] Walking was the chief means of movement for millions of years. Early humans walked most of the day and did this everyday. Their survival was dependent on it. Research suggests that early Homo sapiens foraging on the plains of Africa covered a range of over 10 miles daily hauling weapons, game, and tools.[3-6] Analysis of modern day hunter–gatherers confirms this degree of walking activity.

In addition to this lower intensity activity, survival also depended on higher intensity shorter duration activity. Sprinting away from danger or after wild game as well as lifting and hauling were essential. Both women and men engaged in these more anaerobic bouts of exercise. Although in most cultures women did not participate in the hunt, they did lift and haul wood, help construct shelters, and carry babies. The average baby was carried almost 1000 miles in the first 2 years of life in more traditional cultures.[4] The more intense activities of hunting, hauling, and foraging were done in what is termed the "paleolithic rhythm," where more intense activities were spaced out over 2 to 4 nonconsecutive days per week.[4,6]

Moderate intensity exercise, much like aerobic exercise today, was also a part of life. However, this exercise did not take the shape of going for a jog or leisure run.

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Aerobic exercise was mostly in the form of sporadic running after food and dancing, which occupied an important place in the culture of ancient peoples and still does in modern day hunter–gatherer societies. These dances can last from one to a few hours and take place several times during the week.[4-6]

The movement patterns of our historical ancestors were a necessary part of life and were fully integrated into the lifestyle. This movement was what could be best described as "cross-training," with elements of lifting, jumping, running, walking, throwing, climbing, hauling, hiking, or whatever movement pattern was required to procure food, stay protected from the elements, and defend territory. Our species is adapted from an environment where food was not guaranteed and a nomadic hunter–gatherer way of living dominated. This understanding is essential for the appropriate prescription of exercise. Hunter–gatherer societies in the past and present have been analyzed through a number of different scientific tools, which show that they do not experience the same degenerative and chronic diseases of modern westernized peoples.[3,7,8]

After taking into account body weight, the modern day human energy expenditure is estimated to be only 38% that of our hunter–gatherer ancestors.[4] It has been shown that for modern day humans to approximate the level of activity of hunter–gatherers, they would have to walk 12 miles/day in addition to other activity.[4] Policy leaders on appropriate levels of human activity, such as the American College of Sports Medicine, recommend movement patterns estimated to be 44% less than that of our prehistoric ancestors and modern day hunter–gatherers.[4]

Several studies have shown that total energy consumption from exercise may be the primary health promoting property of movement.[4,9,10] Given the drastically different environment in which humans now reside, we are left with a serious dilemma. How do we get people to do an activity not required for their survival, that takes time, and is not an enjoyable activity for many? It is useful to remember that the number one reason given for not participating in exercise is time.[11,12] These facts, as well as the historical frame of reference provided by evolutionary movement patterns, create a problem. Exercise prescriptions must deliver acceptable caloric expenditure, should mimic the cross-training attributes of our ancestors, but also be time conscious and "doable" for the average population.

A NEW PERSPECTIVE ON MOVEMENT

It is easy to look at the data presented and quickly move to a "more is better" approach to exercise. However, movement quality is an important consideration before simply instructing more exercise. Quality in this segment is discussed in terms of more functional and efficient movement. In other words, movement that provides the perfect balance of range of motion and stability leads to more efficient animation of the body. The body is a chain of parts that are completely integrated. Individual exercises, although viewed in isolation by us, are actually complex and highly entrained patterns of neurologic connections translated into muscular action. These "movement patterns" are the building blocks on which all exercise is constructed. Without a strong foundation, the benefits of exercise can sometimes become a liability, increasing the risk of injury, pain, and dysfunction.

It is both irresponsible and shortsighted to focus exercise prescriptions solely on delivering greater metabolic stimulus if there is not a strong and appropriate base of mobility and stability through basic movement patterns. In other words, doing more activity may not be beneficial if it simply reinforces poor movement mechanics. We must keep in mind that our ancestors were able to move more, because they also moved better.

Human development and survival from infancy to adulthood required mastery of movement. The neurologic and muscular systems are built as a unit and cannot be separated. Movement should not be thought of in terms of isolated anatomy but rather as an integrated system that moves in patterns. A squat, for example, is not simply a matter of contracting certain muscles that move joints. It is instead a coded and rehearsed pattern of neurologic firing translated into physical movement.

Gray Cook, physical therapist and the foremost expert on functional movement, is the author of two of the most foundational pieces of work in movement science. In his books, *Athletic Body in Balance: Optimal Movement Skills* and *Conditioning for Performance* and *Movement: Functional Movement Systems*, Cook described movement science as analogous to the relationship between computer software and hardware.[13,14] The muscles and joints act as the hardware, but the neuromuscular firing pattern is the software. Software obviously is what controls and informs the computer, and so it is with the nervous system controlling the muscle. To address movement, he rightly pointed out that we need to work movement patterns and not simply isolate parts.

The brain does not view exercise as individual muscles working. Instead, the brain has a code or a pattern for each movement. This pattern consists of thousands of different neurons firing in very specific ways to elicit a coordinated action, resulting in a movement. Each movement is to the brain like a computer software program; movement science calls this a motor program. It is these motor programs that need to be attended to in terms of movement quality.

Although exercise science has developed core principles and protocols to be followed, movement has not developed such protocols. Up until very recently, there has been no standardized understanding of what constitutes normal functional movement. This gap has now been filled by the work of Gray Cook and his colleagues. They have put together a system of screening and analyzing movement so it can be objectively measured, tracked, and corrected. If we are to use movement as medicine and stay true to the natural medicine axiom of "first, do no harm," we must establish a standard of practice in movement medicine.

STANDARDS OF MOVEMENT

The Functional Movement Screen and Selective Functional Movement Assessment

The Functional Movement Screen, or FMS, as it is popularly known, is "a ranking and grading system that documents movement patterns that are key to normal function." By acting as a screen for movement, the FMS pinpoints movement dysfunctions that may predispose to injury and/or inefficiency.

The FMS has a scoring system that allows for a hierarchical ranking of the most limiting patterns or asymmetries unique to an individual. This in turn provides direction to clinicians as to what corrective strategies should be implemented and when. The FMS score can then be used to systematically address underlying movement dysfunctions and restore a base of movement from which conditioning can be built.

The FMS is complimented by the Selective Functional Movement Assessment (SFMA). The SFMA is the diagnostic system of functional movement. For the clinician concerned with movement, the two work hand-in-hand. The FMS is both the precursor to and the follow-up from the SFMA. The FMS looks at seven key movement patterns, including a squat, lunge, and hurdle step. Its purpose is to ascertain a baseline of mobility and stability as well

as to determine if movement is pain free. The SFMA is the clinician's tool for diagnostic determination of when pain is present. Together, the screen and the assessment provide a movement system that allows tailored movement plans that can find, address, and track changes in movement from pain and dysfunction to recovery and optimal movement.

The FMS is a screening tool for the clinician; it is not diagnostic, but rather prognostic. The SFMA is diagnostic and helps the clinician pinpoint the issue and further prioritize treatment. Once a patient has been discharged from treatment and no longer has pain with movement, movement quality must still be measured. This is where again the FMS is used.

Several recent studies showed the FMS to be a reliable and repeatable screening tool for movement quality, but also proved its ability to predict injury in several high population groups. Minick et al[15] showed that the FMS demonstrated substantial inter-rater reliability by both novice and expert users. This demonstrates an important quality of any clinical tool, that of repeatability and objective evaluation in the hands of different users.

When the FMS was put to the test in very active population groups its usefulness became clear. American football players were analyzed in a 2009 study in the *Scandinavian Journal of Medicine, Science and Sports*; they demonstrated reliable improvements in FMS scores from a standardized intervention based on the screening examination and established a FMS score cutoff predictive of increased injuries.[16]

Firefighters benefitted from a FMS guided functional exercise program.[16a] The FMS guided intervention resulted in a 62% reduction in time off of work due to injuries and reduced injuries by 42% during a 12-month period.

Movement pattern performance is an important precursor to increased exercise participation and is an important addition to the exercise world. The FMS and SFMA are new and essential tools for the use of exercise as medicine. They provide a much needed "standard operating procedure" for movement quality. Gray Cook and colleagues have a clinical website (www.functionalmovement.com) that teaches and instructs on movement systems and provides valuable clinical tools for clinicians.

NEW INSIGHTS ON EXERCISE FOR WEIGHT LOSS

Once movement quality is attended to, exercise quality needs to be addressed. The current approaches of exercise for weight loss and health are still centered in the low intensity "aerobic zone," calorie-burning paradigms. Recent understanding is redefining this narrow approach to health and fitness. A caloric focused model of metabolism may not be the most useful way to view exercise. If we look at track athletes, both elite marathoners and sprinters have very low percentages of body fat. Sprinters, however, have less body fat and higher amounts of muscle mass, yet they exercise in a very different way.[17-19] Sprinters engage in short bursts of anaerobic effort lasting seconds, whereas marathoners run in an "aerobic zone" for hours and utilize large amounts of caloric energy. If the aerobic model of exercise truly is the best way to gain fitness and fat loss, why is there a discrepancy between these two groups of athletes? In analyzing recent data, we can see that anaerobic contributions to energy expenditure now need to be considered in exercise prescription.

There is a common misunderstanding of fat burning percentages in exercise. Many still perceive exercise done in the aerobic zone, usually defined as between 65% and 80% of maximum heart rate (MHR), burns the most fat per unit time. This is not the case. Lower exercise intensities burn a higher proportion of fat compared with sugar, relatively speaking. However, exercise beyond the aerobic training zone burns more total energy and fat because it is a higher intensity.

Suppose two people exercise for 30 minutes. Person A jogs at an intensity of 60% MHR, whereas person B jogs at an intensity of 60% MHR and then, every few minutes, sprints for a short period, reaching over 90% MHR before returning to a lower intensity. Assume person A burned 200 calories, 60% coming from fat and 40% from sugar. Person A therefore used 120 total units of fat and 80 units of sugar (200 calories × 0.60 = 120 fat calories). Person B exercised at a higher intensity, burning a lower percentage of fat. Assume Person B used 50% fat and 50% sugar, but burned 100 more calories due to the higher workload. Person B therefore burned 150 units of fat and 150 units of sugar (300 × 0.50 = 150 fat calories). When the energy burned is totaled, person B burns more energy (300 calories) and more total fat (150 units compared with 120 units) than person A, despite using a lower percentage of the energy as fat. This example shows that higher intensity exercise of the same duration surpasses lower intensity exercise in fat calorie use. There are further metabolic consequences created through higher intensity exercise that make its application in exercise prescription for fitness and fat loss more intriguing.

Does Aerobic Exercise Work for Weight Loss?

A 2009 review by Melanson et al[20] looked at the impact exercise had on metabolic stimulation. The study primarily looked at moderate intensity aerobic exercises like jogging, biking, or swimming while including a small sample of anaerobic exercise studies. It showed that aerobic exercise of moderate intensity did not provide a metabolic advantage aside from the calories burned during activity. A previous meta-analysis done over a 25-year period came to a similar conclusion.[21] This study analyzed the data from over 400 studies comparing diet alone, aerobic exercise alone, or diet plus aerobic exercise on weight loss. The results showed that aerobic exercise did not provide a significant advantage to weight loss over diet by itself. Although aerobic exercise has been shown to be a reliable tool in the maintenance of weight loss,[22,23] these studies suggest it may not be enough to elicit significant fat loss effects.[21]

At the same time, new lines of research show potentially promising effects from more anaerobic modalities. High-intensity interval training (HIIT) is a method of alternating highly anaerobic activity with more relaxed aerobic movement. This method allows the benefits of intense exertion under more tolerable conditions. Rest is required to sustain intense activity for any length of time. Weight training is another anaerobic-centered activity. These more anaerobic-dominated exercise approaches have unique benefits that may compliment the calorie burning effects of aerobic exercise.

Aerobic Versus Anaerobic Exercise

In very simple terms, aerobic metabolism takes place in the mitochondria and requires the use of oxygen. Anaerobic metabolism proceeds through a different pathway and requires neither the involvement of mitochondria or oxygen. It is well known that as exercise intensity increases, anaerobic metabolism dominates; unfortunately, the exact anaerobic contribution to energy production is exceedingly difficult to measure. The standard way to approximate calorie expenditure and substrate utilization during exercise is through the measure of respiratory gases. The ratio of carbon dioxide expelled to oxygen consumed can give a predictable evaluation of not only energy use but also fuel utilization—glucose versus fat.

However, this method is only valid at lower exercise intensities. At higher intensities, the relationship is less clear. To help address this error, researchers also measure excess postexercise oxygen consumption (EPOC). This is a measure of the recovery energy expenditure after exercise and it has been thought to consist of anaerobic contributions to exercise as well. There is some argument as to how meaningful this EPOC effect can be. Many researchers claim the impact does not last long, only several hours, and amounts to at best 15% of total calories burned.[24-26] However, these approximations come largely from studies with lower exercise intensities involving standard aerobic exercise protocols.

Studies utilizing highly anaerobic protocols including cardiovascular interval protocols and weight training showed a much different picture. In 2001, Schuenke et al[27] showed that circuit resistance training, utilizing heavy weights and short rest periods lasting only 31 minutes, were able to generate an EPOC that persisted for 48 hours. The results showed that metabolism 24 and 48 hours after the exercise session was increased by 21% and 19%, respectively. The researchers pointed out that for a typical 180-lb individual "this equates to 773 calories expended post exercise" while resting and as a result of the workout. This is far from insignificant and greatly exceeds the 15% many researchers quote for EPOC. Similar findings were shown in women using a similar resistance training protocol. In women, the elevation in metabolic rate lasted 16 hours.[28] The same findings were seen with HIIT protocols with significant EPOC values lasting up to 24 hours.[29,30]

Exercise Burn and "After-Burn"

Dr. Christopher Scott of the University of Southern Maine published extensively in this area and is the author of one of the authoritative textbooks in this field, *A Primer for Exercise and Nutritional Sciences: Thermodynamics, Bioenergetics, and Metabolism*.[31] In his works, Dr. Scott pointed out that EPOC did not fully explain anaerobic energy use and that the anaerobic contributions to exercise might be even greater than originally thought, especially where lactic acid production is concerned. Dr. Scott emphasized that to fully account for calories burned during exercise, three components must be measured: (1) calories burned aerobically during exercise, (2) calories burned aerobically after exercise (EPOC), and (3) anaerobic calories burned from exercise.[32-36] EPOC and the anaerobic lactic acid measurements for exercise should be considered separately according to Dr. Scott.

A 2005 study by Dr. Scott demonstrated the potential ramifications of anaerobic exercise. This study compared a 3.5-minute aerobic exercise challenge with 3 work-equivalent 15-second sprints.[37] Calorie use during the exercise bout was calculated to be 29 kcal for the aerobic exercise and approximately 4 kcal for the sprinting. However, when the EPOC contribution was added to the two exercise bouts, energy use rose to 36 kcal for the aerobic bout and 39 kcal for the sprint exercise. Finally, when the purely anaerobic contribution was added to the calorie totals, the numbers for the anaerobic sprint exercise rose significantly. The final tally was 39 kcal for the aerobic exercise compared with 65 kcal for the sprint exercise. By adding both EPOC and the anaerobic contribution to the original calorie total, the sprint exercise was shown to far surpass the aerobic exercise in calories burned. This is interesting when one considers the aerobic exercise session took over four times longer to complete (210 vs 45 seconds). Without including both the EPOC and anaerobic energy use, a full 94% of the calories used during the sprinting would go uncounted.

In studies published in 2006 and 2009 in the *Journal of Strength and Conditioning Research*, the same researchers quantified anaerobic energy use during weight lifting.[32,36] Using the method of measuring and quantifying all three components of calorie burn (aerobic metabolism during exercise, EPOC, and anaerobic contributions), these studies showed that weight training exercise burned 70% more calories than originally thought.

Hormonal Versus Caloric Exercise

To understand the full ramifications of this new exercise science, the discussion must move to hormonal metabolism. Hormones as we describe them in this chapter refer to all signaling molecules in the body, including steroid hormones, muscle-derived cytokines (myokines), and other signaling molecules. Hormonal messengers directly influence the fat burning stimulus during exercise and may be responsible for part of the EPOC after-burn as well.

Brief bouts of anaerobic exercise appear to adjust hormones for greater caloric burn during and after exercise.[38] This increased energy use is partly explained by EPOC. This is a measure of how much oxygen the body consumes in the hours and days after a workout. An example of EPOC in the acute sense is climbing a long flight of stairs. While walking up the stairs breathing is labored, but respiration becomes most difficult after reaching the top. The body does this to recover the "debt" of oxygen used during activity. The EPOC created by climbing a flight of steps is an example of the much larger metabolic effect created from intense movement.

Exercise of sufficient intensity elevates stress hormones like adrenaline, noradrenaline, and cortisol. Together these hormones ensure the switch to glucose metabolism, which historically supplied the energy to fight or flee. As exercise intensity is elevated further, anaerobic contributions to metabolism increase. This produces lactate (lactic acid), which, contrary to common belief, is not a waste product, but a physiologic buffer and signaling molecule.[39-41] As lactate rises, it is correlated with, and some studies suggest actually induces, the anabolic steroids testosterone and human growth hormone (HGH).[42-44] This "hormonal soup," catecholamines along with cortisol, HGH, and testosterone, acts synergistically to increase postexercise fat loss and lean muscle tissue production, thus creating a more fit and functional physiology.

Aerobic and anaerobic exercise have different hormonal effects. Hormones do not work in isolation, and like people they behave differently depending on the social environment. Interestingly, the hormone cortisol, often seen as a fat storing hormone due to its insulin desensitizing effect, behaves differently when combined with growth hormone and testosterone.[41,45,46] When cortisol is "socializing" with testosterone and growth hormone, its catabolic action on muscle is blocked, fat storing at the belly is attenuated, and the three may synergistically enhance fat burning.[46-49] Attempting to blunt the cortisol response to high intensity exercise may be counterproductive for fat burning and not necessary in the context of growth hormones.[50-54]

Long duration lower intensity cardiovascular exercise behaves differently in regards to cortisol. There are also key changes in hunger hormones that are different between lower intensity aerobic exercises compared with higher intensity anaerobic workouts. With aerobic zone exercise, there is a danger of cortisol increasing unopposed by the growth promoting hormones.[45] This, along with a lowering of leptin and an increase in ghrelin, can lead to compensatory eating with specific cravings for fatty, sugary, and salty foods.[55-61] Higher intensity shorter duration activity has the opposite impact on ghrelin, with a more balanced ratio of catabolic versus anabolic hormones.[58,59] This may explain

why standard aerobic prescriptions have not been shown to be as effective for optimal body composition.[20,21,62-65]

Aerobic Zone Versus Interval Training

A 2001 study compared standard aerobic zone training and anaerobic interval exercise in women.[66] The anaerobic interval group exercised for 2 minutes at a highly intense 97% of MHR. They then rested by doing 3 minutes of low intensity activity. The more aerobic group performed moderately intense activity at close to 70% of MHR. The researchers made sure that each group burned 300 calories. Despite exercising longer and burning the same amount of calories, the aerobic group lost less body fat at the end of the study compared with the interval group. In addition, fitness in the interval group was substantially greater than in the aerobic group.

A similar study published in the same journal in 1996 showed that an anaerobic trained interval group burned significantly more fat than their aerobically trained counterparts.[67] Not only did the interval group burn greater amounts of fat during exercise, but they also exhibited increased fat burning effects that persisted for 24 hours after the exercise had stopped. The interval group was able to accomplish this with an exercise session that was a full 15 minutes shorter than the aerobic group.

A 1994 study[68] tracked two groups of people, one group doing aerobic training for a period of 20 weeks, whereas a second group was followed for 15 weeks and engaged in HIIT. The researchers wanted to see how each program would impact body composition. The aerobic group burned 48% more calories than the interval group (120.4 vs 57.9 MJ) during exercise. The interval group, however, enjoyed a ninefold greater loss in subcutaneous fat. At the conclusion of the study, muscle biopsy analysis showed resting levels of 3-hydroxyacyl coenzyme A dehydrogenase, a marker of fatty acid oxidation, were significantly elevated in the interval group, but not in the aerobic group.

A 2008 study looked at intense intermittent exercise compared with steady-state aerobics.[69] Forty-five healthy women between the ages of 18 and 30 were recruited for the study, divided into 3 groups, and studied for 15 weeks. One group did HIIT, where they sprinted on a bike for 8 seconds followed by a 12-second rest. This was repeated for 20 minutes. Another group did moderately intense peddling that was sustained for 40 minutes. The final group did no exercise. At the end of the 15 weeks, the high intensity interval group lost 2.5 lbs of fat, whereas the aerobic group actually gained 0.6 lbs of fat. A measure of the fat-related hormones leptin and insulin were also positively affected in the HIIT group compared with the steady-state group. This was accomplished with a workout that was half as long (20 vs 40 minutes) as the steady-state's group.

Resistance Training Studies

Research hints that resistance training may also provide unique benefits for fat loss and fitness. Recent analyses showed that the clear distinctions once set for aerobic exercise and resistance training are no longer delineated so clearly. Circuit training routines have been shown to provide an aerobic stimulus great enough for cardiovascular benefit while providing strength-training benefits.[70,71] Resistance training may also have great applicability for not just fitness and fat loss but also diseases of insulin resistance.[72,73] Weight training, compared with aerobic exercise, greatly attenuates the natural loss of muscle mass that occurs with aging and dieting,[74] and improves body composition and self-esteem better than aerobic exercise modalities.[75-77]

Resistance training may also have a much greater impact on EPOC. Two studies already discussed[28] showed significant metabolic elevations in men lasting up to 48 hours and in women lasting up to 16 hours. These workouts used exercise regimens that were more intense than most studied resistance-training programs, but they were also shorter. Combining the benefits of resistance training with cardiovascular exercise seems to have the most benefit.[78] This type of training is called concurrent exercise and involves resistance-training workouts that are followed immediately by aerobic exercise or vice versa. Studies showed that these approaches afforded the benefits of both aerobic and resistance-training workouts.[79-82] This "cross-training" approach falls in line with historic movement patterns and saves time.

Concurrent exercise approaches follow two patterns, serial concurrent exercise (SCE) and integrated concurrent exercise (ICE). In SCE, the two modalities (aerobic and resistance training) are done one right after the other, whereas in the integrated format the two modalities are alternated; a weight training movement is done followed by a cardiovascular "burst" of exercise. Based on studies, it appears the benefits of this type of approach can be amplified further using the ICE approach. In a series of three studies in 2008, all published in the *Journal of Strength and Conditioning Research*, Davis et al[83-85] showed the potential benefit of ICE protocols. An ICE workout consisted of brief 60 second bursts of "cardioacceleration" placed between traditional weight training sets. This protocol was able to dramatically amplify multiple fitness parameters over and above the same workout volume done in an SCE format.[84] Fat loss in the ICE group was close to 10 times greater than in the SCE group over an 11-week period. This constituted a time commitment of just over 4 h/week. Because the work was equivalent in both groups, it was the combination of exercises that made the difference. This same workout protocol showed the ability to improve cardiorespiratory and cardiovascular parameters even in well-trained athletes.[83] It also decreased the delayed-onset muscle soreness, the feeling of soreness lasting 24 to 48 hours after the workout, in the ICE group.[85] Similar protocols showed the same promising results in body composition change and cardiovascular benefits.[86,87]

Safety of Interval Exercise

HIIT, as well as intense weight training, can be used effectively and safely when combined with the appropriate use of HR monitoring, perceived exertion rate (PER), and the use of intervals: periods of exertion followed by rest. Studies show this type of activity is manageable in several illness models, including chronic obstructive pulmonary disease,[88,89] post coronary artery bypass patients,[90] congestive heart failure,[91] and heart transplantation patients.[92] This type of anaerobic stimulus more realistically mimics real-world challenge and allows for self-paced exercise that is safe, tolerable, and more beneficial for many heart and lung patients.[88-96] Cardiac patients also may have less risk with this type of activity, since it has more favorable affects on ST-segment changes and heart rate variability (HRV).[94-96]

Monitoring HR is useful for any health care provider prescribing exercise. It is important to understand that HR equations are merely estimates based on age; there is much variability. HR equations, in general, underestimate HRs in the very fit. The old HR equation of 220 – age is an inferior HR equation that underestimates HR in the old and overestimates in the young.[97] Newer equations allow for better predictive value. Based on current understanding, women and men should use separate equations for predicted HR percentages. For men, the MHR equation should

be 208 – age (0.7).[97] For women this equation should be 206 – age (0.88).[98] It is also useful to know the equation for translating percent of MHR to percent of oxygen uptake (VO_2) and vice versa. That equation is %MHR = (0.64) %VO_2 + 37.

Because multiple drugs and disease states can interfere with HR, exertion ratings used alone or combined with HR are a more useful clinical tool. In exercise research, a 16-point exertion scale called the Borg scale is used. It is a cumbersome tool to use and teach in clinical practice. A simple 1 to 10, with 10 being maximum exertion and 1 being at rest is a far more useful tool clinically. It is easy to teach and implement. Traditional aerobic exercise scores between 6 and 8 on the 1 to 10 scale. HIIT will reach between 8 and 10 on the work phase and between 1 and 4 on the rest phase. In clinical practice, this is a useful aid in working with exercise intensity. Combining HR percent monitoring with PERs and heart rate recovery (HRR) allows for tight control of workout safety.

Two other useful clinical tools for health care practitioners are the "talk test" and HRR. Exertion and respiration are closely linked. The ability of a person to talk during exercise is a direct indication of whether they have crossed into the anaerobic zone.[99] For the unfit, this usually occurs around 55% of VO_2 max and for the very fit it occurs around 85% VO_2 max. This corresponds to 72% MHR and 91% MHR, respectively, leaving the average healthy exerciser right around 80% of MHR for the anaerobic threshold, at which point their ability to talk will be compromised. Correlating this "talk test" with an individual's HR allows practitioners to closely monitor exercise. HRR is a measure of how fast the heart recovers from exertion and is an indication of sympathetic and parasympathetic tone. A healthy heart should recover at least 25 beats/min or more within 1 minute after exertion. A heart that recovers 10 or less beats in 1 minute is a concern that should constitute a referral to a cardiologist.[100]



MUSCLE–BODY MESSENGERS AND INFLAMMATION

Every time the body moves, muscles release signaling molecules that communicate to the rest of the body. The endocrine properties of muscle, like fat, have been confirmed.[101-103] In the case of muscle, compounds called myokines are released in response to voluntary contraction. Myokines are cytokines, yet are derived specifically from muscle. These myokines give instructions to the body about how to function and adapt as well as hold the key to controlling chronic inflammation.

Interleukin-6: The Exercise Factor

The most important myokine related to muscle and inflammation is interleukin-6 (IL-6). When muscle contracts, IL-6 is released. IL-6 is a well-known cytokine that has long been thought to be inflammatory in nature and part of what is known as the inflammatory triad: tumor necrosis factor-α (TNF-α), IL-1, and IL-6. However, like people, IL-6 seems to behave differently depending on its origin, amount, and other cytokines around it. When released from muscle and in high concentrations without TNF-α and IL-1, IL-6 is anti-inflammatory.[104,105] IL-6 acts to reduce the amount of TNF-α and IL-1 in circulation by increasing the cytokine inhibitors, IL-1 receptor antagonist (IL-1ra), and soluble TNF receptors (sTNFR).[106-108] IL-1ra antagonizes the IL-1 receptor, decreasing IL-1 effects, whereas sTNFR binds up TNF-α before it can react at its target cells. At the same time, IL-6 triggers the release of the major anti-inflammatory cytokine, IL-10.[107,108] It appears that exercise-induced IL-6 has unique action as opposed to TNF-α mediated release of IL-6.[104] Exercise causes a huge increase in IL-6, far above TNF-α levels. This is in sharp contrast to infection or sepsis, which shows an exponential rise in both. It may be the ratio of IL-6 to TNF-α that is the real concern with regard to chronic inflammation. Epidemiologic studies on TNF-α and IL-6 genetic polymorphisms support this, showing that those with the highest TNF-α and lowest IL-6 levels have the greatest risk of diabetes.[109]

Other researchers support TNF-α as the real inflammatory culprit.[104] They speculate IL-6 levels may be a marker of whole body TNF-α levels and could be acting in direct opposition to the more inflammatory cytokines. The IL-6 effect implicates exercise as a first line defense against inflammation and may explain the "counter intuitive" findings on the benefit of resistance training in highly inflammatory diseases like rheumatoid arthritis.[110] For some time, science has been searching for a molecule that could account for the acute metabolic effects of exercise. Exercise reduces "all-cause mortality" due to its effects on the leading killers: heart disease, diabetes, and cancer.[111,112] IL-6 is beginning to be shown as protective against diseases like diabetes.[109,113-115] These same diseases have strong links to inflammation, which is now suspected as a major underlying cause. It has long been thought that exercise's impact on weight loss was the reason behind this. However, IL-6 also plays a role as a mediating factor in exercise's effects on fuel metabolism.[101-103,114,116] The broad effects IL-6 has on inflammatory cytokines, fuel metabolism, plus its ability to "talk" to the brain, liver, and adipose tissue, has some researchers thinking it is the best candidate for the elusive exercise factor.[106]

As muscle contracts, the genes controlling IL-6 production are turned on. The degree of IL-6 released from muscle is directly proportional to the amount of muscle being contracted; the more muscle used, the greater the response.[106,107,117-119] IL-6 also shows a tight relationship to muscle glycogen and exercise intensity. When muscle sugar stores begin to decrease, an intensity threshold is breached and much larger amounts are released.[120] Increasing exercise intensity, full body muscle contraction, and muscle glycogen depletion are the major exercise elements enhancing IL-6 release from muscle.[102,117,120,121] These factors together can induce an increase of plasma IL-6 that is 20- to 100-fold over resting levels.[102,121] At these levels, IL-6 begins to exert influence over the body, relaying messages about the metabolic needs of the muscle. In this way, IL-6 acts more like a hormone than a cytokine by sending communications from muscle to adipose tissue, immune cells, and the liver. These messages instruct the body to burn fat, control glucose regulation, inhibit the production of the proinflammatory cytokines, and ultimately generate a fully anti-inflammatory effect through the release of IL-10.[122] IL-10 is a potent reducer of TNF-α and IL-1 in its own right.[107]

From the previous scenario, it should be apparent that the ability to harness IL-6 through exercise could have a significant effect not only on inflammation, but also on whole body fuel usage and tissue repair. This process is far different than the usual chronic inflammatory scenario. A situation of chronic inflammation is one where TNF-α is elevated along with IL-6 and IL-1. Exercise-induced, muscle-derived IL-6 shifts the balance, causing a reduction in TNF-α and IL-1 with a simultaneous increase in IL-10.

In addition to its more direct effect, exercise-induced IL-6 has other secondary effects that account for increased benefits. 11β-Hydroxysteroid dehydrogenase type 1 (HSD1) is an enzyme that should be on the radar of physicians. It is responsible for the conversion of cortisone into active cortisol. This cortisol/cortisone ratio is important in determining the possible detrimental effects

of cortisol. This enzyme is present in visceral adipose and is overly active in the overweight and obese.[123] This is an important revelation, since it points to visceral adipose tissue as a new site of cortisol production. TNF-α and IL-1β have both been shown to upregulate HSD1 and contribute to total glucocorticoid production.[123] IL-6 is a potent inhibitor of both TNF-α and IL-1β, and the largest amounts are released through exercise. Intense exercise potentiates these effects by increasing sympathetic stimulation of α-2 receptors as well as adrenocorticotropic hormone; all of these have independent effects in suppressing HSD1 activity. The ability to blunt HSD1 is beneficial in controlling obesity and diabetes, and intense exercise may be the best way to effect these changes.

In addition to the cytokine effects, exercise-induced IL-6 crosses over into hormonal action and allows the muscle to "talk to" the adipose tissue and the liver.[101] Its major action at these sites is to release energy substrate to fuel continued movement. IL-6 is a potent stimulator of adipose tissue fatty acid oxidation[104] and is a major factor in liver glycogenolysis.[101] Although the mechanism for this action has not yet been fully elucidated, studies have confirmed that IL-6 has direct effects on the expression of adenosine monophosphate kinase[117,118] and hormone sensitive lipase,[113] two chief fuel regulating enzymes in human tissue.

Finally, IL-6 has the ability to cross the blood–brain barrier, having direct effects on the brain. The brain produces IL-6 in response to exercise as well. This sparks curiosity as to what brain IL-6 is doing. Animal studies showed that IL-6 had a direct and important effect on the brain, thus playing a role in appetite regulation, fuel regulation, and body composition.[101]

Interleukin-15: The Arnold Cytokine

Along with IL-6, IL-15 is another myokine that works to reduce inflammation in less direct ways. This cytokine works by interacting with transcriptions factors, such as peroxisome proliferator activated receptor-δ, decreasing adipose tissue size while at the same time increasing muscle contractile elements and size.[124-128] The end result will be less adipocytokine release (inflammation) due to a decreased fat mass, and a higher potential secretion of myokines (anti-inflammation) due to a greater contractile potential.

IL-15 is emerging as a potent antiobesity weapon and may explain why resistance exercise, which does not typically burn as many calories as aerobic exercise, dramatically impacts body composition. We like to refer to this myokine as the Arnold cytokine after the famous bodybuilder and actor Arnold Schwarzenegger. Bodybuilders are able to develop extremely lean and muscular physiques while focusing almost all their attention on high intensity resistance exercise as opposed to aerobic exercise.

Research showed that IL-15 release is twofold higher in type-2 dominated muscle tissue and that resistance exercise doubles IL-15 concentrations 24 hours after exercise.[124,125] This shows a novel mechanism of resistance exercise against the accumulation of fat. The effects of IL-15 are not the same in type-1 muscle fibers, which are dominate in aerobic activities. IL-15 has profound effects on reducing adipose tissue size while at the same time acting to increase muscle tissue. These effects are desirable, because muscle mass is frequently lost along with fat in aerobic centered exercise programs.

Interleukin-8: Angiogenesis

IL-8 is another myokine that may help the body heal through its ability to build greater blood supply. It is produced whenever the muscle encounters low oxygen supply, such as when it undergoes intense anaerobic exercise. It appears IL-8 is a potent angiogenic factor that signals the body to begin to build new blood vessels to increase blood supply. The muscle release of IL-8 is intuitive and self-serving for the muscle, allowing the tissue to meet the demands of activity the next time around. It appears that IL-8, like IL-6, is associated with intensity of exercise. It is released in highest concentration as a response to exhaustive aerobic exercise and during eccentric contraction. The myokine appears to act locally, inducing the angiogenic effects in the muscle tissue only. This is in contrast to IL-6 and IL-15, which, despite being cytokines, cross over into hormone-like action when induced through exercise.[129]

Lactate

Lactate has been correlated with several positive benefits to exercise. It is now believed that lactate is directly related to some of these beneficial changes through hormone-like action. As exercise intensity escalates, there is a large surge in catecholamine production. This occurs to supply the body with much needed blood sugar to fuel intense exercise. As the exercise intensity increases, aerobic physiology becomes "maxed out," forcing the body to become more anaerobic. This switch, believed in the past to be due to an oxygen deficit, is currently understood to indicate mitochondrial shuttle saturation. When this occurs, pyruvate and hydrogen ions begin to accumulate in the cytosol. It is the accumulation of hydrogen ions that lowers the pH of the cell, causing fatigue and the familiar muscle burn of intense exercise. In this situation, lactate is quickly formed. Lactate can then be recycled back to glucose via gluconeogenesis, be burned directly by conversion back to pyruvate and entry into the Krebs cycle, and/or engage cellular machinery as a signaling molecule.

The major signal sent by lactate during exercise seems to be an "adaptation signal." Analysis of this action shows that lactate has two major functions: first, it increases cellular events, leading to mitochondrial generation,[130,131] and second, it stimulates the release of growth promoting hormones, including HGH and testosterone.[132-134]

The major action on cellular signaling seems to be the upregulation of MCT-1.[130] MCT-1 is an embedded protein in the mitochondrial membrane that speeds the formation of pyruvate from lactate, thus making existing mitochondria more efficient. In addition, research by Hashimoto et al[131] in 2007 elucidated a complex mechanism whereby lactate interacts directly with key genes involved in mitochondrial biogenesis. Taken together, this opens a whole new understanding for improving metabolic efficiency. By harnessing the power of lactate, mitochondrial levels can be increased and enhanced, resulting in many beneficial effects on total physiology.

The idea of lactate as a hormone is a novel concept. However, it has been made clear through several studies over the last few years that lactate is a key signaling molecule in exercise metabolism. Interestingly, a lactate receptor called GPR81 was recently isolated in rats, confirming it does act like a hormone.[135] Other studies have shown lactate can directly stimulate the release of testosterone, progesterone, and HGH.[132,133,136-138] This lends further credibility to lactate's role in helping the body adapt and grow.

TESTOSTERONE AND HUMAN GROWTH HORMONE

Testosterone and HGH, in particular, are key players in human metabolism, especially as they pertain to physique development, combating obesity, and antiaging effects. Testosterone and

HGH, in addition to other effects, increase lean muscle tissue and decrease fat mass. Both of these anabolic hormones are more pronounced with anaerobic exercise.

EXERCISE APPROACHES TO INFLAMMATION

IL-6's release from muscle cells is not a nervous system phenomenon and is not based on muscle injury. It seems the impetus for IL-6 release is mechanical.[103,121] In other words, just the act of movement is all that is required. However, there are ways to amplify IL-6 production during exercise. The science of exercise metabolism now goes far beyond simple calories. The ability to harness the far-ranging hormonal and cytokine effects of exercise can be accomplished through use of short duration high intensity exercise techniques used in athletic populations for decades. Although the term "high intensity" has the tendency to cause reservation, these tools and techniques can be adapted for use in even the least fit and most populations with inflammation.[110,111,139]

Before discussing the techniques in this approach to exercise, it is important to define why short intense exercise may be more useful than traditional approaches. The damage associated with chronic inflammation is compounded by a lack of offsetting growth factors. The body produces these growth factors in response to intense exercise. Testosterone and especially growth hormone are known to be factors linked closely with intensity. The word intense as used here means exercise that is glycogen depleting, i.e., it significantly reduces the body's muscle and liver sugar stores. Only two types of exercise are likely to produce these effects, long duration exercise lasting hours or short intense sprint type exercise. There are obvious constraints to prescribing hour long exercise sessions, since lack of time is the number one reason cited for lack of exercise participation, making short intense exercise more realistic. In addition, the overall hormonal response to long duration exercise is counterproductive, since it raises cortisol levels above the body's ability to compensate with growth promoters.[46-53]

This type of exercise also makes sense because it creates a hormonal environment that produces sustained fat burning as well as muscle growth.[54,66,140] The amount of glycogen reduction is directly correlated with IL-6 release and high intensity exercise is shown to increase IL-6 and catecholamines together.[103,107,120,121] Catecholamines have their own independent effect in lowering TNF-α and IL-1, synergistically enhancing IL-6. Combining these known effects with techniques that can deliver the same benefit in less time presents the opportunity to supply these anti-inflammatory effects in short time periods.[107,122,141]

Holistic Fitness Prescription

Based on the research reviewed in this chapter of the new understandings emerging from exercise research, it seems a cross-training approach in line with our historic movement patterns would provide the most benefit. This approach would include walking, aerobic zone exercise, and resistance training, as well as cardiovascular interval training. However, realizing exercise prescription needs to be feasible and time consciousness necessitates combining elements to generate the most health benefit.

Putting this information in the historical context, it would appear that daily walking should be done as much as feasible. Walking should be viewed as a necessity rather than exercise. Based on historical information, walking constituted the predominant activity of our ancestors. Walking not only burns calories, but also has restorative and relaxing effects. Because walking and eating are generally incompatible, it may be a suitable replacement for eating behavior. Walking may best be done in the evening and for hormonal benefit; walking in a natural setting may be more beneficial than walking in more urban settings.[142] Studies have shown positive effects on lowering cortisol.[142]

In addition to walking, aerobic zone training should be instituted as well. Based on most data, an aerobic program lasting between 20 and 60 minutes 3 to 5 days/week seems optimal. Based on new information, aerobic exercise may be best for weight maintenance and not the most optimal for attaining weight loss. Given the new data on HIIT, the time spent doing aerobic exercise may be able to be cut in half. A HIIT program done 3 times/week for 20 to 40 minutes could save considerable time[69] and provide the same cardiovascular benefit and perhaps better weight loss results without the compensatory food behaviors.[55-61]

Recommendations capitalizing on the concept of nonexercise associated thermogenesis (NEAT)[143] and burst training[144,145] may have special applicability in today's time-starved world. NEAT involves accumulating as much nonexercise related activity as possible and includes everything from washing the dishes to fidgeting with a pencil, to nervously bouncing a leg up and down and even nonsitting time. Burst training is a concept popularized by Mark Smith, PhD, and involves accumulating several 1-minute anaerobic bouts of activity throughout the day. Several interesting studies showed this approach was able to generate clinically meaningful weight loss results with only minutes of exercise per day.[144-146] Instituting behavioral changes that involve parking further away, doing a burst of activity by running up the steps, standing rather than sitting, and even fidgeting when standing or sitting still can all make a significant impact on total energy expenditure.[143]

Weight training programs should also be a center point of health, fitness, and fat loss.[147] Resistance exercise excels at maintaining muscle mass and helps attenuate rebound weight gain.[148] Three full body workouts per week, using moderately heavy weights in the 8 to 12 repetition range for 3 to 5 sets is optimal. Again, since time is an increasingly limiting factor, integrating resistance training with interval training into one workout 3 to 5 times/week for 30 to 60 minutes can save considerable time yet still yield significant caloric expenditure and fat loss.

Rest-Based Training Method for Exercise Prescription

Rest and movement are often seen as opposites, but they are actually complementary and dependent on each other. Exercisers told to run as fast as possible for 10 minutes will necessarily regulate intensity to complete the task. If they were instead told to run as fast as possible for 10 seconds, the intensity could be dramatically elevated. True high intensity exercise is impossible to achieve without rest. Quality rest leads to quality work and vice versa.

HIIT and intense weight lifting have always coupled work with rest. One issue with these workouts is the rigid structure. The work/rest ratios "force" individuals of varying fitness levels to work at mandated levels. This works to lower intensity, inducing the same pacing effect seen in traditional aerobic exercise. These types of workouts are often too intense for many and can create psychological resistance to participating.

Rest-based training (RBT) uses rest, autonomy, and time manipulation to optimize intensity for all fitness levels. It combines the latest in exercise science and motivational psychology. RBT enjoys the same physiologic benefits of intense interval exercise and weight training but with key psychological benefits.

RBT differs in the application of rest. Although interval training and weight training have clearly defined work and rest ratios, RBT leaves the exerciser in charge of the duration of rest. The

language employed in this type of training is "push until you can't, rest until you can." This shift in paradigm acts as reverse psychology for exercisers.

Motivational psychology of exercise is an important consideration regarding exercise consistency, frequency, and intensity. The primary goal and purpose of interval training is to maximize work effort across all work bouts and employ the shortest recovery time possible to maximize the training stimulus. Contrary to popular belief, research has shown that exercisers who have autonomy over their workout parameters will often work harder and are able to self-regulate to an optimal work/rest ratio for their physiology.[148-150]

There are four key attributes in our RBT system. All are geared towards maximizing work effort in a safe and scalable way. The key tenets of rest-based exercise are represented by the acronym REST.

Rest-Based

Pushing to the point of rest is actually the goal of a rest-based workout. By putting the focus on rest, as opposed to work, RBT not only automatically increases the quality of work, but also makes exercise psychologically easier.[148-151] When exercisers know they have permission to rest, they may voluntarily work harder without even being consciously aware they are doing so.

Interestingly, animal research showed that intermittent exercise is inherent and may be an evolutionary adaptation to maximize distances covered per unit time.[150] Animals naturally engage in sporadic work/rest ratios during movement and self regulate exercise to optimize both performance and recovery. Research showed that humans have the same capability.[148]

Extrinsic Focus

A major inhibitor of intensity is exercisers' focus on intrinsic sensations such as breathlessness, burning, and other uncomfortable feelings.[149,152] RBT uses strategies that focus participants away from these intrinsic sensations to more extrinsic factors. Workout parameters change quickly, monotony is minimized, circuits are utilized, exercise timing is limited, and different movement strategies are incorporated in the same workout. All of this is designed almost as a distraction technique so the exerciser focuses more on what they are doing versus what they are feeling. This helps them work harder and therefore rest more often.

Self-Determined

In psychology research, self-determination theory posits that when people are given control and choice over their options, internal motivation automatically increases.[153-155] With RBT, there is structure in the workout, but the exerciser is left in complete control over how hard to work, when to rest, for how long, and even has flexibility over exercise choice and modifications. These factors serve to not only increase the quality of work within a session,[148] but can also improve exercise adherence from session to session.[148,149,152-155]

Time Conscious

Given that time and intensity are so closely linked, harder workouts by necessity must be shorter. RBT workouts can be as short as a 1-minute burst repeated multiple times throughout the day, to as long as 40 minutes of continuous exercise employing start and stop working and resting. Workouts lasting over 40 minutes suffer in intensity and may have negative hormonal consequences.[58,59,69]

Work/rest ratios employed by traditional interval and weight lifting workouts work for some but can be imperfect for most. By focusing on rest in a workout and allowing exercisers control over when they rest and for how long, optimal intensity for results can be achieved in a safe, scalable way. A 96-year-old grandfather would be able to use the same workout approach to deliver optimal intensity for him, whereas a 24-year-old elite athlete could use the concept to deliver an optimal intensity as well. Rest-based exercise can be seen as a new functional model for fitness and fat loss.

EXERCISE AND THE HEART

Aerobic zone exercise is a well-known preventive and treatment strategy for cardiovascular disease. Virtually all health care providers are aware of the aerobic exercise prescription advocated by most policymaking organizations as "20 to 60 minutes of aerobic exercise done at an intensity of 65 to 80% of MHR on all or most days."[156] Given that these recommendations are well established and universally accepted, we will focus our attention here on new research related to the heart.

Since the publication of the book *Aerobics* by Kenneth Cooper in 1968, participation in activities such as jogging, biking, swimming, marathons, and triathlon training has steadily risen. Newer research suggests, however, that this approach can be taken too far and exercise for health, fitness, and fat loss should not be so one-dimensional. Dr. Cooper himself has conceded "In that book I said, 'The more exercise, the better.' But by 1982, after too many telephone calls from distraught widows whose 55-year-old, overweight smoker husbands had died jogging, I realized I had made a mistake. … Exercise wasn't a panacea that could fix everything, it had risks.… There may be a point of diminishing returns."[157]

The risks of excessive aerobic exercise are now being better understood. Ultra-endurance exercise, such as marathon running and triathlons, can have a negative impact on heart function. Intense long duration aerobic activity dramatically elevates oxidative stress in the heart, alters left and right ventricle function, and causes damage in otherwise normal hearts.[158-160] This is not to say aerobic exercise is dangerous, but rather to highlight the potential downside of an aerobically dominated exercise prescription.

Obesity may actually be a better target for exercise therapy because it is so closely related to heart disease. Any exercise approach that helps lower body fat can be viewed as a heart healthy plan. Because so many view exercise as a time-consuming chore and lack of time is the number one reason cited for lack of participation in exercise, interval training exercise prescriptions may be better suited to heart protection. More research needs to be done at this point, but there is already promising information that intense interval training has all of the upside of aerobic exercise, while being well tolerated**,** safe, and more feasible in terms of time.

Interval Training the Heart and Vascular System

The theory behind interval training is that the heart, like all muscles, needs to be challenged to repair and grow stronger. Theoretically, interval training allows the advantage of a harder challenge with less risk because each high intensity bout is followed by recovery. If done correctly, the heart is forced to alternate between sympathetic stimulation and parasympathetic recovery. This, it is argued, is a more functional way to exercise because it trains HRR and heart stimulation. Because many cardiac events come from sudden unexpected anaerobic challenges, like shoveling the first winter snow, running through an airport to catch a plane, or walking up a large flight of steps, HIIT is believed to help the body prepare for these challenges by teaching the heart to work and recover quickly.

HRV and spontaneous cardiac baroreflex provide functional measures of cardiac parasympathetic activity. A study in April 2005 showed the effect of interval training on both.[161] Eleven healthy elderly men, mean age 74 years, underwent an intensive 14-week interval training program involving nine 1-minute bouts of exercise at 85% MHR followed by 4 minutes of recovery at 65% MHR. Aerobic capacity increased 18.6%, whereas HRV showed a significant parasympathetic shift at night from pre- to post-training. The cardiac baroreflex response also improved, with 10 of the 11 participants showing a favorable response.

Benefits of HIIT may be good for peripheral vascular disease as well as cardiovascular disease. A 2006 study reported an observational study on the effect of HIIT on intermittent claudication.[162] A total of 47 patients were included in the study. Patients were asked to walk on a treadmill to maximal claudication pain six times in each exercise session with 3 minutes of rest in between. Once a patient could walk continuously for 6 minutes without reaching maximal pain, the speed and/or grade was increased. A rehabilitation score was calculated as the product of speed and grade achieved by the participants. Results showed that HIIT led to clinical improvement in symptoms and a higher tolerable workload by patients. No adverse effects were seen from the treatment, suggesting those with peripheral arterial disease could both tolerate and benefit from HIIT.

In 2007, Wisløff et al[163] shed some light on the cardiovascular effects of HIIT versus traditional aerobic training for heart failure patients. Twenty-seven patients with stable postinfarction heart failure were randomized to either aerobic exercise (70% MHR) or HIIT (95% MHR for 4 minutes separated by 3 minutes at 50% to 70% MHR) 3 times/week for 12 weeks or to a control group. The control group was told to follow the exercise advice of their family doctor and met for 47 minutes of walking at 70% MHR every third week. All groups did exercise on a treadmill. The major finding was that HIIT was superior to traditional aerobic training with regard to reversal of left ventricular (LV) remodeling, aerobic capacity, endothelial function, and quality of life. With respect to LV remodeling, in the HIIT group, the LV diastolic and systolic diameters decreased by 12% and 15%, and estimated LV end-diastolic and end-systolic volumes dropped by 18% and 25%, respectively. Prohormone brain natriuretic peptide, a marker of hypertrophy and severity of heart failure, declined by 40% in the HIIT group. There was no change in the traditional aerobic group or control group in LV remodeling, pointing to a rather profound effect of HIIT on traditional aerobic exercise in this patient population.

As mentioned, HIIT has been shown to be safe and well tolerated in chronic obstructive pulmonary disease,[88,89] postbypass patients,[91] congestive heart failure,[90] and even heart transplantation patients.[92] As discussed, HIIT may realistically mimic real-world challenges. It can also be tailored into a self-paced format that is safe, tolerable, and beneficial for many cardiovascular conditions.[93-96] It was shown in one study to have more favorable effects on ST-segment changes than traditional aerobic exercise, in addition to the positive effects on HRV.[94-96,98]

Obviously physicians prescribing exercise for high-risk patients will not want to completely abandon traditional aerobic exercise in favor of HIIT. Traditional aerobic exercise is well established to both treat and prevent cardiovascular diseases. More studies need to be done on HIIT, but it appears it may have some unique cardiovascular benefits. There are some considerations when prescribing this form of exercise. Work/rest ratios should be larger for the more fit and smaller for the less fit or more frail. A beginning exercise protocol for a younger fit person wanting to optimize cardiac prevention would be a work/rest ratio of 1:2. More frail and less fit clients will want to start with a work/rest ratio of 1:4 or greater. The RBT approach highlighted previously may provide increased benefit and safety when using intervals.



EXERCISE AND BONE

When prescribing exercise for bone, there are several important considerations: the mechanostat theory, the concept of osteogenic sheer forces, and most importantly, knowing that bone density does not necessarily equal bone strength. A strong bone is both dense and flexible, whereas a weak bone has only one or none of those qualities.[164]

The mechanostat theory states that bone has set points of minimum effective strain (MES) that determine whether or not bone will be gained or lost.[165,166] If forces on bone increase more than what the bone is accustomed to (i.e., relative MES), mineral flux into bone increases. This, along with compensatory structural changes, helps bone become competent enough to deal with increased functional demand. Likewise, if demands on bone decrease and fall below the MES threshold, bone metabolism changes result in weaker bone.[167] The latter scenario often prevails in age and illness and can happen very quickly. During periods of immobilization, bone mineral density can decline as fast as 1% per month.[168,169]

To understand the concept of osteogenic sheer forces, one must have some idea of the bone's anatomy. Cortical bone contains lacunae (hollowed out areas) that are connected via canals (canaliculi). These lacunae house osteocytes that extend dendritic arms through the canaliculi to communicate with other osteocytes. Osteocytes act as mechanoreceptors. The osteocyte and its dendritic arms are bathed in fluid. The movement of this fluid is believed to be "sensed" by the osteocytes. The degree of intensity of this fluid movement dictates the degree of bone building stimulation. Research hints that exercise that creates large "sheer forces" such as jumping creates the most potent stimuli for bone growth. Another key factor in this physiology is that small jostling forces have a much weaker effect, and continuous exercise may work against bone building by causing desensitization of osteocytes. Optimal bone building exercise therefore is sporadic in nature, alternating work and rest and creates large strain and sheer forces. Multidirectional jumps and hops seem to be most ideal.

Measuring bone density alone does not provide an adequate measure of bone strength.[164] To determine the full impact of exercise, all bone parameters should be assessed. To properly ascertain bone strength, cortical thickness and bone diameter are equally important compared with bone mass. Cortical bone, the outer portion of bone, is responsible for 80% of bone strength. Thicker bones are also stronger bones. By measuring density, cortical bone, and thickness, we get a much more accurate picture of how much force a bone can handle. Effective exercise should address all these areas. In addition, bone-building exercise should be aimed at developing functional parameters that prevent a fall in the first place.[170,171] This means exercise modalities that build strength, flexibility, balance, and reaction speed should not be ignored.



EXERCISE AND CANCER

Yoga therapy has been shown to predict survivability in breast cancer,[172] is correlated with better outcomes in cancers of the head and neck,[173] and allays anxiety and stress-related dysfunction in cancer treatment.[174,175] The research on yoga and its use in cancer is gaining ground. A report by Brauer et al[176] in 2010 looked at the leading cancer treatment hospitals in America. This study showed 56% of these centers incorporated yoga into their clinic offerings.

The wasting of cancer, cachexia, is a difficult condition to treat, with few therapeutic options. Resistance training has several unique mechanisms that seem to address several of the underlying mechanisms of cachexia.[177] Resistance exercise is able to increase phosphorylation of mammalian target of rapamycin (mTOR) and p70S6k.[178] This suggests it has the potential to block a major contributor to decreased muscle synthesis. Resistance training is also a powerful modulator of adenosine triphosphate-dependent ubiquitin-proteosome system (UPS) activity by way of inflammatory cytokine modulation. Two review articles in 2007 by Pajak et al[179] and Al Majid et al[180] showed several complicated mechanisms of how resistance exercise works. Resistance exercise can release IL-6, which is anti-inflammatory when released by muscle,[82] and IL-15, which is strongly anabolic. Muscle-derived IL-6 suppresses TNF-α and IL-1. This action strongly decreases the overactivity of adenosine triphosphate-dependent UPS, which may be the most important component of cancer cachexia. IL-15 also will increase the type II muscle fibers that seem to be selectively lost in cachexia.

EXERCISE FOR THE BRAIN AND MOOD

Exercise increases cerebral blood flow and metabolism and therefore impacts both mood and cognitive function. Exercise has been shown to have many positive benefits on mood, especially in the realm of depression, anxiety, and self esteem.[181] In one depression study, 50 adults classified with depressed mood on the Profile of Mood States-Short Form Depression Scale (POMS) were studied over 10 weeks.[182] The treatment consisted of moderate intensity aerobic exercise for 30 minutes three times per week. At the end of the study, 62% of the exercise group were classified as normal on POMS compared with 29% in the control group. Another study in the elderly showed comparable results.[183] Several mood parameters were assessed, including both depression and anxiety. The study group had decreased scores for depression and anxiety and showed significant improvement in quality of life scores.

Two other studies on depression showed exercise as a potential primary therapy in major depression and among patients refractory to drug therapy. A study published in 2001 showed a small group of subjects with major depression who underwent a daily 30-minute walking program had clinically relevant and statistically significant benefit from exercise in as little as 12 days.[184] The program was a moderate intensity interval-walking program alternating from "somewhat hard" to half that pace on the rest phase. Even subjects refractive to drug therapy were able to improve with the exercise program. Considering the well-known response delay of 2 to 4 weeks with the use of medications, this study showed aerobic exercise as a more immediate fix and a smart integrative approach with drug treatment.

Direct comparisons of exercise versus drug therapy (sertraline) for major depression showed exercise as a powerful mood enhancer.[185] Subjects performed aerobic exercise on a treadmill 3 times per week and were followed over a 12-month period with respect to Zoloft therapy, exercise and Zoloft therapy, and exercise alone. The exercise alone group had significantly better outcomes in terms of treatment effect, remission, and relapse than either the Zoloft group or the Zoloft group plus exercise.

EXERCISE AND ANXIETY

Exercise has favorable effects on anxiety. Past studies have shown exercise to be an anxiolytic in caffeine and carbon dioxide induced symptoms,[186,187] but these compounds did not result in panic. One study showed that direct treatment of panic disorder patients with aerobic exercise led to significant improvement compared with placebo.[188] The study was over a 10-week period, and maximum effect was seen towards the end of the study. This points to exercise as both a preventative and alternative treatment strategy for anxiety. The acute effects of exercise may even be able to allay panic attacks. A recent study used exercise as a treatment against induced panic attacks.[189] Cholecystokinin tertapeptide (CCK-4) is a reliable inducer of panic attacks in humans and mimics the mechanisms associated with anxiety-induced panic attacks. Fifteen subjects were studied in a crossover design. Exercise for 30 minutes at 70% of maximum oxygen consumption was compared against no exercise. The following day, subjects received a bolus of CCK-4 and were monitored for signs and symptoms of panic attack. Previous exercise the day before produced half as many panic attacks, 6 compared with 12. This appears to indicate exercise as a modifier of anxiety-induced panic attacks.

EXERCISE AND MEMORY

Exercise also impacts memory and has shown benefit in multiple brain parameters.[190] Even weight lifting can improve brain function in the elderly.[191] Exercise is known to increase neurotransmission as well as myelin synthesis. Taken together, this can both increase the speed and quality of mental activity. Studies have shown exercise positively impacts attention deficit disorder/attention deficit hyperactivity disorder, dementia, Alzheimer's, and other mental disorders.[192-195] Recent studies also showed that exercise has the potential to create new neurons.[194,195]

SUMMARY

This chapter illustrated the vast potential of exercise to both prevent and treat multiple medical issues from obesity to mental and emotional dysfunction. There are many aspects of exercise and health that were not covered or were only discussed briefly. However, the key concepts covered should allow smart manipulation of exercise parameters to fit many conditions. It is our hope that understanding the new science of exercise, as well as the historical construct in which movement evolved, will allow health practitioners to move beyond one-dimensional exercise models focused solely on aerobic exercise to a more holistic and functional model of prescriptive movement.

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CHAPTER 37

Fasting

Alan Goldhamer, DC, Stephen Helms, NMD, and Trevor K. Salloum, BA, ND

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INTRODUCTION

Humans, unlike chimpanzees, have the ability to survive on water for extended periods of time.[1] The primary adaptation is the ability to use ketones from fat metabolism as an alternate fuel for the central nervous system.[2] The beauty of this adaptation is that during fasting the body prioritizes fat catabolism, the most concentrated caloric energy resource (9 vs 4 kcal for carbohydrates and protein), and thus safeguards catabolism of essential structures (nerves, muscles, organs, etc.) until stored adipose tissue is severely depleted—after fasting several weeks to months, depending on fat stores as well as metabolic, stress, and activity level. However, once this threshold is crossed in unattended fasting, starvation ensues (the body uses essential tissue for fuel, relying on protein as a major fuel source), resulting in death due to organ failure.[3]

Therapeutic fasting is voluntary, supervised abstinence from all food and drink except water for a specific time. The health promoting benefits are due to the marshalling of our metabolic potential as cellular systems manage internal resources more efficiently. The body thus can restore structure and function in a way analogous to rebooting a computer that has stopped working properly. Unlike a machine, however, the body can adapt dynamically to its internal environment, allowing the body to do what it does best, heal itself.

HISTORY

Throughout history, people of various cultures and religions have recognized the value of fasting. Numerous references appear in the Bible, Koran, pagan writings, and writings of the ancient Greeks.[4-6] One of the earliest doctors to use therapeutic fasting in the United States was Isaac Jennings (1788 to 1874). In 1822, Jennings discarded the use of drugs and, through the influence of Presbyterian preacher Sylvester Graham (1794 to 1851), began advocating fasting and other aspects of hygienic treatment (vegetarian diet, pure water, sunshine, clean air, exercise, emotional poise, and rest). This treatment later came to be known as "natural hygiene."[5-9] Other doctors who followed in the hygienic tradition were James C. Jackson (1811 to 1895), Russell T. Trall (1812 to 1877), William A. Alcott (1798 to 1859), Mary Grove Nichols (1810 to 1884), Thomas L. Nichols (1815 to 1901), Edward H. Dewey (1837 to 1904), George H. Taylor (1821 to 1896), Harriet Austin (1826 to 1891), Charles E. Page (1840 to 1925), Emmett Densmore (1837 to 1911), Helen Densmore (? to 1904), Susanna W. Dodds (1830 to 1915), Felix Oswald (1845 to 1906), Robert Walter (1841 to 1921), John H. Tilden (1851 to 1940), and George S. Weger (1874 to 1935). Most of these physicians graduated as medical doctors (MDs) from eclectic medical schools and published various works on lifestyle, diet, and fasting.[7-14]

The hygienic lineage continued into the mid-1900s, mainly due to Herbert M. Shelton, DC, ND (1895 to 1985), who developed a stricter protocol for fasting (water only; no enemas, exercise, or treatments; and complete rest). Shelton began his study of fasting in 1911 by reading the popular writers of his day: Sinclair, Carrington, Hazzard, Haskell, Purinton, Tilden, and MacFadden. He studied under the fasting authorities of his time at MacFadden's College (Chicago, Ill.), Crane's Sanatorium (Elmhurst, Ill.), and Crandall's Health School (York, Penn.).[7,12] (Among the earliest fasting institutions of this time were Lindlahr's Nature Cure Sanatoriums, including the Jungborn—the last operated by Benedict Lust, the

TABLE 37-1 **Mobilizable Fuel Reserves in a 70-kg Man**

	Glucose/Glycogen		Protein		Triglyceride	
TISSUE (WEIGHT IN kg)	**g**	**kcal**	**g**	**kcal**	**g**	**kcal**
Blood (10)	15	60	100	400	5	45
Liver (1)	100	400	100	400	50	450
Intestines (1)	0	0	100	400	0	0
Brain (1.4)	2	8	40	160	0	0
Muscle (30)	300	1200	4000	16,000	600	5400
Adipose (15)	20	80	300	1200	12,000	108,000
Skin, lung, spleen (4)	13	52	240	960	40	360
Total	450	1800	4880	19,520	12,695	114,255

Data from Elkeles RS, Tavill AS. Biochemical aspects of human disease. Boston: Blackwell Scientific, 1983.

founder of naturopathy in the United States, the MacFadden's Healthatorium, and the Tilden's Health School.)[8] In 1928, he founded a fasting institution and health school that provided services for more than 40 years.[7]

In 1949, Dr, Shelton along with William Esser, ND, DC; Christopher Gian-Cursio, ND, DC; and Gerald Benesh, ND, DC, formed the American Natural Hygiene Society, now called the National Health Association,[7,14] a lay organization dedicated to preserving the tenets of hygiene. In 1978, a professional branch was formed (International Association of Hygienic Physicians [IAHP]) to study and promote therapeutic fasting. Today, the IAHP organizes clinical training and examination, leading to certification in therapeutic fasting.[15]

PHYSIOLOGY

It has been suggested that humans, like other species, have evolved special biochemical pathways to subsist for long periods without food during periods of food scarcity (climate, injury, illness).[16] While fasting, the body primarily uses fat stores from adipose tissue for energy while recycling nonessential tissue for maintenance of pivotal systems. This streamlining utilizes nonessential protein sources, including digestive and glycolytic enzymes, muscle contractile fibers, and other connective tissue. Research has determined that an average 70-kg man has the fat stores to maintain basic caloric requirements for 2 to 3 months of fasting[17-21] (Tables 37-1 and 37-2). However, as this threshold approaches, the body can no longer effectively or efficiently mobilize fat stores for fuel, and significant protein catabolism again becomes necessary for energy production.[17]

During feeding, the conversion of fatty acids to acetyl coenzyme-A (CoA) is regulated by the availability of L-glycerol 3-phosphate (derived from glucose through the glycolytic pathway). As the concentration of acetyl CoA rises, it is resynthesized into triglycerides, with L-glycerol 3-phosphate serving as the accepter to which three acyl CoA groups are attached (through esterification). Conversely, during fasting, there is inadequate glucose to provide the needed glycerol for triglyceride synthesis, resulting in acetyl CoA levels in excess of the oxidative capacity of the Krebs cycle. The excess is then shunted into the synthesis of ketone bodies.[22]

Research using respiratory quotient and urinary nitrogen studies has repeatedly shown that triglycerides are the major fuel during fasting.[17-23] Inadequate blood glucose in fasting prompts hydrolysis (lipolysis) of triglycerides within adipocytes, allowing fatty acids and glycerol to leave the cell. The fatty acids are transported in a physical complex with albumin to the liver, muscle, and other tissues. Fatty acid oxidation results in large quantities of ketones secreted into the blood stream, usually noted on urinalysis by day three.[24] These ketone bodies (acetoacetic acid, acetone, and β-hydroxybutyric acid) are utilized by the heart and, in fasting, by the brain for energy production.[2] Because the ketone bodies are acids, their entry into the plasma results in a rise in hydrogen ions. This change is buffered by the conversion of bicarbonate into carbonic acid and then to carbon dioxide, which is exhaled. In extended fasts, the buffering capacity is surpassed and the plasma pH decreases, leading to mild metabolic acidosis with a compensatory increase in respiratory rate with noted electrolyte imbalance.[22]

The initial physiologic response to fasting is the liver's increased release of glucose to maintain adequate blood levels as undigested calories are exhausted in 4 to 8 hours. After only 12 hours, the liver's glycogen stores become exhausted, and blood glucose is maintained by gluconeogenesis from triglyceride glycerol in fat reserves as well as from glucogenic amino acids and primarily from lactate (Cori) and alanine cycle from muscles.[25,26] Interestingly, muscles contain more glycogen than the liver, but lack the enzyme required to convert glycogen to glucose (D-glucose-6-phosphatase). Through the Cori cycle, stored energy is shuttled as lactate to the liver and then used by body systems as glucose, where as in the feeding state, it would commonly be shuttled back to the muscles[19] (Figure 37-1). As the fast proceeds, the kidneys become

TABLE 37-2 **Utilization of Energy Reserves**

ENERGY SOURCE	RESERVE*
Glucose	1 h
Digestion	4-8 h
Glycogen	12 h
Amino acids	48 h
Protein	3 wks (if protein were the only fuel used for gluconeogenesis) 24 wks (obligatory loss only)
Triglycerides	8 wks

*These estimates are based on 100% utilization of each fuel.
Data from Shils ME. Modern nutrition in health and disease, 9th ed. Philadelphia: Lea & Febiger, 1998; White A, Handler P, Smith EL. Principles of biochemistry, 6th ed. New York: McGraw-Hill, 1978; Montgomery R, Dryer RL, Conway TW, Spector AA. Biochemistry: a case-oriented approach, 6th ed. St Louis: CV Mosby, 1996; Nutrition reviews' present knowledge in nutrition, 5th ed. Washington, DC: Nutrition Foundation, 1984:439-453.

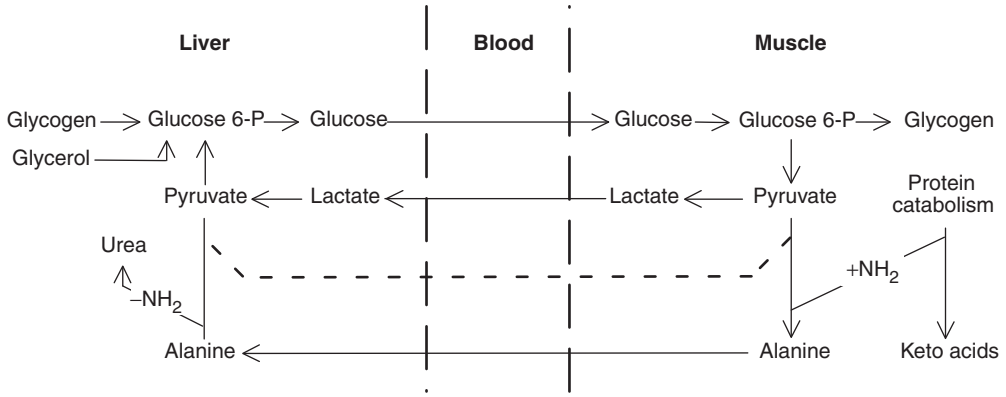


FIGURE 37-1 Mechanisms of glucose production during fasting.

progressively more important in the maintenance of blood glucose levels, and eventually, the renal cortex synthesizes more glucose from amino acids than does the liver.[16] Note that glucose is also recycled by the breakdown of blood cells in the liver.[19-21]

Under normal feeding conditions, the energy requirement of the mature brain is met almost entirely by glucose. Because the glycogen content of the brain is very low (0.1%), there is essentially no brain glucose reserve. Although the brain converts to oxidation of β-hydroxybutyrate after 4 to 7 days, there is still an obligatory need for approximately 80 g/day of glucose for the brain, red cells, muscles, and other tissues (400 to 600 kcal/day of glucose).[24,27] Approximately 16 g of glucose is synthesized from triglyceride glycerol, with the rest of the glucose requirement (and the other metabolic processes requiring amino acids, such as enzyme turnover) being met by the catabolism of 18 to 24 g/day of protein.

All amino acids are glucogenic (with the exception of leucine, which appears to be a regulator of protein turnover in muscle),[28] but alanine plays a prominent role analogous to lactate in the Cori cycle.[25,26] The alanine cycle provides the mechanism for the recycling of a fixed supply of glucose and the effective transportation to the liver of amino acid nitrogen derived from muscle breakdown. Because muscle, unlike the liver, is incapable of synthesizing urea, most of the amino nitrogen from protein breakdown is transferred to pyruvate to form alanine. The alanine enters the blood and is taken up by the liver. The amino groups are removed to form urea, and the resulting pyruvate is converted to glucose. The newly synthesized glucose is secreted into the blood, taken up by the muscle, and catabolized to pyruvate to reseed the alanine cycle.[22]

During physical activity and exercise, there are incremental increases in the glucose requirement by the heart and skeletal muscle that require protein catabolism. Although much of the lactate produced by anaerobic metabolism of glucose and glycogen is resynthesized to glucose by the liver via the Cori cycle, the need for glucose is increased, because there is a net loss due to urinary excretion of lactic acid and metabolic inefficiency. Conversely, the energy for resting heart and skeletal muscle is met primarily by oxidation of fatty acids and acetoacetate (ketone). Therefore, during fasting, cannibalized protein reserves are directly related to the degree of physical activity.

Specific physical changes during fasting include decreases in body weight, pulse,[3,18,29] and blood pressure (BP),[3,18,30,31] and a drop in the basal metabolic rate by about 1% per day until stabilizing at about 75% of normal.[31] Other cardiac adaptations noted on an electrocardiogram present as sinus bradycardia, decreased QRS complex and T-wave amplitude, elongation of the QT interval, and shifts to the right of the QRS and T-wave axes. These changes return to normal with return to food,[3,29,31,32] similar to those animals that have prescribed adaptive mechanisms and hibernation cycles.

RESEARCH

Research into fasting has been reported since 1880, with the earliest record of therapeutic fasting in the medical literature appearing in 1910. The earliest research was primarily observational, as physiologic and metabolic changes were recorded while an individual fasted—Tanner (40 days in 1880),[33] Jacques (30 days in 1887 and 40 days in 1888),[34] Penny (30 days in 1905),[35] and Levanzin (31 days in 1912).[18]

In 1923, the classic *Fasting and Undernutrition* provided in-depth analysis of animal and human physiologic changes and reactions during fasting by Morgulis at the University of Nebraska.[30] In 1950, Ancel Keys[3] at the University of Minnesota compiled two volumes entitled *The Biology of Human Starvation* describing the detailed observations of 32 volunteers who fasted for up to 8 months with comparisons to food deprivation observations made during the Second World War. Perhaps the most important observation was that fasting did not cause vitamin or mineral deficiencies. Related starvation research in developing countries noted that those who fasted completely lived longer than those on protein-deficient diets.[16]

Since these groundbreaking works, published clinical studies on therapeutic fasting have demonstrated benefit in almost every organ system. The following is a partial list of diseases and conditions that are beneficially influenced by fasting: chemical poisoning, cardiovascular disease and hypertension, diabetes, epilepsy, obesity, pancreatitis, and immune/inflammatory conditions (all expanded upon), as well as asthma, lumbago, depression and psychosomatic diseases, neurogenic bladder, irritable bowel syndrome, dysorexia nervosa (impaired or deranged appetite),[36] neurosis and schizophrenia,[37] parasites,[38] duodenal ulcers,[39] uterine fibroids,[40] varicose ulcers,[41] thrombophlebitis,[42] eczema,[3,43] and psoriasis.[3,44,45]

Appendicitis

A case report, published in 2011, of a patient advised of mainstream treatment for appendicitis refused surgery to try medically supervised water-only fasting. Pre-fasting ultrasound confirmed inflammatory dilation of the appendix, which was found to be relieved post-fasting by negative clinical and ultrasound findings with no return of symptoms at 2-year follow-up.[46]

Chemical Poisoning

Another encouraging finding for the use of fasting was published in the *American Journal of Industrial Medicine* in 1984. This study involved patients who had ingested rice oil contaminated with polychlorinated biphenyls. All patients reported improvement in symptoms, and some experienced "dramatic" relief, after undergoing 7- to 10-day fasts.[47] This research supported past studies conducted by Inamura with polychlorinated biphenyls poisoned patients and suggested a detoxification effect of fasting.

Cardiovascular Disease

Studies of the effects of fasting on patients with heart disease began in the early 1960s. Duncan et al[44] noted improvements in hypertension and chronic cardiac disease. Others also found fasting to be beneficial in heart disease: Gresham,[48] Lawlor,[42] Imamura,[47] and Vessby.[49] Improvements noted included reductions in serum triglyceride values, BP, atheromas, and total cholesterol levels; increased ratio of high-density lipoprotein cholesterol to total cholesterol; and alleviation of congestive heart failure.[3,24,48,50-53]

In the June 2001 issue of the *Journal of Manipulative and Physiological Therapeutics*, Goldhamer et al[54] reported on a study involving medically supervised water-only fasting in the treatment of hypertension. In this evaluation of 174 consecutive patients with high BP, all patients were able to achieve BP sufficient to eliminate the need for medication, and more than 90% became normotensive. In patients with Stage III hypertension (systolic BP greater than 180 mm Hg) the average reduction in systolic BP exceeded 60 points. This is the largest effect ever published in the scientific literature. Nine months later, Goldhamer et al[55] reported on a study involving 68 consecutive patients with borderline high BP. The average ending BP in these subjects was 99 mm Hg systolic/67 mm Hg diastolic. In a letter to the editor published in *Journal of Alternative and Complementary Medicine* in December 2002, Goldhamer[56] described initial results in 30 patients with high BP participating in a residential health education program that included the supervision of water-only fasting for an average of 14 days. BP, weight, and cost of treatment and medications were compared for the year before and the year after fasting. Preliminary data demonstrated sustained clinical improvement in terms of BP reduction and weight reduction and an average reduction in combined medical and drug costs of almost $2700 per year per subject.

Diabetes

Guelpa recorded the benefits of fasting in type 2 diabetes and gout as well as in inflammation and after surgery.[57] The treatment of diabetes with fasting was further explored by Allen in 1915. He noted that rest and fasting usually stopped glycosuria, and he also observed improvements in gangrene and carbuncles.[58] In 1950, Keys also noted improvement in diabetic patients.[3] Over the last 25 years, type 2 diabetics have successfully fasted, with subsequent reduction or elimination of required medications through successful long-term follow-up, given appropriate lifestyle maintenance post-fasting.[59]

Epilepsy

The treatment of seizures through fasting began in the early 1900s in France by Guelpa and Marie.[60] In 1924, Hoeffel and Moriarty[61] described fasting's beneficial effects in epilepsy. In 1928, concurring with other researchers, Lennox[62] found that the induction of ketosis via fasting decreased the duration, severity, and number of seizures.

Immune and Inflammatory Disorders

The beneficial effect of fasting on certain autoimmune diseases was reported in *Lancet* in 1958. The researchers found that fasting shortened the early stages of acute glomerulonephritis (reduced glomerular filtration rate, high BP, and edema), thus improving prognosis. They concluded that "all patients with acute glomerulonephritis should fast."[63] Other autoimmune diseases that have responded to fasting are rosacea, systemic lupus erythematosus, chronic urticaria, and colitis.[40,64,65]

The subject of arthritis and fasting has received substantial attention in the scientific literature, with most of the research coming from Scandinavia. Scientists documented the anti-inflammatory effects of fasting with observations of decreases in the erythrocyte sedimentation rate (ESR), arthralgia, pain, stiffness, and need for medication.[43,66-72] Consistent with those findings, a 1984 U.S. study of 43 patients with definite or classic rheumatoid arthritis found significant improvements in grip strength, pain, swelling of proximal interphalangeal joints, ESR, and functional activity after a fast of 7 days.[69]

A strong link between arthritis and food intolerance has been revealed through fasting (see also Chapter 205). The diminution in symptoms of rheumatoid arthritis during fasting may be due to the decrease in gut permeability that accompanies fasting,[68] which would reduce the absorption of antigenic molecules into the blood from the gastrointestinal tract. In a 1984 study in *Bulletin on Rheumatic Diseases*, Panush[73] proposed the following theories: (1) nutritional modification might alter immune responsiveness and thereby affect manifestations of rheumatic diseases, and (2) that rheumatic disease may be a manifestation of a food allergy or hypersensitivity.

Fasting, in conjunction with food challenging, is now being used as a diagnostic test to determine food intolerances. Patients fast for a minimum of 4 days, and then individual foods are given to determine whether a reaction occurs. This method correlates well with skin prick and radioallergosorbent testing. A letter in a 1984 *Lancet* issue states, "When food avoidances prevent headaches, [irritable bowel syndrome], arthralgia and depression, it is more effective and less costly than traditional treatment and the observation also throws light on the etiology of the disorder."[74]

Obesity

Fasting for obesity has probably received more attention in the scientific literature than any other aspect. The earliest studies were conducted by Folin and Denis,[50] who in 1915, advocated short fasts as a safe and effective way to lose weight. Bloom,[75] Duncan et al,[44,45] Drenick et al,[51,76] and Thompson et al[52] published numerous works on the use of short and long fasts in obesity. Perhaps the most famous study on obesity appeared in the *Postgraduate Medical Journal* of 1973, which reported the experience of a 27-year-old man who fasted without complications for 382 days and lost 276 pounds.[53]

In general, initial weight loss during fasting is approximately 0.30% of body weight per day, with a gradual decrease to 0.10% per day after 30 days. The initial weight lost is primarily that of water, glycogen, and salt. For every pound lost, the body loses approximately 140 g of protein and 250 g of fat.[24]

Although fasting is very effective for weight reduction, fasting alone, without counseling and other lifestyle modifications, does

not ensure long-term maintenance of the lower body weight. This fact is well documented in a study of 121 obese patients who were monitored for 7.3 years after fasts that averaged 2 months. After 2 to 3 years, 50% of patients returned to their pre-fast weights, and by the end of the study, 90% weighed the same as before their fasts.[77]

Pancreatitis

In a 1984 randomized clinical trial (n = 88), fasting was determined to be the treatment of choice for patients with acute pancreatitis. The researchers suggested that "fasting alone be initially used as the simpler and more economical therapy." They found that "neither nasogastric suction nor cimetidine offer any advantage over fasting alone in the treatment of mild to moderate acute pancreatitis of any etiology."[78]

APPLICATION

Therapeutic fasting is best conducted under supervision at an inpatient facility. Such facilities will exercise care in terminating a fast and supervising post-fast recuperation, monitor laboratory values in light of fasting physiology, review imaging as necessary, and demonstrate prudence when using adjunctive therapies during fasting. Several facilities now exist in the United States, Canada, England, and Australia, and these centers follow the standards of care and principles of ethics established by the IAHP.[15]

It is important to recognize that therapeutic fasting can be viewed to have three stages or phases. Stage I fasting (also called early or turbulent fasting) lasts up to 7 days, as the body adapts to fasting physiology with the common symptoms of excessive cellular waste or slowed elimination—malaise, headaches, and muscle aches—that are generally transitory, but can be disconcerting. Only the most genetically capable detoxifiers or the least toxic individuals glide comfortably through this stage. After passing through this period, it is more "the mind" rather than "the body" that continually obsesses on eating. Stage II, or balanced fasting, is the most significant fasting stage, as remodeling of tissues promotes healing. It can last for weeks to months. Patients often experience one or more "healing crisis" (where chronic conditions/symptoms become acute) and/or go through less significant detoxification reactions. Stage III fasting is often called depletion fasting (or simply "starvation") as the body can no longer effectively or efficiently mobilize fat stores. Although many old texts refer to "fasting to completion" (i.e., exhaustion of nutrient reserves), this practice is now uncommon and not usually necessary,[79] as serial fasting after appropriate refeeding appears to be a safer alternative.

When we fast, we recreate the natural occurrence of our ancestors when a "late spring" meant depleted food reserves followed by unintentional fasting while waiting for the snow to melt and the new shoots to rise for sustenance. Today, voluntary and attended therapeutic fasting provides the opportunity to mobilize or peel back the layers of our structural and functional adaptations within and between cells that are no longer required or beneficial. Therefore, like an onion that may have a superficial bruise, during a fast, the body "peels the onion" by deconstructing the buttressing ("the disease") back to a healthy vital core or foundation that health can be built upon. Thus, a health promoting diet is pivotal to growth and maintenance of healing, and further, even with shorter annual fasts, allows less symptomatology and the ability to retain vitality throughout the year.[59]

Unfortunately, determining optimal fast length is difficult to predict and includes many factors, including size of reserves, individual metabolism, financial limitations, work schedule, severity of disease, age, and sex. This decision is based on all factors, especially the patient's mental state. Experience shows that extending a fast beyond a healing crisis (or noteworthy detoxification reaction) provides significant clinical benefit where stopping midcourse suppresses healing until the same symptomatology appears, albeit earlier, in the course of a subsequent fast. Overall, "[the] doctor will look for good practical recovery where patient is symptom free and signs of regeneration are present."[79]

General Principles

The use of a low salt, vegan, high fiber, low fat, low protein, and low sugar diet before and after fasting has been found beneficial and avoids complications of fasting. This diet also promotes pre-fast bowel movements and subsequent post-fast bowel movements that are sooner to evolve, easier to pass, and less problematic. (To commence fasting, bowel movement frequency must be at least daily.) Using broth or fruit and other juices are examples of restricted diets. They do not initiate fasting metabolic processes since they contain carbohydrates, protein, and/or fat. Nonetheless, restricted diets are often useful before and after fasting and for patients in whom a healing crisis develops during a fast or when a fast is contraindicated.[80] In most cases, a fast is superior to the restricted diet because (1) hunger almost totally disappears,[3,44] (2) ketosis occurs more quickly and efficiently,[3,44] (3) famine edema does not occur,[3] (4) sodium diuresis is more pronounced,[75] (5) weight loss is more dramatic and is from fat rather than protein stores, (6) healing time is shorter, and (7) patient strength may be greater.[81]

Individual variation (predominantly diet and lifestyle history) determines the level of comfort experienced through the mobilization process of fasting from the initial transition of utilizing energy stores from digestion and stored glycogen to the energy generation from gluconeogenesis and the β-oxidation of triglycerides.

Rest is a most important aspect of the fast and patients may nap throughout the day. Less sleep is common at night, possibly owing to the decreased daily activity and the increase in daytime rest.

Exercise while fasting is discouraged. Fuel conservation is necessary to allow maximal healing and the avoidance of unnecessary gluconeogenesis.[81,82] The body utilizes certain muscle proteins early in a fast, thus initiating the natural restriction of activity. Short walks or light stretching is permissible, but intense exercise inhibits repair and elimination. In serious chronic disease, an excess of activity has been suspected as cause of death during fasting.[83] Even moderate activity can double caloric utilization.[84]

Sunlight is important for general health during fasting, and patients should try to obtain 10 to 20 min/day. Sun dehydration does promote orthostatic hypotension and subsequent injury from falls. An increase in heart rate of 10 to 15 beats/min may indicate excessive sun exposure.

Pure water (distilled, filtered, or reverse osmosis) is recommended.[81,82] Researchers of fasting obese individuals often recommend 3 L/day,[24] and 64 to 96 oz/day is commonly adequate, although upwards of 160 oz is commonly ingested without affecting serum sodium status. Although increased water intake will allow for less detoxification reactions during days of greater mobilization, excess consumption will cause electrolyte depressions that are clinically significant and require refeeding. Physiologically, the body is able to modulate "available water" through reduced

obligatory water excretion (owing to lower excretion of urea, the major osmotic solute) and by access to released water from catabolized fat.[16]

Laboratory tests such as a complete blood count and serum chemistry screen are usually performed weekly and others are performed as necessary. Regular urine tests are performed and vital signs are checked daily.[77,85]

Upon refeeding there is a sudden shift from a low insulin, fat-burning metabolism to a high insulin, glucose-based state. As the plasma insulin rises, potassium, phosphate, and magnesium are driven intracellularly and sodium extracellularly, acting to expand and dilute the circulating volume. Sodium restriction during refeeding therefore should be emphasized to not precipitate dilution, edema, or acute heart failure.[86]

LABORATORY VALUES

Most laboratory values for body fluids during fasting do not follow specific patterns, but are unique to the individual and the disease process.[32,52] Assessment of a fasting patient's progress is based not on a sign or symptom, but on the total clinical picture. Although specific predictions of laboratory values during fasting are not possible, some general observations have been made.

Urinalyses may be difficult to interpret during fasting, because the body discards considerable waste via the kidneys.[77] It is not uncommon to see various types of casts, red blood cells, white blood cells (WBC), bilirubin (+1 to +2), protein (trace, +2), and ketones (+4), and, if liver disease is present, urobilinogen elevation. Trace leukocytes and blood are common incidental findings, particularly in women. Specific gravity is commonly elevated (possibly to 1.035), a finding that may reflect inadequate hydration.[85]

Complete blood counts usually show no significant change.[77] Low hemoglobin and hematocrit values have been observed,[42,85,87] requiring rule out of hemolysis or hemorrhage,[88] whereas elevations in hematocrit, hemoglobin, and red blood cell count usually indicate reduced hydration.[77,85,89] WBC counts are usually unchanged or decrease slightly with fasting; however, infection may cause an increase. Further, WBCs may increase, particularly if levels are low before fasting.[88]

All of the electrolytes have reductions over the long term as the body's mobilized stores are lost, but it is significant to note the ability to redistribute stores even with only distilled water during extended fasts. Serum electrolyte levels are not good indicators of tissue stores, but they are considered the most important blood values during fasting,[88] because they usually do not change significantly during fasting unless there is a concern that needs management.

The total body store of sodium is 83 to 97 g (of which 65% is exchangeable), and that of potassium is 115 to 131 g (of which 98% is exchangeable). The typical daily dietary intake of sodium is 3 to 7 g, and of potassium, 3 to 5 g.[90] During early fasting, the body loses 150 to 250 mEq (3.5 to 5.8 g) of sodium and 40 to 45 mEq (1.6 to 1.8 g) of potassium a day; later, these values drop to 1 to 15 mEq (0.02 to 0.35 g) and 10 to 15 mEq (0.4 to 0.6 g), respectively. Serum potassium usually decreases (but may become elevated) and values less than 3 mEq/L or above 6 mEq/L often require breaking of the fast. The electrolytes calcium and chloride are usually stable, but levels often diminish, especially if vomiting is present.[88]

Liver enzyme values may increase considerably if liver disease is present and may rise even if liver disease is not present. Triglyceride, cholesterol, and uric acid levels usually rise during fasting,[85,91,92] indicating mobilization of tissue stores. Post-fast values often show a decrease from pre-fast values,[49,61,91] but lipid panels will not show a new baseline value until 4 to 6 weeks post-fast. The serum protein value usually declines with fasting. Pancreatic lipase and amylase values also usually drop with fasting.[88]

A rise in blood urea nitrogen (BUN) value may occur, but some authorities have observed a decrease.[3,62,42] The serum creatinine value may be elevated[49,85] or may remain stable,[93] and depression requires prompt retesting or fast termination. Closely monitor creatinine for elevations, particularly in those with renal compromise. Blood glucose values drop in most patients,[43,58,61,62] possibly below 30 mg/dL. If the blood glucose value is low before fasting, it may rise after fasting. ESR and C-reactive protein usually drop after fasting, although they may rise during the fast.[68,70,85]

Hormonal changes during fasting typically consist of decreases in insulin[16,20,23,32,94] and thyroid hormone levels.[29,32,95] Increased levels of growth hormone,[29,32,95] cortisol,[89] glucagon,[16,20] plasma norepinephrine,[96] serum melatonin,[96] and certain prostaglandins (in animals) usually occur.[97] In contrast, a decrease in growth hormone is usually found in obese individuals.[32] In one study conducted in 10 postmenopausal women who underwent short-term fasts, no significant changes in adrenal hormones, androgens, serum and urinary estrogens, plasma epinephrine, or dopamine were recorded.[96]

After a 44 day fast, the following changes were noted in less commonly ordered bloodwork—elevations: cortisol, somatostatin, insulin-like growth factor–binding protein 1; very low levels: leptin, ghrelin, insulin-like growth factor 1; normal values: peptide YY, agoutirelated peptide, α-melanocortin-stimulating hormone, neuropeptide Y, and pro-opiomelanocortin.[98]

Adjunctive Care

Some medical studies recommend supplementation with vitamins, fruit and vegetable juices, acaloric fluids (coffee, tea, etc.), and drugs while the patient is "fasting." These practices have not been shown to produce any advantage, and serious problems have sometimes occurred, especially when nonessential medication was permitted.

Dietary Supplements

Loss of minerals or vitamins is usually not a concern, and deficiencies during fasting are rare. Problems such as nausea and indigestion were reported when mineral and vitamin supplements were taken during fasting.[76,93] For example, it is well known that nicotinic acid supplementation inhibits the release of free fatty acids from adipose tissue.[24] In one patient in whom vitamin deficiency was reported in the medical literature, the actual fasting protocol was not described; in addition, the patient's physical activity was not restricted and oral medication for intercurrent illness was maintained during fasting.[76] Vitamin and mineral excretion becomes very low after 10 days.

Enemas

Enemas are not usually necessary and do not generally offer any added benefit during fasting.[66] Some authorities have found that enemas also cause discomfort.[81] To help prevent constipation, pre-fast meals of only fresh fruit and vegetables for at least 2 days will assist in establishing proper elimination before the fast is initiated. Lack of bowel movement 3 to 5 days post-fast (particularly on longer fasts) may point to the need for stewed prunes with meals until resolution or an enema becomes necessary.

Hydrotherapy

Constitutional hydrotherapy and sitz baths have been implemented with fasting. Strong treatments, both in frequency and/or temperature interval size, should be limited to early fasting.

Intravenous Therapy

Intravenous administration requires much care and is best avoided entirely, except for emergent conditions. Saline should be avoided due to plasma expansion and edema, which has precipitated acute heart failure. Glucose, in contrast, should be accompanied by vitamin B_1 and B_6 co-administration to avoid acute thiamine deficiency and lactic acidosis.[99]

Pharmaceuticals

The primary concern of fasting medicated patients is potentiation of pharmaceutic action during fasting physiology. Specifically troubling is the potentiation of the known mechanism of action, urinary/hepatic metabolism, as well as known side effects and adverse events. Appropriately removing pharmaceuticals allows for ease of clinical assessment while ensuring patient safety. Successful fasting has been continually repeated while maintaining some hormonal medications (insulin, thyroid, and reproductive organ hormones, often at reduced dosage), but not with adrenal maintenance.

CONTRAINDICATIONS

Contraindications to fasting are few, and each case must be judged individually, because no two cases are alike. For example, an inexperienced practitioner may assume that emaciated patients should not fast, but about this issue Shelton[81] had the following to say: "Extreme emaciation: In such cases a long fast is impossible. A short fast of 1-3 days may be found beneficial, or a series of such short fasts with longer periods of proper feeding intervening may be found advisable."

Contraindications to fasting include severe anemia, porphyria, and serious malnutrition. Individuals with a rare fatty acid deficiency of the enzyme medium-chain acyl-CoA dehydrogenase should also avoid fasting.[40]

The fasting of children and pregnant women is controversial. Although a short fast is appropriate for the sick child who does not want to eat, fasting in a pregnant woman may be strongly contraindicated; ketosis in pregnant diabetic women is known to be associated with fetal damage. Although this association is commonly recognized, the fact that this information has come only from research of diabetic pregnant women is not as widely known.[100] There appear to be no studies of the effects of nondiabetic ketosis on fetal development. Doctors (e.g., Shelton, Benesh, Sidwha, and Burton) with considerable experience of fasting pregnant women during all three trimesters have found no adverse effects with fasts of a few days to 2 to 3 weeks. Although the fasting of pregnant women appears from clinical observation to be safe, definitive pronouncement cannot be made until careful research is performed (such as a controlled retrospective analysis of existing cases).

Fasts for children and pregnant women should be shorter and should be meticulously supervised by an experienced doctor. In *The Science and Fine Art of Fasting*, Shelton[81] wrote, "Few infants require more than 2-3 days of fasting. … I have never hesitated to permit a sick infant to fast and I have yet to see one harmed by it." Regarding pregnancy he said, "The author would object to a long fast in chronic 'disease' during this period. There can, however, be no objection to a short fast."[81]

It is well recognized that fasting during lactation is not generally advised, because milk flow is halted by fasting and is difficult to resume.[81] Although fasting is considered inappropriate in renal insufficiency,[24] we have seen patients with 65% renal function return to normal as a result of fasting and dietary management.

With regard to fasting contraindications in general, Burton[79] stated:

> *I have found few health problems which are absolute contraindications to fasting. In my experience, if the need is evident, the only genuine contraindication is fear…. As for the other conditions often mentioned, e.g. kidney disease, heart impairment, [tuberculosis], etc., they merely require extreme caution, because of the limits imposed by pathology, but they are not inexorable contraindications.*

Supervised fasting as a therapeutic procedure is generally safe and effective. The incidence of death at fasting institutions is low, a fact that is promising because many of the patients have serious chronic diseases and have exhausted other therapeutic options. Of the hundreds of cases of fasting described in the scientific literature, only seven cases of death were reported before 1985.[36,83,101-104] In all cases, the patients had serious chronic disease before fasting, and in five of the seven cases, drugs were given to the patients while fasting; in the other two, no description of protocol was provided.

There is no evidence in the scientific literature to suggest that fasting itself can be considered a cause of death. Death during fasting indicates that the remedial efforts of the body have been overpowered by the pathologic process. This situation occurs in serious disease, whether the patient is eating or fasting. In examining the fallacy of attributing the cause of death to fasting, Stewart and Fleming[105] wrote, "Fasting short of emaciation is not hazardous; if death results, reasons other than those of the fast should be considered before concluding that all supervised fasts should be discouraged."

SIDE EFFECTS

Side effects of fasting are rarely serious, but fasting may uncover disease and reveal weaknesses that were previously subclinical.[44] Discomfort during fasting may be due to withdrawal from stimulants, hypoglycemia, acidosis, elimination of wastes, and enhancement of repair. Patients may experience headaches, insomnia, skin irritations, dizziness, nausea, coated tongue, body odor, aching limbs, palpitations, mucous discharge, and visual and hearing disturbances. Hair growth is usually arrested, and skin may become dry and scaly. Most signs and symptoms are usually brief as the body works to remove the disease.

In certain cases, complications occur that may necessitate breaking the fast early. Examples of such conditions are as follows:

- A sudden drop in BP (possibly due to peripheral circulatory collapse)
- Delirium
- Prolonged hypothermia
- Rapid, slow, feeble, or irregular pulse
- Extreme weakness
- Dyspnea
- Vomiting and diarrhea leading to dehydration
- Gastrointestinal bleeding
- Hepatic decompensation
- Renal insufficiency
- Severe gout
- Cardiac arrhythmias
- Emotional distress

Fasting elevates serum uric acid values and uric acid excretion, and if fluid intake is insufficient, gout or renal stones may be precipitated.[24,106]

A few studies have discussed the development of Wernicke encephalopathy during prolonged fasting, but because it rarely occurs during therapeutic fasting, it is difficult to determine whether the condition is related to methodology. It is important, however, to acknowledge the importance of utilizing B vitamins, especially thiamine, when any fast is broken with intravenous glucose.[107,108] The decision to terminate the fast should be based on the complete clinical picture and not on an isolated sign or symptom.

CONCLUSION

The vast potential of therapeutic fasting is only beginning to be realized, although results have been recorded since the early 1900s.[109-114] Considerable empiric study has been accomplished, and fasting is generally a safe, economical, and effective therapy. Extensive research revealed pervasive and important effects, including the enhancement of immune system function.[70,89,115-118] Unfortunately, a lot of prejudice exists. When we fast or assist another in fasting, perhaps the deepest human instinct is struck at depth—our need to eat, to survive, to exist. This often prevents otherwise intelligent and open-minded individuals from considering the facts regarding fasting and its unique benefits to human evolution and even health. There have been tragic deaths from fasting (almost exclusively inappropriately supervised), but fasting is not synonymous with starvation as our "instinctual self" would like to have us believe. Individual centers have successfully supervised the fasts of over 7000 people without fatalities over the last 27 years,[59] and as more appreciate the "healing power of nature," this therapy will become more mainstream.

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CHAPTER 38

Glandular Therapy

Michael T. Murray, ND

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INTRODUCTION

For almost as long as historic records have been kept, glandular therapy has been an important form of medicine. The basic concept underlying the medicinal use of glandular substances from animals is that "like heals like." For example, if the liver needs support or a patient is suffering from liver disease, then he or she may benefit from eating beef liver. Modern glandular therapy, however, primarily involves the use of concentrated glandular extracts.

A gland is defined as a secretory organ. The internal secretory organs of the body are called endocrine glands. These ductless glands secrete hormones directly into the bloodstream. The glands known to have endocrine function include the pineal, pituitary, thyroid, parathyroid, thymus, adrenal, pancreas, and gonads (testes or ovaries). Although not technically glands, it is common to refer to other organs of the body as glandulars when they are used in glandular therapy. For example, tissue extracts of heart, spleen, prostate, uterus, brain, and other tissues are often used in glandular or organotherapy.

Research has shown that certain glandular preparations and hormones are quite effective when taken orally. A number of glandular preparations are effective orally because of active hormone or enzyme content (e.g., thyroid, adrenal cortex, and pancreatin preparations). A good deal of literature supports pharmaceutical grade liver, aorta, and thymus extracts, and some support exists for pituitary, spleen, orchic (testes), and ovarian extracts as well. However, despite this scientific support, many still question the effectiveness of glandular products on human health.

A key challenge to the use of glandulars is the lack of widely accepted standards for extraction and quantification. Each manufacturer of a glandular product claims its method of extraction is the most ideal. However, the majority of these contentions are based on theoretic or philosophic grounds, not on research or clinical results. No quality control procedures or standards are enforced in the glandular industry. It is left up to the individual company to adopt quality control and good manufacturing procedures. Nonetheless, many glandular preparations available in the U.S. marketplace appear to be effective.

METHODS OF MANUFACTURE OF GLANDULAR PREPARATIONS

It is critical that properly processed glandular material be used, since the biologically active material such as enzymes, soluble proteins, natural lipid factors, vitamins, minerals, and hormone precursors are destroyed or eliminated if the product is not prepared properly.

Most glandular products are derived from beef (bovine) sources, the exception being pancreatic extracts, which are most often derived from pork (porcine) sources. The four most widely known methods of processing are the azeotrophic method, salt precipitation, freeze-drying, and predigestion.

The Azeotrophic Method

The azeotrophic method begins by quick freezing the material at well below 0°F, and then washing the material with a solvent (such as ethylene dichloride) to remove the fatty tissue. The solvent is then distilled off, and the material is dried and ground into a powder so that it can be placed in tablets or capsules. Although the azeotrophic

method eliminates the problem of fat-stored toxins like pesticides and healthy metals, unfortunately, it also removes fat-soluble hormones, enzymes, essential fatty acids, and other potentially beneficial materials; in addition, traces of the solvent still remain.

The Salt Precipitation Method

This method involves the maceration of fresh glandular material in salt and water. Because the salt increases the density of the water-soluble material, when the mixture is centrifuged, the lighter fat-soluble material can be separated out. The material is then dried and powdered. The benefit with the salt precipitation method is that no toxic solvents are used to separate the fatty material. The downside is the increased salt content of the product.

Freeze-Drying

The freeze-drying process involves quickly freezing the glandular material at temperatures of –40°F to –60°F and then placing the material into a vacuum chamber, which removes the water by direct vaporization from its frozen state (hence, the term freeze-drying). The benefit of freeze-drying is that it contains a higher concentration of unaltered protein and enzymes, as well as all of the fat-soluble components. Because the fat is not removed, it is critical that the glands are derived from livestock that have grazed on open ranges not sprayed with pesticides or herbicides. The animals must also be free from antibiotics, synthetic hormones, and infection.

Predigestion

The predigestion method employs plant and animal enzymes or some other method to partially digest or hydrolyze the glandular material. The partially digested material is then passed through a series of filtrations to separate out fat-soluble and large molecules. The purified material is then freeze-dried. This method of extraction is best for glandulars (such as the liver and thymus) where the polypeptide and other water-soluble fractions are desired.

SPONGIFORM ENCEPHALOPATHY

Bovine spongiform encephalopathy (BSE), also known as mad cow disease, is a transmissible, slowly progressive, degenerative, fatal disease affecting the central nervous system of adult cattle. The transmissible agent in BSE is a modified form of a normal cell surface component known as a prion protein. Unlike infectious organisms, prions are resistant to common treatments, such as heat and digestive secretions. Eating the meat of an animal with BSE may lead to a disease similar to BSE in humans called variant Creutzfeldt-Jakob disease.

BSE was first reported among cattle in the United Kingdom in 1986 and has been a major concern since then. The outbreak in the United Kingdom may have started from the feeding of scrapie-contaminated sheep meat-and-bone meal to cattle. Scrapie is a disease of sheep that is related to BSE in cattle. Evidence is strong that the outbreak in cattle was amplified in the United Kingdom by feeding rendered bovine meat-and-bone meal to young calves.

BSE has been reported in cattle throughout Europe. There has been a single case in Canada and, most recently, in the United States from a cow imported from Canada. Wild game in the United States such as deer and elk have been affected with a similar disease known as chronic wasting disease. The reason American cattle have been spared may be due to the active surveillance and import measures taken by the U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA).

The USDA has restricted the importation of live ruminants, such as cows and sheep, and food products from these animals from BSE countries since 1989, and from all European countries since 1997. In addition, the FDA prohibits the use of most mammalian protein in the manufacture of animal feeds given to ruminants because this kind of feeding practice is believed to have initiated and amplified the outbreak of BSE in the United Kingdom.

To reduce the risk of ingesting beef with BSE, it is critical to use products manufactured under the following guidelines:

- The June 2000 European Commission Decision regulating the use of material presenting risks for BSE
- A "Certification of Suitability" by the European Directorate of Quality of Medicines to ensure the highest quality, pharmaceutic grade material is being used
- The FDA's guidelines for sourcing and processing of bovine material

EVIDENCE FOR INTACT PROTEIN ABSORPTION

There is now considerable evidence that large macromolecules pass intact from the normal human gut into the bloodstream. In some instances, the body appears to recognize which molecules it needs to absorb intact and which molecules it needs to break down into smaller units. This phenomenon may help to explain the effectiveness of glandular therapy.

Numerous whole proteins have been shown in human and animal studies to be absorbed intact into the bloodstream after oral administration.[1-7] These include human albumin and lactalbumin, bovine albumin, ovalbumin, lactoglobulin, ferritin (molecular weight 500,000), chymotrypsinogen, elastase, and other large molecules.

Furthermore, proteins and polypeptides, as well as various hormones that are absorbed intact from the gut, have been shown to exert effects in target tissues. For example, in addition to thyroxine or thyroid hormone and cortisone, several peptide hormones are known to be biologically active when administered orally, including luteinizing hormone-releasing factor and thyrotropin-releasing hormone.[8,9] Even insulin has been shown to be absorbed orally under certain circumstances (e.g., in the presence of protease inhibitors or hypertonic solutions in the intestines).[10,11]

These data indicate that at least some of the larger molecules in glandular products are absorbed intact to induce physiologic effects, particularly polypeptides, which exert hormone or hormone-like action.

CLINICAL APPLICATIONS

An adequate body of research now exists to support the use of orally administered glandular extracts. The following is a brief discussion of several glandular preparations and their use. Table 38-1 lists the primary conditions responding to glandular therapy.

Adrenal Extracts

Oral adrenal extracts have been used in medicine since at least 1931.[12] Adrenal extracts may be made from the whole adrenal gland or just from the adrenal cortex. Whole adrenal extracts (usually in combination with essential nutrients for the adrenal gland) are most often used in cases of low adrenal function, presenting as fatigue, inability to cope with stress, and reduced resistance. Because extracts made from the adrenal cortex contain small

TABLE 38-1 **Therapeutic Uses of Glandular Extracts**

EXTRACT	CLINICAL APPLICATIONS
Adrenal extracts	Chronic fatigue Asthma Eczema Psoriasis Rheumatoid arthritis
Aortic glycosaminoglycans	Cerebral and peripheral arterial insufficiency Venous insufficiency and varicose veins Hemorrhoids Vascular retinopathies, including macular degeneration Postsurgical edema
Liver extracts	Chronic hepatitis Chronic liver disease
Pancreatic extracts	Pancreatic insufficiency Cystic fibrosis Inflammatory and autoimmune diseases such as rheumatoid arthritis, scleroderma, athletic injuries, and tendinitis Cancer Infections
Spleen extracts	After splenectomy Immune potentiation Infection Cancer Hyposplenia Celiac disease Dermatitis herpetiformis Ulcerative colitis Rheumatoid arthritis Glomerulonephritis Systemic lupus erythematosus Vasculitis Low white cell counts Thrombocytopenia
Thymus extracts	Recurrent and chronic viral infections, such as chronic fatigue syndrome, respiratory infections, AIDS, acute hepatitis B infection Cancer patients with immune depression from chemotherapy or radiation Asthma, hay fever, eczema, and food allergies Autoimmune disorders, such as rheumatoid arthritis, lupus erythematosus, and scleroderma
Thyroid extracts	Hypothyroidism

AIDS, acquired immunodeficiency syndrome.

amounts of corticosteroids, they are typically used as a "natural" cortisone in severe cases of allergy and inflammation (e.g., asthma, eczema, psoriasis, rheumatoid arthritis).

Dosage

The dosage of adrenal extract depends on the quality and potency of the product. The best measure of an effective dose for a preparation may be the level of stimulation (irritability, restlessness, and insomnia) the patient experiences. When prescribing adrenal extracts, start at one third of the recommended dosage on the label and slowly increase the dosage every 2 days until a stimulatory effect is noted. Once this effect is noticed, reduce the dosage to a level just below the level that produces stimulation.

Aortic Glycosaminoglycans

A mixture of highly purified bovine-derived glycosaminoglycans (GAGs) are naturally present in the aorta, including dermatan sulfate, heparan sulfate, hyaluronic acid, and chondroitin sulfate; related hexosaminoglycans have been shown to protect and promote normal artery and vein function. More than 50 clinical studies have shown an orally administered complex of aortic GAGs to be effective in a number of vascular disorders, including the following:

- Cerebral and peripheral arterial insufficiency
- Venous insufficiency and varicose veins
- Hemorrhoids
- Vascular retinopathies, including macular degeneration postsurgical edema[13-22]

Significant improvements in both symptoms and blood flow have been noted.

In addition, aortic GAGs have many important effects that interfere with the progression of atherosclerosis, including prevention of damage to the surface of the artery, formation of damaging blood clots, migration of smooth muscle cells into the intima, and formation of fat and cholesterol deposits, as well as lowering total cholesterol levels while raising high-density lipoprotein cholesterol.[23-27]

Dosage

The dosage of the mixture of highly purified bovine-derived GAGs naturally present in the aorta is 100 mg/day. Similar, but not nearly as impressive, results in the treatment of atherosclerosis have been noted with chondroitin sulfate at a daily dose of 3 g (1 g, three times daily).[28]

Liver Extracts

Beef (bovine) liver extracts and concentrates are a rich natural source of many vitamins and minerals, including iron. Liver extracts can contain as much as 3 to 4 mg of heme iron per gram. In addition to its use as a source of iron and other nutrients, hydrolyzed liver extracts have been used to treat chronic liver diseases since 1896. Numerous scientific investigations into the therapeutic efficacy of liver extracts demonstrated that these extracts improved fat utilization, promoted tissue regeneration, and prevented damage to the liver.[29-32] In short, clinical studies demonstrated that oral administration of hydrolyzed liver extracts can be quite effective in improving liver function.

For example, in one double-blind study, 556 patients with chronic hepatitis were given either 70 mg of liver hydrolysate or a placebo three times daily.[32] After 3 months of treatment, the group that received the liver extract had far lower serum liver enzyme levels. Because the level of liver enzymes in the blood reflects damage to the liver, it can be concluded that liver extract is effective in chronic hepatitis via an ability to improve the function of damaged liver cells, as well as prevent further damage to the liver.

Dosage

The dosage is entirely dependent on the concentration, method of preparation, and quality of the liver extract. The highest quality products are aqueous hydrolyzed extracts because they have the

fat-soluble components removed and typically contain more than 20 times the nutritional content of raw liver, including 3 to 4 mg of heme iron per gram.

Contraindication

Liver extracts should not be used in patients experiencing an iron-storage disorder, such as hemochromatosis.

Pancreatic Extracts

Pancreatic enzymes are most often employed in the treatment of pancreatic insufficiency. Pancreatic insufficiency is characterized by impaired digestion, malabsorption, nutrient deficiencies, and abdominal discomfort. Pancreatic enzymes are also used by physicians in the treatment of the following:

- Cystic fibrosis
- Inflammatory and autoimmune diseases like rheumatoid arthritis, scleroderma, athletic injuries, and tendinitis
- Cancer
- Infections

For a full discussion of pancreatic enzymes, see Chapter 111.

Dosage

Full-strength products are preferred to lower potency pancreatin products because lower potency products are often diluted with salt, lactose, or galactose to achieve desired strength (e.g., 4× or 1×). The dosage recommendation for a 10× U.S. Pharmacopoeia (USP) pancreatic enzyme product is 500 to 1000 mg three times a day immediately before meals when used as a digestive aid and at least 20 minutes before meals or on an empty stomach when anti-inflammatory effects are desired.

Pancreatic extracts are generally well tolerated and are not associated with any significant side effects.

Spleen Extracts

As early as the 1930s, orally administered bovine spleen extracts were shown to possess some physiologic action in increasing white blood cell counts in patients with extreme deficiencies of white blood cells, as well as being of some benefit in patients with malaria and typhoid fever.[33-35]

Like thymus extracts, pharmaceutic-grade bovine spleen extracts are currently quite popular in Germany for the treatment of infectious conditions and as immune-enhancing agents in cancer. Spleen tissue extracts may be of benefit in enhancing general immune function, since many potent immune system–enhancing compounds secreted by the spleen are low-molecular-weight peptides. For example, the potent immunostimulants tuftsin and splenopentin are composed of only four and five amino acids, respectively.

Both tuftsin and splenopentin have been shown to exert profound immune-enhancing activity. Tuftsin stimulates macrophages that have taken up residence in specific tissues like the liver, spleen, and lymph nodes. Tuftsin also helps to mobilize other white blood cells to fight against infection and cancer. A deficiency of tuftsin has been associated with signs and symptoms of frequent infections.[36]

Splenopentin, like tuftsin, has also demonstrated significant immune-enhancing effects. Its effects are primarily directed toward enhancing the immune system's response to regulating compounds such as colony-stimulating factors.[37] Colony-stimulating factors, such as interleukin-3, and granulocyte/macrophage colony–stimulating factors stimulate the production of white blood cells. Splenopentin is probably the factor responsible for the results noted in clinical studies during the 1930s in which spleen extracts were used in the treatment of depressed white blood cell counts.

Splenopentin has also been shown to enhance natural killer cell activity.[38] Natural killer cells destroy cells that have become cancerous or infected with viruses and are the body's first line of defense against cancer.

In addition to tuftsin and splenopentin, hydrolyzed (predigested) spleen extracts concentrated for peptides demonstrated impressive immune restorative properties in mice.[39] In one study, mice were exposed to radiation to significantly damage the immune system. Mice treated with the spleen extract recovered within 6 to 8 weeks. In contrast, those treated with a placebo recovered after 10 weeks at the earliest.

The primary clinical uses of spleen extracts are after removal of the spleen and the following conditions associated with low spleen function (hyposplenia):

- Celiac disease
- Dermatitis herpetiformis
- Ulcerative colitis
- Rheumatoid arthritis
- Glomerulonephritis
- Systemic lupus erythematosus
- Vasculitis
- Thrombocytopenia

Spleen extracts may also be useful in the treatment of low white blood cell counts, bacterial infections, and as an adjunct in cancer therapy. Individuals who have had splenectomies or who have low tuftsin levels or autoimmune conditions linked to low activity of the reticuloendothelial system should use spleen extracts.

Because the spleen is difficult to repair, severe spleen trauma usually requires splenectomy to stop the severe hemorrhage. The spleen is also removed in the medical treatment of certain diseases, such as idiopathic thrombocytic purpura and to determine the extent of Hodgkin disease.

Removal of the spleen is associated with an increased risk for infection. This increased risk of infection makes children and adults particularly susceptible to pneumococcal pneumonia. About 2.5% of patients who have their spleen removed die from pneumococcal pneumonia within 5 years of splenectomy. It is often recommended that a child who has undergone a splenectomy receive a pneumococcal vaccine and receive long-term antibiotic treatment. Use of spleen extracts, especially those rich in tuftsin, may be a natural alternative.

Spleen extracts should probably be viewed as a necessary medicine for people who have had their spleen removed. If the thyroid, adrenals, or ovaries are removed, most patients would be prescribed the corresponding hormone. It only makes sense that if the spleen is removed, the body should be supplied with necessary spleen substances like tuftsin and splenopentin.

The increased risk of infection is attributed primarily to a deficiency of tuftsin.[40,41] Tuftsin is produced only in the spleen; without the spleen there simply is no tuftsin in the circulation. Without tuftsin, the body is without one of its key stimulators of the immune system. Individuals without spleens need an outside source of tuftsin, like spleen extracts.

Dosage

Clinically, hydrolyzed (predigested) products concentrated for tuftsin and splenopentin content are preferable to crude preparations. The daily dose should provide 50 mg tuftsin and splenopentin or roughly 1.5 g of total spleen peptides.

No side effects or adverse effects have been reported with the use of oral spleen preparations.

Polyerga

Before the development of manufacturing techniques for human insulin to be used in the treatment of diabetes, the source was insulin isolated from pig pancreas. In Germany, after World War II, there was a shortage of pigs and subsequently a shortage of insulin. A German researcher, Walter Kuhlmey, MD, PhD, subsequently sought to produce insulin from other animal organs, most notably the spleen. In the process, this led to the serendipitous discovery of Polyerga. Kuhlmey found that the pig spleen extract not only had some insulin-like activity, but that it also increased the general sense of well-being and gave people more energy. He named his new product Polyerga (in Latin poly means "multiple" and erga means "power").

Initially, Polyerga had a general use. In 1951, an event changed Polyerga's clinical use. Julia Meir was a patient of oncologist Heinrich Pophanken, MD. She had an advanced cancer of the pancreas. She was considered incurable, and her death was expected shortly. In an effort to ease her pain, lift her fatigue, and stimulate a sense of well-being in Julia, Pophanken gave her Polyerga (via injection). Surprisingly, the dying patient began to recover. Pophanken gave Julia three to six intramuscular injections of Polyerga per week during the first 2 months and then just two injections a week thereafter. In 1954 Julia died of causes unrelated to her cancer. When the autopsy was conducted, the egg-sized tumor in her pancreas had disappeared entirely. This single case history led to the focus of research on Polyerga as a cancer therapy.

Cancer Therapy

Polyerga has been evaluated in several clinical studies in cancer patients. In one of the largest trials, 158 breast cancer patients were divided into two groups. The women in the Polyerga group received injections of Polyerga three times per week, whereas the women in the control group received a placebo injection. In the Polyerga group, the percentage of white blood cells, various parameters of immune function, body weight, and general sense of well-being all improved significantly compared with the control group.[42]

In a double-blind, placebo-controlled study in patients with head and neck cancers, Polyerga was shown to support patients who received the chemotherapy drugs 5-FU and cisplatin.[43] Polyerga was shown to stabilize the levels of lymphocytes. Typically, patients receiving 5-FU, cisplatin, and other chemotherapy drugs experienced a reduction in lymphocytes. This effect was noted in the placebo group but not in the patients receiving Polyerga. In addition, the Polyerga group reported less fatigue and higher energy levels than the placebo group, and there was no weight loss. Prevention of weight loss is a major goal in the support of the cancer patient, since significant weight loss reduces the tolerance to anticancer drugs, reduces the functioning of the immune system, and is considered to be a major cause of death in the cancer patient.

In another study of 248 cancer patients, giving them Polyerga orally for 4 months improved appetite, reduced pain, increased energy and activity levels, and improved their general sense of well-being.[44] Furthermore, a reduction of the extent of the illness, along with a clear improvement of health, was recorded by observing physicians. Best results were obtained in breast cancer patients and patients experiencing colon and other carcinomas, whereas lung cancer patients and patients with metastases did not seem to respond as well to Polyerga.

Other studies have shown Polyerga to produce similar benefits, as well as enhance survival time and reduce metastasis (spreading) in patients with cancers of the colon, stomach, and lungs.[45] From the totality of existing clinical studies, animal studies, and test tube (in vitro) studies, it can be concluded that Polyerga does the following:

- Exerts significant immune-enhancing effects
- Prevents some side effects of chemotherapy, especially the detrimental effects on the immune system
- Enhances the effectiveness of conventional chemotherapy and radiation treatment
- Prevents metastasis
- Enhances the general sense of well-being, improves energy levels, and prevents detrimental weight loss in cancer patients
- Enhances both the quality of life and survival time in cancer patients

The Mechanism of Action

Many effects of Polyerga may be the result of boosting the output of γ-interferon.[46] This important chemical acts as the communication link between the macrophages and lymphocytes. Reduction in the level of γ-interferon results in significantly impaired immune function. Low γ-interferon levels are common in cancer patients. By increasing γ-interferon levels, Polyerga creates a cascading of effects that lead to enhanced immune function in cancer patients. Polyerga increases activation of natural killer cells.[47-50]

Other Uses

Polyerga may be helpful any time immune support is required, such as in chronic viral infections, including hepatitis C, human immunodeficiency virus (HIV), and Epstein-Barr syndrome. In a study of 10 patients with chronic hepatitis B, Polyerga administration (intramuscularly twice weekly and orally 3 tablets daily for 24 weeks) led to complete resolution in 3 of the 10 patients and lowering of liver enzymes in individuals with lower viral loads.[51] Polyerga may also be quite helpful to people who have had their spleens removed.

Dosage

Most studies with Polyerga used injectable preparations. Based on dose-effect studies in animals, as well as human clinical data, an effective oral dosage was determined. Each Polyerga tablet contains 100 mg of polypeptides. The optimum dosage recommendation is one to two tablets three times per day. For patients up to 140 lb body weight, the dosage is one tablet three times per day. For each additional 40 lb body weight, add a tablet (e.g., a 220-lb person would take five tablets daily in divided dosages). There is no toxicity with Polyerga, so there is no concern about overdosage.[52] However, taking more than recommended does not necessarily produce better results. For best results, Polyerga should be ingested on an empty stomach before meals.

Thymus Extracts

A substantial amount of clinical research supports the effectiveness of orally administered thymus extracts. Specifically, numerous clinical trials have shown that oral administration of predigested calf thymus extract, rich in thymus-derived polypeptides, is effective in doing the following:

- Preventing recurrent respiratory infections in children
- Correcting the T-cell defects in HIV infections (acquired immunodeficiency syndrome [AIDS])

- Treating acute hepatitis B infections
- Restoring the number of peripheral leukocytes in cancer patients with chemotherapy-induced depression of white blood cell counts
- Treating asthma, hay fever, and food allergies in children[53,54]

The effectiveness of the thymus extract in these conditions is reflective of broad-spectrum immune system enhancement presumably mediated by improved thymus gland activity. This effect fits in nicely with one of the basic concepts of glandular therapy (i.e., that the oral ingestion of glandular material of a certain animal gland strengthens the corresponding human gland). The result is a broad general effect indicative of improved glandular function. Interestingly, thymus extracts have been shown to normalize the ratio of T-helper cells to suppressor cells whether the ratio is low, as in AIDS, chronic infections, and cancer, or high, as in allergies, migraine headaches, and autoimmune diseases like rheumatoid arthritis.

Chronic Viral Infections

Recurrent or chronic infections, including chronic fatigue syndrome and chronic post-viral syndrome, are characterized by a depressed immune system. This is a difficult condition to treat due to the repetitive cycle of a compromised immune system leading to infection, which leads to damage to the immune system, further weakening resistance to viral infection. Thymus extracts may provide the answer to chronic infections by restoring healthy immune function.

The ability of thymus extracts to treat and then reduce the number of recurrent infections has been studied in groups of children with a history of recurrent respiratory tract infections. Controlled clinical studies revealed not only that orally administered thymus extracts were able to effectively eliminate infection, but also that treatment over the course of a year significantly reduced the number of respiratory infections and significantly improved numerous immune parameters.[55]

One of the most difficult viral infections for the body to eliminate is type B viral hepatitis. Thymus extracts have been shown to be effective in several clinical studies in both acute and chronic cases. In these studies, a therapeutic effect was noted by accelerated decreases of liver enzymes (transaminases), elimination of the virus, and a higher rate of seroconversion to anti-HBe, signifying clinical remission.[56,57]

The most extreme example of a chronic viral infection is AIDS. Although thymus extracts have not been shown to reverse this difficult disease, studies have shown an ability to improve several immune parameters, including an ability to raise the T-helper cells, a critical goal in AIDS treatment.[58]

Cancer

The primary application of thymus extracts in cancer has been to counteract the immune-suppressing effects of radiation and chemotherapy. The net effect of thymus extract administration is to prevent the tremendous depression of white blood cell levels and activity that result from chemotherapy or radiation.[54,59]

Allergies

In patients with allergies, levels of the allergic immunoglobulin-E antibody and eosinophils are typically elevated, whereas levels of suppressor T-cells are typically depressed. These abnormalities are clear indications of altered immune function.

The oral administration of thymus extracts has been shown in double-blind clinical studies to improve the symptoms and course of hay fever, allergic rhinitis, asthma, eczema, and food allergies.[54,60-62] Presumably this clinical improvement is the result of restoration of proper immune function, since levels of immunoglobulin-E and eosinophils have been shown to be reduced, whereas the ratio of helper to suppressor T-cells improved.

Interestingly, in several clinical studies, children receiving thymus extracts during food allergy elimination diets are often able to tolerate foods that had previously been allergenic and symptom producing.[61,62]

Autoimmune Disorders

Autoimmune disorders, such as rheumatoid arthritis, are characterized by autoimmunity. Central to this immune dysfunction is a high T-helper/suppressor cell ratio. A high T-helper/suppressor cell ratio results in increased antibody formation. The higher the ratio, the higher the number of antibodies being produced to damage body structures. In one clinical study, rheumatoid arthritis patients with a T-helper/suppressor cell ratio of 3.3 achieved normal ratios (1.02 to 2.46) after 3 months of therapy with a thymus extract.[54]

Although use of a thymus extract may not result in substantial clinical improvement, it appears to be useful in restoring proper immune function in autoimmune diseases, including rheumatoid arthritis, lupus, and scleroderma.

Dosage

From a practical view, products concentrated and standardized for polypeptide content are preferable to crude preparations. The daily dose should be equivalent to 120 mg pure polypeptides with molecular weights less than 10,000, or roughly 750 mg of the crude polypeptide fraction.

No side effects or adverse effects have been reported with the use of thymus preparations.

Thyroid Extracts

Desiccated natural thyroid is available by prescription according to USP guidelines. Preparations are derived from porcine thyroid glands. Many naturopathic physicians prefer natural thyroid to isolated synthetic T_4, since it contains both thyroxine (T_4) and tri-iodothyronine (T_3). Typical levels of thyroid hormone contained per grain in USP thyroid are 38 mcg of T_4 and 9 mcg of T_3.

The thyroid extracts sold as "nutritional supplements" are required by the FDA to be thyroxine free. However, it is nearly impossible to remove all the hormone from the gland. These nutritional thyroid preparations can be considered milder forms of desiccated natural thyroid.

The primary use of thyroid preparations is in the medical treatment of hypothyroidism. In all but its mildest forms, treatment involves the use of desiccated thyroid or synthetic thyroid hormone. For more discussion, see Chapter 177.

Dosage

Dosage is determined by clinical evaluation, including blood measurements of thyroid hormones (see Chapter 177 for directions).



SUMMARY

From the scientific data that currently exists, there is enough evidence to support the use of orally administered glandular extracts. For best results, physicians should choose glandular products made by reputable companies that employ established methods of manufacture to produce extracts of known concentration.

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CHAPTER 39

Homeopathy

Andrew Lange, ND, and Susan A. Gaylord, PhD

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INTRODUCTION

Homeopathy is a highly systematized method of medical therapeutics and clinical evaluation. The term "homeopathy" is derived from the Greek words "homeos," meaning "similar," and "pathos," meaning "suffering." The medicines used in this system of therapeutics are chosen according to the Law of Similars (the concept of like curing like), a fundamental homeopathic principle based on the observed relationship between a medicine's ability to produce a specific constellation of signs and symptoms in a healthy individual and the same medicine's ability to cure a sick patient with similar signs and symptoms. This principle was first recognized by Hippocrates, who noticed that herbs given in low doses tended to cure the same symptoms they produced when given in toxic doses.

Homeopathic medicines are derived from a wide variety of plant, mineral, and chemical substances. They are prepared according to standards of the U.S. Homeopathic Pharmacopoeia, a revised version of which has been approved by the U.S. Food and Drug Administration and U.S. Congress.

HISTORY

The homeopathic school of medicine was founded by a German physician, Samuel Hahnemann. He had already gained a reputation in chemistry and medicine, having formulated a soluble form of mercury and developed a safer method for its use, and having written a number of works on pharmacology, hygiene and public health, industrial toxicology, and psychiatry. His treatise on arsenic poisoning (1786) is still considered authoritative. A prolific writer, Hahnemann collected, compiled, revised, and edited the existing pharmacologic knowledge. The work was well received by the medical profession of the time. Hahnemann was one of the most learned men of his generation in medicine, chemistry, and pharmacology, making his later criticisms of medicine all the more significant.[1]

Disillusioned with the theories and practice of eighteenth century medicine, Hahnemann retired from practice in 1782 and spent the next 14 years earning a meager living doing chemical research; writing; and translating English, French, Italian, and Latin works. He wrote of his time of practice:

> *It was painful for me to grope in the dark, guided only by books in the treatment of the sick. To prescribe according to this or that (fanciful) view of the nature of diseases, substances that only owed to mere opinion their place in the materia medica; I had conscientious scruples about treating unknown morbid states in my suffering fellow creatures with these unknown medicines which, being powerful substances, may, if they were not* exactly *suitable (and how could the physician know whether they were suitable or not, seeing that their peculiar special actions were not yet elucidated) easily change life into death, or produce new affections and chronic ailments, which are often more difficult to remove than the original disease.*

In his struggle to determine a reliable basis for therapeutics, he was distressed by his inability to provide medical care for the acute illnesses of even his own growing family. In 1790, during his translation of William Cullen's (a Scottish physician) *Materia Medica*, he added a footnote disagreeing with Cullen's conclusions that the basis of cinchona bark's effectiveness was its bitter and astringent qualities. *Cinchona officinalis* (peruvian bark), from which the drug quinine is derived, was known to be clinically effective in malaria and intermittent fevers (then called ague). He argued that there

were several drugs in common usage that, in smaller doses, had greater bitter and astringent qualities yet had no specific action on fevers. As an experiment, Hahnemann took four drachms of cinchona twice daily and soon developed the paroxysmal symptoms characteristic of intermittent fevers.

This duplication of symptoms was a revelation to him and ultimately resulted in his formulation of the concept of determining the properties of a medicine by studying its effects on healthy humans.

Although homeopathy offers a profoundly deep and unified evaluation in the treatment of chronic diseases (see the section on "Follow-Up and Case Evaluation"), it had gained most of its early reputation in the treatment of acute and epidemic diseases. An uproar was caused in Cincinnati in 1849, when two immigrant German homeopaths, treating cholera with camphor and other homeopathically prescribed remedies, published statistics in newspapers indicating that only 35 of their 1116 treated cases had died. During the nineteenth century, 33% to 50% of patients with cholera who were given standard medical care died. In the 1879 epidemic of yellow fever, New Orleans homeopaths treated 1945 cases with a mortality rate of 5.6%, whereas standard medical doctors were losing 16% of patients. These and similar statistics had a profound effect on Congress and public opinion.[2]

Over time, homeopaths established their own network of treatment facilities. By 1892, in the United States, they controlled 110 hospitals, 145 dispensaries, 62 orphan asylums and retirement homes, more than 30 nursing homes and sanatoria, and 16 insane asylums.

Constantine Hering established the first homeopathic medical school in the United States in 1835. It later moved from its original site in Allentown, Pennsylvania, to Philadelphia, where it remains today as an orthodox medical school: the Hahnemann Medical College and Hospital. Hering's promotion of homeopathy and development of the materia medica was equaled only by Hahnemann himself. His 10-volume work, *The Guiding Symptoms of Our Materia Medica*, remains a definitive work on the clinical verifications of the homeopathic approach. Unfortunately, of the many medicines introduced by Hering, only nitroglycerine remains in orthodox medical practice as a tribute to his medical genius.

Throughout the world, homeopathy has maintained a consistent tradition. Frederick Harvey Foster Quinn introduced it to England in the 1840s. It has since become a postgraduate medical specialty, recognized by the Department of Health by virtue of an Act of Parliament. Homeopathic hospitals and outpatient clinics are part of England's national health system. Homeopaths have been engaged as personal physicians to the Royal family for the past four generations.

Homeopathy is widely practiced in Europe, India, Argentina, and Mexico, and is experiencing a renaissance in the United States.

PHILOSOPHY

Provings

Hahnemann defined his method of testing medicines on healthy people as "provings." He expanded his investigations to include a wide range of substances, using his family, friends, and associates as experimental subjects.

Historically, Hahnemann was not the first to use this methodology. In 1760, Anton Stoerck reported testing *stramonium* (datura) by rubbing it on the skin, inhaling the vapors of the freshly crushed leaves, and, finally, ingesting the fresh extract. He theorized that if *stramonium* disturbs the senses and produces mental derangements in healthy people, it might be administered to maniacs for the purpose of restoring the senses by effecting a change of ideas.

Medical literature contains examples of inadvertent provings: in 1983 a study in the *New England Journal of Medicine* reported that pyridoxine (vitamin B_6), which is used in the treatment of some types of peripheral neuropathy, was also capable of producing neuropathies when given in large doses.[3] In 1796, Hahnemann published, in *Hufeland's Journal*, the fruit of his investigations in an article, "Essay on a New Principle for Ascertaining the Curative Power of Drugs, with a Few Glances at Those Hitherto Employed."

Like Treating Like

Hahnemann also recognized the tendency of a natural disease to have a "homeopathic effect" (i.e., a preventive or therapeutic effect) on other diseases with similar symptomatology. Although he ascribed this to the stimulation of the organism to eradicate the disease, he felt the deliberate induction of a disease to be difficult, uncertain, and dangerous.[4] This concept has many parallels in modern medical science. Descriptions of viral interference under natural conditions were described in 1937 by G. Findlely and F. MacCallum, who found that monkeys infected with the Raft Valley fever virus were protected from the more fatal yellow fever virus. They adopted the term "virus interference" and believed that when one virus infects a group of cells, a second virus is somehow excluded.[5] This eventually led to the discovery of interferon in 1957 by Alick Isaacs and Jean Lindenmann. These methods of inducing self-regulation are critical in enhancing the ability for the body to recognize and resolve illness.

In 1799, Hahnemann gained increased professional acceptance of his ideas by the successful application of *atropa belladonna* (deadly nightshade) in the prevention and treatment of scarlet fever (which had at that time reached epidemic proportions). In 1860, it was recommended as the treatment of choice in the National Dispensatory, which stated: "As long as persons are under the influence of belladonna the liability to contract scarlatina is very much diminished."[6]

The Organon of Medicine

In 1810, Hahnemann published his *Organon of Medicine*, a book that, through six editions, formed the foundation and definition of the homeopathic practice of medicine. It contains the philosophy, observations, and clinical applications of homeopathy, as well as citations from the historical and current literature of the time. Hahnemann challenged the reductionistic and mechanistic practices of his time, stating that the nature of disease is dynamic and could not be defined by isolating processes, grasping for an explanation. He further asserted that the cause of disease could not be known and that the categorization of disease states and attempts to manipulate physiology were insufficient, because they did not address the integrity and complexity of organization of the organism as a whole.

He described this organization as dynamic, meaning in accordance with the animating principle of life, which is the underlying energetic pattern to which matter conforms.

Disease is therefore addressed descriptively in the context of the whole patient, with the patient's unique symptoms being indicative of that individual's vital response to the condition. For any given disease there may be a long list of remedies that have been clinically effective, but it is the individualization and differentiation among medicines, based on the patient's unique indications, that leads to a successful homeopathic prescription.

Vitalism

Disease, in the homeopathic model, is thought to arise from inherent or developed weaknesses in the patient's defense mechanisms, creating a susceptibility to "morbific influences" (e.g., toxic factors in the environment, bacteria, psychological stresses). This viewpoint is considered "vitalistic" (see Chapter 3, Hierarchy of Healing, and Chapter 5, Philosophy of Naturopathic Medicine, for further discussion) and, although it does not deny a corporeal reality, considers pathology to be but a singular focus in a complex net of interactions.

William Boyd, in *A Textbook of Pathology*, discussed the limitations of the causal approach to disease currently in vogue in medicine when he stated[7]:

> *We must admit, however unwillingly, that we seldom or never really know the cause of anything. Many a beautiful idea has been slain by ugly fact. We merely note a constant association with one thing always following another. We say that the tubercle bacillus is the cause of tuberculosis. That is merely another way of saying that the bacillus is associated with a constant type of lesion; it is no explanation of how the lesions are produced by the bacillus. Nor does it explain why some persons and animals are susceptible to the infection while others are immune.*

Vitalism can be better understood in the context of Hahnemann's time, when theories of the causation of disease and its treatment abounded, such as Galen's doctrine that the secondary quality of a medicine (i.e., its action on the disease) could be determined from its primary qualities, such as its taste or smell; the evaluation of medicines by the study of their interactions when mixed with human blood in a jar; iatrochemistry, which had been reduced from the Paracelsian application of spagyric tinctures or oils of metals to dangerous toxic doses; the classification of drugs according to the Dioscoridian approach, which was based on the physiologic action (e.g., diuresis, diaphoresis) and chemical composition; and the "doctrine of signatures," which held that the outer form and color of a plant revealed its inner archetypal action.[8,9]

Although some studies of the effects of medicinal agents were done with animals, Hahnemann observed that they had different effects on humans; pigs could safely eat *nux vomica* in quantities that would immediately kill humans. Dogs could eat *aconitum napellus*, a deadly poison to humans, without injury. He also rejected the method of testing drugs by studying their effects on the sick as haphazard and unreliable, particularly because the results being sought were often only symptomatic relief rather than eradication of the disease state.

Hahnemann defined the application of medicines whose purpose was to alter physiology or act as an antagonist to disease as the practice of "allopathy" ("allo," meaning "contrary" in Greek). The current dominant medical system is heavily influenced by the causalistic and allopathic paradigms. This results in the diagnosis being the focal point of practice, without which appropriate therapy cannot be instituted. The pharmacologic approach is limited to the end results of disease rather than the origins of pathogenesis. Subsequent problems are classified as unwanted side effects, because only the primary action of the pharmaceutic agent is used for treating a specific disease state. By focusing on only the primary effects of a drug, a diverse remaining range of physiologic, as well as psychological effects, are ignored.

In the homeopathic model, the side effects are an important part of the agent's action and the body's response to them, and by ignoring them, a drug's range of usefulness is greatly limited, whereas its toxicity is increased. Hahnemann's empiric investigations not only led to new applications of medicines but provided a method for integrating the physical, mental, and emotional effects of a drug. This allowed the treatment of the totality of a patient's symptoms as a dynamic pattern of interaction.

Vitalists stress the teleologic behavior of organisms (i.e., the goal directedness and design in biological phenomena). Disease is therefore regarded as a positive expression of the organism's self-regulatory process in response to environmental or other stresses. Disease is not accidental but is rather the effort of the organism to ward off deeper or more internal disorganization. It is the natural wisdom of the body, the *vis medicatrix naturae*, or, using current scientific terminology, the tendency of the body to maintain homeostasis. Medical intervention often acts in conflict with these vital intracellular and extracellular regulatory functions.

Karl Menninger, in 1948, commented on this medical dilemma[10]:

> *I believe that clinicians have come to think more and more in terms of a disturbance in the total economics of the personality, a temporary overwhelming of the efforts of the organism to maintain a continuous internal and external adaptation to continuously changing relationships, threats, pressures, instinctive needs and reality demands … It is the imbalance, the organismic disequilibrium, which is the real pathology, and when that imbalance reaches a degree or duration that threatens the comfort or survival of the individual, it may correctly be denoted disease.*

Homeopathy is a method of specific induction of nonspecific resistance that stimulates the body's inherent defense and self-regulatory mechanisms, rather than by taking over a function of the body, initiating dependency on the medicine itself.

THE CLINICAL APPLICATION OF HOMEOPATHIC PRINCIPLES

The homeopathic clinical and therapeutic process consists of three interrelated processes: case taking, evaluation, and prescribing. The process is comprehensive and engages the observations of the patient, as well as those of the doctor. Hahnemann described the process in paragraphs 84 to 103 of the *Organon* and stressed the importance of distinguishing between chronic and acute, or self-limiting, disease.

The Homeopathic Interview

The initial history of complaints is elicited from the patient with as little interruption as possible (as long as the patient does not digress unduly), so that the patient's train of thought is not disrupted or directed along lines imposed by the physician's biases. According to Hahnemann:

> *The physician elicits further particulars about each of the patient's statements without ever putting words in his mouth, or asking a question that can be answered only by yes or no, which induces the patient to affirm something untrue or half true or else deny something really there to avoid discomfort or out of desire to please, thereby giving a wrong picture of the disease, which would lead to the wrong treatment.*

An entire review of symptoms is recorded in descriptive detail, taking into consideration all modalities that affect a symptom. Hahnemann emphasized the general symptoms (i.e., those affecting the entire organism), as the leading indications for the remedy. These key symptoms include mental and emotional affects, the

metabolism and its reactions to environmental stimuli, sleep positions, food cravings and aversions, thirst, body type, and all manifestations of unconscious and autonomic regulation.

Unique characteristic symptoms, particularly those regarded as "strange, rare, and peculiar," are important considerations in the selection of the remedy. These might be the expression of a paradoxic or unusual relationship, such as pain ameliorated by pressure or the sensation of the legs being made of wood or glass. The association of the start of a disease or symptom complex with an environmental or emotional event can be key and emphasizes the importance of an accurate and extensive interview.

Hahnemann emphasized the importance of taking a comprehensive case, particularly in chronic disease[11]:

> *In chronic diseases in women one should pay particular attention to such things as pregnancy, infertility, sexual desire, confinement, miscarriages, nursing, vaginal discharges, and the condition of the monthly flow, especially noting whether it recurs at intervals that are too short or too long, how many days it lasts, whether or not it is interrupted, the quantity, how dark with color, any leukorrhea before or after the flow. If there is leukorrhea, what it is like, what symptoms accompany it, what is its quantity, under what conditions does it appear, what brings it on?*

Because the patient's symptoms are the expressions of the body's attempts to heal itself, symptomatic treatment (i.e., many allopathic therapies) can impair the physician's ability to obtain vital information and complicate the taking of the case. This problem has also been recognized by some medical authors, such as Boyd, who stated: "We recognize that the pattern of disease has changed out of recognition during the last 30 to 40 years owing to modern drugs, particularly the antibiotics."[7]

Follow-Up and Case Evaluation

Considering the vitalistic and holistic perspective of the homeopathic approach, a clear definition of cure is necessary to establish the treatment goal. Mere palliation or suppression of symptoms at the cost of the overall vitality and function of the individual is considered negligent by the homeopathic practitioner. For example, if a patient's skin disease is treated and appears to resolve but is followed by asthma, fatigue, and confusion, the treatment is evaluated as having been suppressive. If, upon proper treatment, the more serious lung and systemic disruptions are alleviated and the previous skin lesions return, the patient is considered as progressing toward a cure. When further appropriate therapy results in final alleviation of the skin disease, without any undue stress to the patient, it is then considered a true cure.

This evaluative procedure is part of Hering's Law of Cure, an observation of the principles of curative responses that can be applied to any healing process, regardless of the school of thought. In true healing, according to this set of observations, symptoms follow these patterns:

- From above, down the body to the extremities
- From within to without (often in the form of discharges and other eliminative processes)
- From the most important organs (e.g., the central nervous system) to the least important organs (typically, the skin)
- In reverse order of their appearance (i.e., the chronologically most recent being replaced by those of the earlier stages of the disease, and, in some instances, earlier in the patient's life)

Homeopathy holds that the disease first affects the vital force and is manifested first by a change in the patient's well-being, long before any objective changes can be observed. Illness is usually first recognized when the patient becomes aware of the early manifestations of the disease.

Disease and cure must also be considered in the context of the belief system and culture of the patient. Much of what we call disease arises from the individual's inability to find meaning and purpose. Many forms of healing are capable of enabling the person to integrate into the fabric of daily life and of providing ways to help the person address personal needs for fulfillment.

In his study of disease, Hahnemann noted that there were inherited predispositions to disease, which he related to the improper treatment, and therefore suppression, of skin eruptions and venereal disease. He called these predispositions miasmas and, in 1828, published his findings in *Chronic Diseases: Their Nature and Homeopathic Cure*. He observed that many people, despite apparently healthy lifestyles, develop degenerative diseases. These often become established in childhood and continue to plague the person throughout life, despite medical treatment. He described three miasmas: psora, which represents a fundamental flaw in human ability to eradicate disease related to the suppression of skin disease; syphilis; and sycosis, which is caused by the suppression of the figwort, or what is now known as human papilloma virus. Hahnemann described the chronic effects of bacterial and viral diseases in his explanation of miasmas. In his discussion of viral diseases such as smallpox and other epidemic diseases, Hahnemann's descriptions of the nature of viruses and their treatment predate their discovery by 50 years. He was a contemporary of Edward Jenner and supported his use of smallpox vaccination.

More recently, George Vithoulkas, a contemporary homeopathic author and teacher, defined health on three levels: mental, emotional, and physical. The mind should be capable of functioning with clarity, rationality, coherence, and logical sequence. It should be capable of engaging in creative service for the good of others, as well as for the good of oneself, demonstrating a freedom from selfishness and possessiveness. On the emotional level, there should be a state of serenity free from excessive passion, a state that should not be confused with lack of emotional response generated as a protection against emotional vulnerability. Finally, on the physical level, there should be freedom from pain. The healing person should experience a subjective sense of well-being and a progressive increase in vitality.[12]

Prescription

Because homeopathy is oriented toward the administration of a single medicine at a time, careful prescribing is important. It is through the application of single medicines that homeopathic physicians have been able to record clinical verification of the provings and amass an impressive body of literature.

Combination homeopathic medicines have been introduced as specific remedies for diseases and therefore have not represented homeopathic methods, although many studies support their efficacy.

The process of selecting the correct remedy involves both careful study of the patient's symptomatology and medical history and matching these with the appropriate remedy. This requires a sound understanding of the homeopathic materia medica (see section on "The Study of the *Materia Medica*").

The symptoms of the homeopathic materia medica are indexed in repertories that have evolved both in reference books and computer analysis programs.

Homeopathic Pharmacy and Potency Selection

This leads to a discussion of what has remained the greatest mystery of homeopathic medicine (and the source of considerable ridicule and misunderstanding): the use of "potentized" substances.

As Hahnemann began his research, he found that when treating patients according to the Law of Similars there was an initial aggravation of the symptoms, the "healing crisis," when using the high dosages typical of that era. He empirically tried using progressive dilutions of the medicines, beginning with tinctures from plants and triturations with milk sugar for metals and salts. He made the dilutions serially by mixing 1 drop of the tincture to 100 drops of alcohol, which were then "succussed" (shaken by pounding against a resilient surface) vigorously. He found that, with increasing dilution, the severity of the aggravation lessened while the patient continued to improve, often with deeper and more enduring results. He called these diluted remedies "potentized." As an analytic chemist, he was aware of Avogadro's theories (they were contemporaries), but he persisted in evaluating dilutions beyond the point where chemical activity could be detected.

This challenge to the present understanding of therapeutic mechanism has been addressed by recent workers, who have suggested that the therapeutic properties of the remedy lie in the energetic impression they make on the diluting vehicle (typically alcohol and water or lactose). Various techniques have been used to determine if there is a physical difference between the potentized dilution and the unmodified vehicle. These studies have used ultraviolet spectroscopy, conductivity measurements, infrared spectroscopy, surface tension measurements, Ranian-Laser spectroscopy, nuclear magnetic resonance, and other methods. Much of this work has shown regular peaks and troughs in activity with progressive dilutions, and Heintz claimed that the peaks corresponded to the maximum effects found in the biological studies he reported (see section on "Basic Research").[13]

Mechanism of Action

To date there is no conclusive understanding of the mechanism of action of the potentizing process. However, this has not inhibited the use of potencies, which have been diluted by a factor of 100 up to 100,000 times ($10^{200,000}$). At this time, most explanations for the mechanism of homeopathic high potencies are provisional (such as the postulate that the remedies act in resonance with the magnetic fields of the body, or that the physiochemical properties of water can be modified by a solute and remain so even in the absence of the solute).[14]

This has not affected clinical practice or demonstration of efficacy in clinical trials any more than the use of aspirin did, despite the fact that the discovery of its mechanism of action through modulation of prostaglandins did not occur until the 1980s. There are many forces whose nature can only be recognized by their results (e.g., gravity). These observations of relationships, confirmations of experience, are the basis of an empiric system. Medicine remains an art in the field of science.

Interestingly, a group operating in the Hematology Department of the School of Pharmacy in Bordeaux, France, tested both the effect of common aspirin and homeopathic preparations on the vascular walls of rats. Aspirin at high concentrations (100 mg/kg) induced a decrease in platelet aggregation (amplitude and speed), as well as a decrease in the area of the thrombi (arterial and venous) and the number of emboli (arterials and venous).

Aspirin at ultra-low doses (9, 15, 30 CH) induced an increase in platelet aggregation (amplitude and speed), as well as an increase in the area of thrombi (arterial and venous) and the number of emboli (arterial and venous). The antiaggregation and antithrombotic action of aspirin at high concentrations (100 mg/kg) was inhibited by the concomitant injection of aspirin 15 CH.[15]

This confirmed Hahnemann's observations of the primary and secondary effects of medicines mentioned in the *Organon.*[16] Bellavite described these effects as "biologically active compounds (which) may cause inverse or paradoxical effects on a complex homeostatic system when either the doses of the compound, or the methods of preparation and of administering, or the sensitivity of the target system are changed."[17,18]

Research into both the pharmacologic effects of homeopathic preparations and the paradoxic effects of orthodox drugs that confirm the Law of Similars' underlying homeopathic prescribing are a growing body of literature. Certain pharmacologic substances when tested in high dilutions act on the same biological systems.[19-25]

The reaction to the high dilutions can also be the opposite to a drug at low dilutions (e.g., proinflammatory agents can be anti-inflammatory at high dilutions).[26-29]

Paradoxic effects of medicines are the basis of the Arndt-Schulz Law in pharmacology and hormesis. The Arndt-Schulz law states that weak stimuli slightly accelerate vital activity, medium strong stimuli raise it, strong ones suppress it, and strong ones arrest it.[30]

Southam and Erlich[31] reported the stimulatory effect of an antifungal agent when used at low doses and proposed the term "hormesis." Hormesis is defined as "the stimulatory effect of subinhibitory concentrations of any toxic substance on any organism."[32] Hormesis is considered a nonspecific phenomenon that increases the resistance and growth of the treated organism. It exists in all living organisms. This "action–reaction" model shows the efficacy of the "vital activity" in fighting the poison in a nonspecific way, although specific defense molecules are also synthetized.[33-38] A modern and important pathologic model showed that a single dose of an antitumoral immunosuppressive substance (cisplatin) induced increased lymphokine-activated killer activity.[39] Wagner and colleagues demonstrated that low doses of cytostatic agents stimulated human granulocyte and lymphocyte growth.[40]

The goals and methods of homeopathic pharmacy have their roots in earlier Paracelsian and spagyric medical systems. The challenge remains to define homeopathic empiric science in the context of a modern science. It may be that homeopathy presents a challenge to science itself that will bring forth new models for pharmacology. The more central challenge is for homeopathy to discover how it can apply its own critical methods to develop a more effective health care service.

The assumption that we can find substances in nature that can alter disease underlies the history of medicine and pharmacology, yet healing remains a mystery. Further studies are necessary to confirm and develop the understanding of the mechanisms and validity of homeopathic medicines.

Determination of Potency

In terms of clinical practice, general guidelines have evolved for the determination of potency. In the sixth edition of the *Organon*, Hahnemann recommended ascending the scale of potencies gradually. In paragraph 248, he suggested that the medicinal solution be "succussed anew with use." In chronic cases, the patient is directed to take one teaspoonful daily or every other day, and in acute diseases, as frequently as needed. If the solution is used up before the problem alleviates, the next higher dilution is used (if still indicated by the symptom pattern).[41]

The higher potencies, whose use largely developed in the United States, are repeated much less frequently and are generally reserved for the experienced practitioner. The more potentized the remedy, the closer it must meet the Law of Similars (i.e., the accuracy of the prescription must be high for a curative effect). Lower potencies are often repeated daily, depending on the condition being treated.

Several ranges of potencies include the decimal scale, which uses a 1:10 dilution; the centesimal scale, which is diluted 1:100; and the LM potencies introduced in the sixth edition of the *Organon*, using daily doses of 1:50,000 dilutions.

It is important to note that the sixth edition was unavailable until 1924, 76 years after Hahnemann's death. The predominant clinical application of homeopathic potencies had developed using an ascending scale. A single dose was used until its action had ceased, when the same potency would be repeated. When that potency seemed to no longer demonstrate an enduring effect, a higher potency was used. There have been regular arguments between low- and high-potency prescribers as to the most effective method.

The Study of the *Materia Medica*

Constantine Hering once stated the following:

> *A mere acquaintance with the principal symptoms cannot be called studying the* materia medica, *although we make it the basis of our study. The study of* materia medica *must be regarded and dealt with in exactly the same manner as that of other natural sciences.*

To give a perspective on the way in which homeopathic physicians organize the proving symptoms into clinical pictures, we draw from an essay on *Sepia* by E.B. Nash[42]:

> *This is another of our wonderful remedies of which the dominant school knows nothing, except what they have learned from us. Its chief sphere of action seems to be in the abdomen and pelvis, especially in women. No remedy produces stronger symptoms here. We quote from different but equally good observers.*
>
> *Sensation of bearing down in the pelvic region, with dragging pains from the sacrum; or feeling of bearing down of all pelvic organs. (Hahnemann)*
>
> *Labor-like pains accompanied with the feeling as though she must cross her legs and "sit close" to keep something from coming out through the vagina. (Guernsey)*
>
> *Pain in uterus, bearing down, comes from back to abdomen, causing oppression of breathing; crosses limbs to prevent protrusion of parts. (Hering)*
>
> *Prolapse of the uterus, of the vagina, with pressure as if everything would protrude. (Lippe)*
>
> *Experience has shown its value in cases of ulceration and congestion of the os and cervix uteri. Its use supersedes all local applications. (Dunham)*
>
> *No higher authority than the united testimony of these five of our best observers could be brought to show the action of* Sepia *upon the pelvic organs.*
>
> *Now when we come to examine the provings in Allen's* Encyclopedia*, we find that these symptoms were mainly produced by Hahnemann and his provers, and Hahnemann advocated proving remedies in the 30th, and some of them were produced by the 200th, especially those most strongly verified by black-faced type.*
>
> *We confess that we cannot understand how so many question the value of potencies for proving or curing* Sepia*, like* Sulphur*, affects the general circulation in a very marked manner. Flashes of heat with perspiration and faintness is almost as characteristic of this remedy as of* Sulphur*. But there are, with* Sepia*, more apt to be associated with them the pelvic symptoms already given, and they are also more apt to occur in conjunction with the climacteric. Indeed, these flashes often seem with* Sepia *to start in the pelvic organs and from thence to spread over the body.*
>
> *But this irregularity of circulation extends as far as that of* Sulphur*. The hands and feet are hot alternately, that is, if the feet are hot, the hands are cold, and* vice versa*. There is not so much sensation of burning with* Sepia *as with* Sulphur*, but there is actual heat, and the venous congestion, which seems to be the real state of the organs where the pressive bearing down et cetera is felt, is also accompanied with much throbbing and beating.*
>
> *This local congestion to the pelvic organs is not simply sensational. There are actual displacements in consequence of it, and the long continued congestion results in inflammations, ulcerations, leukorrheas and even malignancies or cancerous organizations. Induration with a painful* **sense** *of stiffness in the uterine region is characteristic.*
>
> *This pelvic congestion also affects the rectum in a marked degree. The rectum prolapses, there is a sensation of fullness, or of a foreign substance as of a ball or weight, and oozing of moisture from the rectum. Indeed, the rectal and anal symptoms are almost as strong as the uterine and vaginal. It is impossible to enumerate all the symptoms connected with the circulatory disturbances of* Sepia *in such a work as this, only a general study of the Materia Medica can do it.*
>
> *The urinary organs come in for their share of symptoms. The same pressure and fullness consequent upon the portal congestion reaches here. We will now proceed to give what we have found to be particularly valuable symptoms under the various organs in this region. "Pressure on bladder and frequent micturation with tension in lower abdomen." "Sediment in the urine like clay; as if clay burnt on the bottom of the vessel; urine very offensive* (Indium)*, can't endure to have it in the room, it is reddish or may be bloody." This is found mostly in women. With children there is one peculiar symptom which has often been verified. "The child always wets the bed during its first sleep."*
>
> *Upon the male organs I have found it particularly useful in chronic infection. There is not much discharge, but a few drops, perhaps, which glue up the orifice of the urethra in the morning; but it is so persistent and the usual remedies will not "dry it up." In my early practice I used to use a weak injection of* Sulphate of Zinc*, but it used to annoy me that I could not use it without resorting to local measures.* Sepia *does it in the majority of cases and* Kali iodatum *will do it in the rest. I have, where there was a thick discharge of long standing and the smarting and burning on urination continued, several times finished the case with* Capsicum.
>
> *As a rule, this long continued slight, passive gleety discharge is a result of weakness of the male genitals,* as is shown by a flaccidity of the organs and frequent seminal emissions. The emissions are thin and watery. Sepia *covers all of this and often sets all to rights in a short time.*
>
> *The mind symptoms of* Sepia *are like* Pulsatilla*, in that she is sad and cries frequently without knowing the reason why. So if in a tearful mind with uterine disturbances* Pulsatilla *should fail*

you, the next remedy to be studied is Sepia*. But there is another condition of mind not found under* Pulsatilla *or any other remedy in the same degree, and that is, that, notwithstanding there is no sign of dementia from actual brain lesion, the patient, contrary to her usual habit, becomes indifferent to her occupation, her house work, her family or their comfort, even to those whom she loves the best. This is a very peculiar symptom and a genuine keynote for the exhibition of* Sepia…

I once cured a very obstinate case of entero-colitis (so-called cholera infantum), after the complete failure of two eminent allopaths, with Sepia*, the leading symptom being, always worse after taking milk. Oozing of moisture from the anus finds its remedy here sometimes, but oftener in* Antimonium crudum*. The* Sepia *patient is very weak. A short walk fatigues her very much. She faints easily from extremes of cold and eat, after getting wet, from riding in a carriage, while kneeling at church, and on other trifling occasions. This fainting, or sense of sinking faintness, may be found in pregnancy, child bed, or during lactation; or, again, it may come on after hard work, such as "laundry work;" so it has come to be called the "washer woman's" remedy.*

As can be seen by this excerpt, the indications for a remedy are complex, requiring study and understanding.

RESEARCH IN HOMEOPATHY

Homeopathy arose from empiric observations and operates from empiric clinical evidence and phenomenologically descriptive fields. Samuel Hahnemann was the first to use the methodology of provings, to gather information about the reactions of healthy subjects to the ingestion of minute amounts of substances. Both clinical trials and laboratory research, although relatively sparse and often inconclusive, do point to efficacy and activity beyond placebo. Homeopathy has faced challenges in the scientific as well as political arena, because its mechanism of action is still unknown. For example, quoting from a recent review, "…according to current pharmacological theory it would appear impossible that homeopathic therapy could have any effect over placebo." [43] However, as the authors go on to say, "The available hypotheses for a possible mechanism of action, however, do not claim that homeopathic remedies act through pharmacological but through biophysical pathways and all include the idea of some form of information transfer…."[43] Despite adversaries who claim that research has determined that homeopathy is nothing more than placebo, homeopathy researchers, utilizing increasingly sophisticated research designs, continue to produce intriguing evidence regarding the effects and efficacy of homeopathic substances. This evidence, which emerged from several types of research, including provings, clinical trials, and laboratory studies, may soon converge to build a promising case for homeopathy's impact.

Evidence from a Modern Proving Study

Although traditionally provings, also called pathogenetic trials, first involved material doses of substances, Hahnemann himself, as well as later provers, conducted proving studies using potencies beyond Avogadro's number. One recent proving study provided convincing evidence that ultramolecular doses of homeopathic substances can produce symptoms different from placebo.[44] This double-blind, placebo-controlled experimental study randomized 25 medical doctors into three groups who received 30 CH potentized doses of either *Natrum muriaticum* or *Arsenicum album*, or an identical placebo. All substances were beyond Avogadro's number in terms of dilution. The main outcome parameter was number of remedy-specific symptoms per group. The actual remedies themselves were chosen randomly from a list of 20 already proven remedies that are frequently used in homeopathic practice; this list was not known to subjects or the study team, other than the study director and pharmacist; the two selected remedies were not known to anyone on the study team, including the study director. Participants were advised to ingest five remedy globules on day one, then 2 × 5 on day two, or until symptoms appeared, and then write their symptoms in a diary over 4 days. These symptoms were compiled and reviewed by an independent homeopathic expert, blinded to group assignment, who analyzed each symptom via a computer program for its typicality, or not, for one of the two remedies tested. The results showed that symptoms typical for the respective remedy were significantly more likely to occur in both the *Natrum muriaticum* or *Arsenicum album* groups, whereas nonspecific symptoms were more frequent in the placebo group ($P = 0.001$). Typical symptoms reported by subjects ingesting *Arsenicum album* included "strange restlessness"; "increased desire to swallow"; "lack of desire to urinate"; and "gushing diarrhea." Typical symptoms reported by subjects ingesting *Natrum muriaticum* were "difficulty concentrating"; "slight vertigo when seated"; "tearing pain in scalp"; "twitching in right eye"; and "cramping like labor in abdomen."[44] This impressive finding showed that nonmaterial doses of substances produced specific and distinctive effects—characteristic of the remedy—in subjects who were blinded to which remedy they were ingesting.

Human Clinical Trials

Although the above study provides evidence for an effect of ultramolecular homepathic substances on the human organism, what is of primary interest to humans, and particularly clinicians, is whether such effects are therapeutic. In one early classic study, Gibson et al[45] published a double-blind clinical trial of homeopathic treatment in rheumatoid arthritis. The 3-month study was elegantly designed in that the prescribing was individualized to the patient's symptoms and was controlled, on a double-blind basis, by giving half the patients the correct remedy and the rest a placebo. All patients continued to use conventional, nonsteroidal, anti-inflammatory drugs, and the treated group showed significant improvement in subjective pain, articular index, stiffness, and grip strength. Other published studies demonstrated the efficacy of homeopathic treatment for treatment of headache, bruising, cancer-related symptoms, attention-deficit-hyperactivity disorder in children, asthma, upper respiratory tract infections, otitis media, arthritis, allergies, male infertility, influenza, cardiac insufficiency, herpes, osteoarthritis, acquired immunodeficiency syndrome, and chronic fatigue syndrome.[46-83]

Meta-Analyses and Systematic Reviews of Human Clinical Trials

Hundreds of human clinical trials, of varying quality, with both positive and negative results, have now been carried out. Meta-analyses and systematic reviews have been helpful in identifying promising treatments and areas where more research is needed, thus moving the field forward.

In 1991, a meta-analysis by Kleijnen et al[84] was published in the *British Medical Journal* of a total of 105 controlled trials. The quality of trials was described as poor for two thirds of those reviewed. Positive results for homeopathic treatment were found in 81 trials, leading the authors to state, "The evidence in this review would

probably be sufficient for establishing homeopathy as a regular treatment for certain indications."

In 1997, Linde et al[85] published another meta-analysis of 119 trials that met the inclusion criteria; 89 had adequate data for meta-analysis, and 2 sets of trials were used to assess reproducibility. The combined odds ratio for the 89 studies was 2.45 in favor of homeopathy, with an odds ratio of 1.78 for the 26 good quality studies. The authors concluded, "The results of our metaanalysis are not compatible with the hypothesis that the clinical effects of homeopathy are completely due to placebo."

Accumulating evidence is beginning to make it feasible to carry out systematic reviews to evaluate homeopathy's use for treatment for specific conditions. For example, in a review of homeopathic treatment of people with human immunodeficiency virus or acquired immune deficiency syndrome, five controlled clinical trials were identified, with evidence for improved CD4 and CD8 counts, and specific physical, immunologic, neurologic, metabolic, and quality-of-life benefits. The author concluded that homeopathy might play a useful role as an adjunctive therapy in this condition.[82] Pilkington et al[83] examined the use of homeopathy for anxiety and anxiety disorders, concluding that homeopathy might be beneficial. One particularly fruitful and positive research, for which there are several positive trials, is in the use of homeopathy for treatment of respiratory allergies.[75]

Human Effectiveness Studies

Effectiveness research involves evaluation of a treatment's usefulness in more natural or real-world settings. For example, during World War II, isopathic preparations were given prophylactically, and homeopathic therapies were used in mustard gas burns. A subsequent statistical analysis found that these treatments yielded significant results compared with placebos. The remedies used were mustard gas, *Rhus toxicodendron*, and kali bichromium.[13]

More recently, Witt et al[86] evaluated health status changes of chronically ill patients after 8 years of homeopathic treatment. This prospective, multicenter cohort study involved 103 homeopathic primary care practices in Germany and Switzerland; a total of 3709 patients were studied, with the most frequent diagnoses being allergic rhinitis, headache in adults, and atopic dermatitis and multiple recurrent infections in children. Disease severity decreased significantly over this time, with considerable improvement in physical and mental quality of life. Another prospective multicenter observational study of 129 patients treated homeopathically by 48 physicians for low-back pain found sustained physical and quality of life improvements, with decreased use of conventional health care services and pharmacologic therapies.[87] A similar prospective multicenter observational study evaluated symptom changes in 212 adult patients with chronic migraines who were treated with individualized homeopathy by 68 physicians. Migraine severity showed marked improvement at 3 and 24 months, with improved quality of life and decreased use of conventional health services.[88]

Animal Studies: Field and Laboratory Research

In a now classic study, *Caulophyllum* (in the thirtieth centesimal potency) was given to 10 sows to test its efficacy in the control of stillbirths. The results showed a statistically significant drop in the number of stillbirths and led to a larger, uncontrolled study in a whole herd. After 4 months of therapy, piglet mortality dropped from 20% to 2.6%.[89]

Cloudhury obtained dramatic results from injecting mice intraperitoneally with kali phosphoricum, calcarea phosphorica, or ferrum phosphorica (in the thirtieth decimal potency) 12 days after implantation of fibrosarcoma. Of the 77 treated mice, 52% were cured and survived more than 1 year, whereas all of the 77 controls died within 10 to 15 days.[90]

Scofield, in his review article, discussed numerous experiments with humans, animals, and plants using isopathic treatment for poisoning and experimental liver damage and various in vitro studies.[13]

A number of studies have been conducted to investigate the ability for homeopathic preparations to effect either the elimination or consequences of toxic substances.

There is good evidence that homeopathy may be effective in assisting in the elimination and treatment of heavy metals and other toxins. Studies of arsenic,[91,92] bismuth,[19,20,93] lead,[94] mercury,[95,96] carbon tetrachloride,[21,26] a-amanitine (from the mushroom *Amanita phalloides*),[27] and carcinogens such as 2-acetylaminofluorene and phenobarbital[97] have been published.

The use of homeopathic dilutions of hormones and immunomodulators have shown potential. Immunostimulatory effects of high dilutions of thymic hormones and interferons were demonstrated in mice by Bastide's group.[27,98-101] Other studies demonstrated that extremely small amounts of antigens were specific for immunomodulation.[102-106] In one study, half of a group of mice were given preparations of reticuloendothelial tissue from *F. tularensis*-infected mice in six different serial agitated dilutions (SADs), three of which were beyond Avogadro's number in terms of molecular content. The other half of the group of mice were given control dilutents. All mice were then challenged with lethal doses of *F. tularensis* and evaluated for time to death and total number of deaths per group. The SAD preparations resulted in increased mean times to death (18.6 vs 13.7 days) and decreased mortality (53% vs 75%). The protective effect was not related to the level of dilution of substance.[106]

Magnani et al used a well-designed mouse model to examine the anxiolytic-like activity of several potencies of ultra-diluted *Gelsemium sempervirens*, compared with the drug buspirone and placebo. *Gelsemium*-treated mice spent more time in a lighted compartment (a measure of reduced anxiety), similar to the effects of buspirone and significantly greater than the placebo group. The authors concluded that *Gelsemium* acted on the emotional reactivity of mice, with anxiolytic-like effects even at ultra-high dilutions.[107]

These and other such dramatic results have tremendous implications in pharmacy, immunology, and clinical health care that demand continued research.

Basic Research

Clinical and experimental data obtained in studies about the effect of homeopathic preparations in inflammatory conditions present a considerable degree of reproducibility.[108-112]

The inability of Ovelgonne et al[113] and Hirst et al[114] to replicate their study published in the journal *Nature*, using the human basophil degranulation test (HBDT) to establish the ability for high dilutions to trigger the degranulation of anti–immunoglobulin-E caused considerable distraction from other more credible research.

Brown and Ennis[115] used different methods to demonstrate the efficacy of high dilutions of histamine to inhibit the activation of basophils using HBDT. Instead of measuring degranulation provoked by ultramolecular dilutions of anti–immunoglobulin-E, as Ovelgonne et al and Hirst et al did, they examined the inhibition of activation of basophils by ultramolecular dilutions of histamine.

The experiments used ultramolecular dilutions of histamine (15 to 19 c), prepared with vortexing (instead of succussion).

The main experiment, performed by all the laboratories, was based on inhibition of basophil activation as measured by degranulation. Flow cytometry experiments at three laboratories showed compatible results, with inhibition of activation as high as 43%. Nearly all experiments showed statistically significant inhibition of basophil activation.[116-119]

Experimental study of homeopathy in allergology[120] effects have been reported in vivo,[121-123] as well as in vitro.[124-128]

The physical properties of homeopathic preparations are gaining considerable understanding via research. Studies demonstrated that the physicochemical properties of extremely diluted solutions (EDS) are different from those of pure untreated water, notwithstanding the identical chemical composition of the two liquids.[129-131] The same conclusions were inferred by Lo.[132,133] Rey[134] showed that the structure of hydrogen bonds in pure water was different from that of an EDS obtained by an iterative procedure of successive dilutions and succussions, and was not identical as expected. Recent studies on the physicochemical properties of water provided evidence that the most studied liquid by far, water, still exhibits unexpected properties.[135-141] Lobyshev et al[142] showed that low concentrations and electromagnetic fields can produce large-scale realignments of its structure, which can be either reversible or irreversible. One can deduce from these studies that water and aqueous solutions are complex systems, capable of auto-organization as a consequence of small perturbations of various kinds.

The question of whether water can maintain "memory" of solutes in EDS is best understood by understanding the physical characteristics of water and its ability to form stable clusters and crystals. This aspect of physics is not widely studied but is well documented.[129-132,135,140,143]

Sukal et al[144] pointed out that ethanol molecules, via which potentized homeopathic substances are prepared and stored, are thought to promote or preserve water structures in the potentized substance. These researchers examined the Fourier transform infrared spectra of various ultra-diluted homeopathic substances—*Nux vomica* 30C, *Lycopodium* 30C, *Santonin*, 30C, *Cina* 30C, *Cina* 206C, and *Cina* 1006C—as well as their diluent media, 90% ethanol and ethanol 30C. The potencies differed from each other, and from their diluent media, in the number of oxygen–hydrogen bending vibrational bands, as well as their wave number, shape, and halfwidth of the bands. This study illustrated that medicated sucrose globules used in homeopathic practice can retain specific spectral properties and can be differentiated from each other by Fourier transform infrared spectra with regard to the oxygen–hydrogen bending vibrational band.[144]

Such meticulously designed and executed studies are bringing us ever closer to understanding the mechanisms by which homeopathy may work.

SUMMARY

Homeopathy plays an important role in the context of modern naturopathic medicine. Hahnemann emphasized the importance of lifestyle in the treatment of the patient. One of his primary dictums was to first remove the obstacles to cure, as he said:

> *While taking a case of chronic disease one should examine and weigh the particular conditions of the patient's day to day activities, living habits, diet, domestic situation, and so on. One should ascertain whether there is anything in them which may cause or sustain the disease and remove it to help the cure.*

Unfortunately, homeopathy is also an extremely challenging system to master, requiring both considerable understanding of case taking and materia medica, as well as extensive consultation time with the patient. It has therefore often been discarded, even by those aware of its efficacy. Although attempts have been made to reduce it to simpler systems (e.g., allergy desensitizations, vaccinations, Schuessler's cell salts, and isopathic preparations from diseased tissues and heavy metals), they are not considered strictly homeopathic unless prescribed according to their effects upon healthy people or the confirmed observations of cured symptoms.

The greatest challenge to homeopathy is not how it fits into the current scientific paradigm, but how it fits into health care. The same biases against homeopathy have been used against other nonpharmacologic approaches to medicine, including psychology and nutritional medicine.

The wide acceptance in the homeopathic community of unaccredited educational programs has favored the spread of nonclinically trained homeopaths. Naturopathic medical schools in the United States have remained one of the few resources for clinical training in homeopathy. Homeopathic medical schools in other countries have maintained homeopathy in the context of medical and clinical training.

There have been many individualized styles of prescribing introduced into homeopathy that have created breaches between different practitioners. In addition, many new medicines are being introduced without adequate clinical verification. Unfortunately, there are few forums for critical discourse within the homeopathic community.

The divisions between different schools of homeopathic practice are attempts to parlay new ideas against an orthodox view that solely seeks to maintain the integrity of principles developed by Hahnemann.

One basic argument by some of these schools has been that because a homeopathic prescription should not be based on a specific disease, extensive training in current medical sciences would not be primary. However, this ignores an essential part of Hahnemann's instructions. In the third paragraph of the *Organon* he stated, "The physician should distinctly understand…what is curable in diseases in general, and in each case in particular; that is, the recognition of disease."

Correct diagnosis is primary in understanding the context and pathogenesis of a disease. So it would not be possible to understand the relation of much of drug proving symptoms, their clinical application, and the evaluation of efficacy or subsequent case management without understanding the nature of disease. Homeopathy is proven in the context of good health care. It is a system of therapeutics, not a replacement for common standards of diagnosis and preventive care.

Homeopathy is representative of a principle found throughout nature and its role in bringing forth concepts of resonance, constitution, and holism are shared throughout fields of science and healing. Homeopathy represents an integrated holistic system of natural therapeutics. Its capacity for addressing psychosomatic disease and acute pathology as a dynamic process is unique. It has remained a coherent system, with extensive clinical verification, for more than 2 centuries. Homeopathy is an economical and effective method that has been established as an integral part of the medical system in many countries. With the resurgence of interest in natural medicine, this discipline will undoubtedly be more widely used.

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FURTHER READING

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Homeopathic Links, International Journal for Classical Homeopathy.
Simillimum, Journal of the Homeopathic Academy of Naturopathic Physicians.
The American Homeopath, Journal of the North American Society of Homeopaths.
The Homeopath, Journal of the Society of Homeopaths (UK).

Web Resources

Ad Hom. the Academic Departments of Homeopathy at Glasgow Homeopathic Hospital. Website www.adhom.com.
British Homeopathic Library is a library and information service dedicated to the research and practice of homeopathy. Website http://dspace.dial.pipex.com/hom-inform/index.shtml.
HOMINT Documentation Information System VSM. Alkmaar (Netherlands)/DHU, Karlsruhe (Germany) containing 35,000 references, major articles, homeopathic journals, literature-search on request. Arjo Bol, information specialist VSM/Susanne Rehm, DHU. E-mail vsm@gn.apc.org.
Homoepathic Educational Resources Database. Compiled by Dr. Russell Malcolm of the Glasgow Homoeopathic Hospital. E-mail ghl@gn.apc.org.

CHAPTER 40

Hydrotherapy*

Aimee Huyck, ND, PT and Kate Broderick, JD, ND, LAc

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INTRODUCTION

Hydrotherapy may be defined as the use of water, in any of its forms, for the maintenance of health or the treatment of disease. It is a cornerstone of naturopathic therapeutics, drawing on the vitalistic roots of the nature cure tradition as it stimulates the body's inherent self-healing mechanisms. The power of hydrotherapy is demonstrated by the persistence of its use now, two centuries after it was first systematized as a therapeutic modality in Western medicine. Naturopathic colleges and universities universally teach hydrotherapy as a core therapeutic modality and utilize it in their teaching clinics on general medicine, physical medicine, and specialized hydrotherapy shifts. Practicing naturopathic physicians utilize hydrotherapy widely in their practices, with some notable doctors, such as Cathy Rogers, ND; Nancy Welliver, ND; and Letitia Dick-Kronenberg, ND; having long-standing practices that emphasize hydrotherapy as their primary therapeutic modality. Additionally, many students at the various naturopathic colleges and universities seek preceptorships and supplementary education specific to hydrotherapy, as well as organizing campus clubs designed to give students greater exposure to and experience with this powerful medicine.

In his original chapter in the first edition of the *Textbook of Naturopathic Medicine*, Dr. Barry wrote: "Although one of the oldest known therapies, it [hydrotherapy] has received little attention from the research community, particularly recently. Much of the information presented here is compiled from older works which, although they lack the quantification available with current technology, show a remarkable attention to clinical effects and patient response." What these older works tell us about the uses and effects of hydrotherapy and the specific details of the means employed is invaluable, and physicians practicing hydrotherapy will find its greatest effectiveness by mining the wisdom of the original practitioners of Western hydrotherapy. For example, the individualization of a particular treatment to suit the vitality, or lack thereof, in each patient, must be attended to for treatments to have their greatest impact. It is this need for individualization that, like other aspects of holistic medicine, confounds the conducting of modern hydrotherapy research. However, in the last few years, attention has increased around the topic of hydrotherapy research and practice.

HISTORY

As one of the ancient methods of treatment, hydrotherapy has been used to treat disease and injury by many different peoples, including the Egyptians, Assyrians, Persians, Greeks, Hebrews, Hindus, and Chinese. For example, in the *Riga Veda*, circa 1500 BC, we read that "water cures the fever's glow."

Hippocrates used hydrotherapy extensively around 400 BC, and his writings concerning baths contain some of the earliest dictums on the therapeutic uses of water[1]:

> *In general it suits better with cases of pneumonia than in ardent fevers; for the bath soothes the pain in the side, chest and back; cuts the sputum, promotes*

*Editor's Note: We would like to acknowledge the foundational contributions to this chapter as authored originally by Robert Barry, ND, in the first and second editions, and updated by Doug Lewis, ND, for the third edition of the *Textbook of Natural Medicine*.

expectoration, improves the respiration, and allays lassitude; for it soothes the joints and outer skin, and is diuretic, removes heaviness of the head, and moistens the nose.

As these early writings show, the healing effects of water were observed and used therapeutically for centuries before the modern hydrotherapy movement. Modern hydrotherapy has had many contributors, including Sir John Floyer, William Winternitz, Johann Schroth, Johann Hahn, and J.H. Rausse to name a few.

Naturopathy grew out of the hydrotherapy movement, which traces its roots to two prominent hydrotherapists: Vincent Priessnitz of Austria and Father Sebastian Kneipp of Bavaria. Neither had formal medical training, but learned their craft through personal experience and astute observation. Priessnitz observed wounded animals bathing in cold water and was inspired to heal his own broken ribs using cold compresses. Father Kneipp healed his tuberculosis after reading Johann Hahn's Lectures on the *Wonderful Healing Power of Fresh Water.*

Priessnitz opened his first hydrotherapy institution at Grafenburg in 1826 and successfully treated over 40,000 people with little loss of life. Many of his patients were very ill and unable to be helped by medical doctors. He was arrested many times for practicing medicine without adequate training but eventually was given all the privileges of a medical doctor because his treatments were so effective.

Father Kneipp became an ordained priest in 1852 and was assigned as a chaplain to a number of parishes. He began using the water cure to treat his parishioners who were unable to be helped by medical doctors. Although church leaders did not approve of his practices and forbade him continuing, still he continued. He was transferred to Worishofen, where his successes became known, and people came from near and far to receive the cure. He never charged for his services, believing care should be available to anyone in need. His first book, *My Water Cure,* was written for the common people in clear and plain language and is an excellent instructional manual for anyone interested in hydrotherapy today.

Priessnitz's philosophy of water cure was brought to the United States in the mid-nineteenth century. Joel Shew, a medical doctor from New York, studied with Priessnitz and returned to the United States to start a hydropathy institute based on his teachings. An associate of Shew's, Russell Trall, MD, started his own hydrotherapy institute in Manhattan in the 1850s and later published the *Hydropathic Encyclopedia*. John Harvey Kellogg attended Trall's institute, and in 1900 published *Rational Hydrotherapy,*[2] in which he considered the physiologic and therapeutic effects of water, along with an extensive discussion of hydrotherapeutic techniques.

There were other notable individuals who were influenced by Priessnitz's water cure philosophy. Robert and William Wesselhoeft studied with Priessnitz and opened a sanitarium in Vermont after immigrating to the United States from Germany. David Ruggles, a black abolitionist who was treated by the Wesselhoefts, opened his own clinic; his patrons included fellow abolitionists Sojourner Truth and William Lloyd Garrison. Mary Gove Nichols, a woman denied any formal education but with a keen interest in medical science and determination to learn, opened her own institute in New York in 1845. She studied with both the Wesselhoefts and Joel Shew.

Benedict Lust, considered to be the father of naturopathy, was successfully treated by Father Kneipp and was charged with introducing the water cure to the United States. Lust successfully combined water cure with other nature cure modalities, establishing the foundation of naturopathic medicine. Henry Lindlahr, a wealthy U.S. banker suffering from diabetes, visited Kneipp after being told by his physicians that there was nothing they could do for him. He was put on a strict diet and daily regimen of cold water treatments. Once cured, he returned to the United States, completed medical training and opened a sanitarium in Chicago in 1906. He believed the vis medicatrix naturae was the true physician and wrote *Nature Cure,*[3] the definitive guide to the philosophy and practice of nature cure medicine.

Otis G. Carroll, one of the modern forefathers of naturopathic medicine, studied with Lindlahr and Alex Ledoux, another student of Sebastian Kneipp. He pioneered constitutional hydrotherapy, the combining of compresses with electrical stimulation, believing this therapy changed the constitution of the body's cells. Carroll's work was continued by Harold Dick, a naturopath in Spokane, Washington. His daughter, Letitia Dick-Kronenberg, worked with her father after completing her studies at the National College of Naturopathic Medicine and continues to practice and teach the hydrotherapy practices passed on to her.

Hydrotherapy has a long, rich history, and naturopathy is rooted in its practice. Thus, it is still taught in naturopathic educational institutions and practiced in their associated teaching clinics as a highly effective, fundamental naturopathic modality.



PHYSIOLOGIC EFFECTS OF WATER

The physiologic effects of hydrotherapy may be classified as thermal, mechanical, and chemical. Thermal effects are produced by the application of water at temperatures above or below body temperature. The greater the variation from body temperature, the greater the effect produced, other factors being equal and allowing for individual patient variability. Mechanical effects are produced by the impact of water acting on the body surface in the form of sprays, douches, frictions, immersions, whirlpools, etc. Chemical effects are produced when water is taken by mouth or used to irrigate a body cavity, such as the large colon. Thermal effects are the most commonly used therapeutically and are, thus, the main subject of this chapter.

In general, hot relaxes and sedates, whereas cold stimulates, invigorates, and tonifies. However, very hot can stimulate and also be destructive, whereas prolonged cold can be depressive and destructive. A comparison of the effects of hot and cold on several body systems is given in Table 40-1.

Principles of Blood Movement with Hydrotherapy

To promote healing, either locally or systemically, it is important to maximize circulation of well-oxygenated, nutrient-rich blood, which also has the effect of carrying away metabolic and other waste products. Hydrotherapy techniques are one of the most effective means of accomplishing this, especially when used in conjunction with proper levels of activity, optimal nutritional intake, and adequate detoxification.

Using different temperatures of water, one can either increase or decrease the rate of blood flow (BF) through an organ or area of the body and can either increase or decrease the total volume of blood in an organ or area of the body, according to whether the area is anemic or congested. To accomplish these changes, five relevant physiologic principles must be considered:

- Revulsive effect
- Derivative effect
- Spinal cord reflex

TABLE 40-1 **Comparison of the Effects of Hot and Cold on Several Body Systems**

SYSTEM/ORGAN	COLD		HOT
	PRIMARY	SECONDARY	
Skin			
• Blood vessels	Constriction	Dilation	Dilation
• Respiration	Decreased	Increased	Increased
• Heat loss	Decreased	Increased	Increased
Blood vessels	Constriction	Dilation	Dilation (constriction if intense)
Heart	Rate increased	Rate decreased	First decreased, then increased
Nerves	Numbed		Excited
Muscles	Volume decreased		Volume increased
Respiration	Slowed and deepened		Rate increased
Stomach	Motility and HCl increased		Motility and HCl decreased

HCl, hydrochloride.
Modified from Kellogg JH. Rational hydrotherapy, ed 4, Battle Creek, MI: Modern Medicine, 1923:721-722.

- Collateral circulation
- Arterial trunk reflex

Revulsive Effect

The revulsive effect provides a means of increasing the rate of BF through an organ or area of the body and is most effectively accomplished using contrast hydrotherapy: alternating hot and cold in the form of compresses, baths, showers, sprays, etc. Local contrast applications produce marked stimulation of local circulation. A 30-minute local contrast bath produces a 95% increase in local BF when the lower extremities alone are immersed. When all four extremities are immersed at the same time, there is a 100% increase in BF in the upper extremities and a 70% increase in the lower extremities.[4]

Contrast applications to the area of skin that is in a reflex relationship (see Spinal Reflex Effect, following) to an organ increase the functional activity of that organ. Hence, liver function is increased by contrast application over the right upper quadrant of the abdomen.

Several studies have researched the optimal treatment times for revulsive effects. Woodmansey et al[5] found 6 minutes of hot application and 4 minutes of cold to be optimal for the British subjects he studied. Krussen[6] found 4 minutes of hot and 1 minute of cold to be the best treatment protocol. Moor[7] stated that 3 minutes of hot followed by 30 to 60 seconds of cold provided satisfactory clinical results. These variations create an inference that, due to variations in patients and locales, it is best for practitioners to determine their own ideals, based on their own observations of clinical results. Most importantly, the cold application needs to be long enough to produce vasoconstriction, which can occur in as short a period as 20 seconds. Additionally, the course of treatment should always end on cold to discourage congestion in the area.

Repetition of applications is another important variable to consider when applying revulsive treatments. A series of three hot/cold applications seems to be practical. Most individuals show a decreasing reaction to repeated applications of cold.

The revulsive effect is ideal for treating situations presenting primarily as congestion, for example, the use of alternating hot/cold compresses over the face for sinus congestion. As a powerful decongestant, the revulsive effect also acts as an analgesic for pain resulting from congestion. Because of its marked stimulation of local circulation, the revulsive treatment is an exceptionally effective hydrotherapeutic procedure, and one of the most generally useful considering its simplicity.

Derivative Effect

Congestion can also be treated using the derivative effect, which moves blood from one area of the body to another. This effect is best obtained by the prolonged use of either cold or heat, depending on whether one wants to draw blood into an area (hot application) or to drive blood out of an area (cold application). For example, prolonged application of heat to the feet, as with a hot foot bath, will decrease congestion in the head by increasing BF to the feet. Alternatively, a cold compress can be applied to the forehead or back of the neck to restrict BF in the head, or the two treatments can be combined for even greater effect. This form of treatment is often quite effective for certain forms of congestive headaches.

Spinal Reflex Effect

A sufficiently intense local application of hot or cold not only affects the immediate skin area but also causes remote physiologic changes, mediated through spinal reflex arcs (see Moor[7]), thus providing a means of affecting a distant area of the body through a local application. These effects have been carefully observed over many years and have led to a mapping that correlates each surface area with a corresponding internal area and/or organ. Most texts on hydrotherapy contain such a diagram.[2,7]

Hewlett,[8] Stewart,[9] and Briscoe[10] all noted changes in BF in the opposite arm and hand when one arm and hand were placed in hot or cold water. Poulton[11] demonstrated that esophageal function could be influenced by irritation of the skin over the sternum. Bing and Tobiassen[12] showed reflex relationships between the skin of the abdominal wall and the colon. They also demonstrated a reflex relationship between the lungs and the skin of the chest wall.

Fisher and Solomon[13] stated: "externally applied heat not only decreases intestinal blood flow, but also diminishes intestinal motility and decreases acid secretion in the stomach, while cold has the opposite effect." This is an example of a contrary effect, in which the reflex effect is the opposite of that observed in the local reflex skin area (i.e., local heat increases BF to the local skin, but decreases BF to the reflex organs).

Tables 40-2 to 40-4 show some of the observed reflex effects of hydrotherapeutic procedures.[7]

Collateral Circulation Effect

The collateral circulation effect may be considered a special case of the derivative effect.[2] In general use, the derivative effect involves blood volume changes from one area of the body to another, as previously discussed. The collateral circulation effect, in contrast, more specifically considers the local circulatory effects on deep (rather than superficial) collateral branches of the same artery.

Considering the circulatory patterns of a large body part, such as the thigh, it is clear that both superficial and deep areas are

TABLE 40-2 **Reflex Effects of Prolonged Heat**

APPLICATION LOCATION	EFFECT
One extremity	Vasodilation in contralateral extremity
Abdominal wall	Decreased intestinal blood flow, intestinal motility, and acid secretion
Pelvis	Relaxes pelvic muscles, dilates blood vessels, and increases menstrual flow
Precordium	Increases heart rate, decreases its force, and lowers blood pressure
Chest	Promotes ease of respiration and expectoration
Trunk	Relaxes ureters or bile ducts and relieves renal or gallbladder colic
Over kidney	Increases production of urine

TABLE 40-3 **Reflex Effects of Prolonged Cold**

APPLICATION LOCATION	EFFECT
Trunk of an artery	Contraction of the artery and its branches
Nose, back of neck	Contraction of the blood vessels of the feet and hands and nasal mucosa
Precordium (ice bag)	Slows the heart rate and increases its stroke volume
Abdomen	Increases intestinal blood flow, intestinal motility, and acid secretion
Pelvic area	Stimulates muscles of the pelvic organs
Thyroid gland	Contracts its blood vessels and decreases its function
Hands and scalp	Contraction of brain–blood vessels
Acutely inflamed areas	Vasoconstriction and relief of painful joints or bursae

supplied by the same artery. A hot application to this area dilates the surface vessels, drawing blood to the superficial areas and concurrently decreasing the BF to the deep areas. A cold application causes the opposite effect. Local compresses and fomentations are the most commonly used techniques to affect collateral circulatory changes.

Arterial Trunk Reflex

The arterial trunk reflex effect is a special case of the general reflex effect.[2] Prolonged cold applied over the trunk of an artery produces contraction of the artery and its branches distal to the application. Prolonged hot applications have the opposite effect, producing dilatation in the distal arterial bed. For example, prolonged cold application over the femoral artery in the groin will decrease BF in a foot or ankle with an acute injury involving either internal or external hemorrhage. After the acute phase, prolonged hot applications can be used to increase circulation and speed healing of the injured part.

Local and Systemic Effects of Cold Applications

Local cold applications produce vasoconstriction in the local tissues, leading to a decrease in local circulation. If the cold application is long, intense, and covering a large enough area, a slowing of the general circulation may occur. The migration of leukocytes and inflammatory agents from the vascular system into the local tissues and local metabolic activity are decreased, leading to a more moderated healing response to acute injury. Nerve conduction velocities are diminished, resulting in decreased sensation, including pain, as well as slowed motor response. Muscle tissue tends to contract, and connective tissues become less plastic. Thus, cold applications may assist in the tonification of muscle tissue, leading to benefits such as increased urinary sphincter tone. General applications of cold are hypothermic and produce a peripheral vasoconstriction with shunting of the blood to the core.

TABLE 40-4 **Reflex Effects of Short Cold**

APPLICATION LOCATION	EFFECT
Local application of intense cold as brief as 30 s	General peripheral vasoconstriction
Face, hands, and head	Increase in mental alertness and activity
Precordial area	Increase in heart rate and stroke volume
Chest, with friction or percussion	Initial increase in respiratory rate, then slower, deeper respiration

Water temperatures below 50°F are considered very cold and may be depleting to many patients if used generally, although ice packs can be an effective local treatment for swelling and pain. Temperatures between 50°F and 70°F are considered cold and are often the more desired range for many cold water treatments.

Cold applications are often prescribed for the relief of pain. Saeki[5] found cold, but not hot, applications to be useful in the relief of prickly pain sensations experimentally induced in study subjects. Pain sensations were measured on the visual analog scale, and skin BF and skin conductance levels (SCL) were also measured. Cold applications decreased pain, BF, and SCL, whereas hot applications increased pain, BF, and SCL.

In 2002, a small (19 patients) study entitled "To Evaluate the Effect of Local Application of Ice on Duration and Severity of Acute Gouty Arthritis" was published.[14] Treatment and control groups both received oral prednisone 30 mg tapered to 0 mg over 6 days and colchicine 0.6 mg daily. The treatment group received daily ice applications, whereas the control group did not. After 7 days, treatment group participants had a significant reduction in pain compared with the control group.

Cold water is very effective in lowering body temperature caused by fever due to illness or increased core temperature from exposure or exercise. Cold sponging has often been recommended for the reduction of fevers in children. Two articles published in 1997[15,16] compared the use of sponging to oral antipyretics. Both studies concluded that sponging was more effective than medication in the first 30 minutes, but after that, the antipyretic medications were more effective. This makes sense, because it takes time for the medications to be absorbed and circulate in the body, whereas the body responds immediately to the application of water to the skin. One of the primary precepts of naturopathic medicine is to work with the vis medicatrix naturae, and fever is one of the body's responses to acute illness, assisting in the healing process. Lindlahr stated, "every so called acute disease is the result of a cleansing and healing effort of nature."[3] The benefit of sponging to reduce fever versus use of antipyretic medication is the ability to better control how much we reduce the fever, if at all.

After a cold application, a secondary, or indirect, effect occurs, also termed the "reaction." This effect is in contrast to the primary effects, as the body responds over time to the general decrease in circulation from the application of cold. Secondary effects include peripheral vasodilation, increased white blood cell and red blood cell circulation, increased metabolism, increased muscle tone, and sense of vigor and well-being. If the cold application is a short one, the reaction follows quickly, its intensity reflecting the intensity (i.e., coldness) of the application. The reaction to a brief cold application produces a slowing of the heart rate with a mild increase in blood pressure. The secondary effects are what is utilized primarily in nonacute cold water treatments.

Local and Systemic Effects of Hot Applications

Heat may be applied to the body in various ways, including hot packs, fomentations, steam, baths, and showers. All hot applications produce physiologic responses that are attempts by the body to eliminate heat to prevent a damaging rise in local and systemic temperatures. The effects produced by hot applications depend on the mode, temperature, and duration of the application and the condition of the patient.

Water at 98° F or above is generally perceived as hot, and water higher than 104° F is considered very hot. At 120° F, an immersion bath becomes unendurable, although small areas of the body, such as the hand, may be conditioned to endure a temperature of 10° to 15° higher for short periods. The mucus membranes, unlike the skin, may endure temperatures as high as 135° F, which accounts for our ability to drink very hot liquids or benefit from steam inhalation treatment. Although exposure to the high temperatures of hot tubs and saunas has become quite popular in recent years, Kneipp, Preissnitz, and Kellogg all believed that repeated and prolonged use could weaken the individual unless counteracted by frequent cold applications, such as showers or ablutions.[2]

Local hot applications result in vasodilation, with resulting increase in capillary BF, oxygen delivery to the tissues, local metabolic activity, and migration of lymphocytes through vessel walls and into the local tissues. Local sweating is increased, and muscle relaxation occurs. Intense moist heat applied for a long period of time (several minutes) has a depth of penetration not exceeding about 3.4 cm. The increased BF through the area carries away heat conducted into the tissues from a hot application and limits the depth of penetration. (This "radiator-like" effect can be overcome by more intense applications of heat, and deep tissue destruction can occur.)

General hot applications can have dramatic effects on the cardiovascular system. Peripheral dilation occurs with a marked increase in BF (as much as 400%), pulse rate (6 to 10 beats/min per 1° F rise in body temperature) and pulse pressure, and a decrease in cardiac stroke volume. Respiratory rate increases 5 to 6 breaths/min per 1° F rise in body temperature. Hyperventilation may occur and result in respiratory alkalosis. The blood volume increases as a result of the uptake of fluids from the tissues, leading to a decrease in the hematocrit. A transient leukopenia occurs in the first few minutes after a hyperthermia treatment, followed thereafter by leukocytosis. Sweating increases, leading to a loss of water, salt, urea, uric acid, creatinine, sulfates, lactic acid, and other metabolites.

A 2009 study of congestive heart failure patients showed improved biventricular cardiac function, increased output, decreased heart rate, and decreased blood pressure during warm water therapy over an 8-week period. The beneficial effects were found statistically significant during the therapy but did not change cardiac function overall. Authors concluded that warm water therapy is safe for patients with congestive heart failure.[17] Similarly, a 2003 study showed improved mood, physical capacity, enjoyment, and heart failure-related symptoms (subjective), as well as significant decreases in heart rate and rate–pressure product at rest in patients with congestive heart failure. This study used warm water baths and cold water pours, which might account for the sustained therapeutic effect.[18]

In addition to the local hot applications discussed in previous sections, local hot applications are common and varied. For example, inhalation of steam for the treatment of the common cold has often been prescribed. Four studies[19-22] published between 1987 and 1994 demonstrated the benefit of steam inhalation for nasal symptoms, with one of these studies[21] demonstrating a decrease in inflammatory mediators in the local tissues.

A recent study of the treatment of benign prostatic hypertrophy using thermotherapy demonstrated a significant decrease in bladder outlet obstruction by using heated water in a closed loop catheter system.[23] A Cochrane Review[24] of interventions for chronic abacterial prostatitis concluded: "The routine use of antibiotics and alpha blockers for chronic abacterial prostatitis is not supported by the existing evidence. The small studies examining thermal therapy appear to demonstrate benefit of clinical significance and merit further evaluation."

Physicians do not normally think of hot applications in the treatment of acute sports injuries. However, one recent study[25] compared the use of hyperthermia to therapeutic ultrasound. In comparing 21 randomized patients with acute muscular injuries of different sites and severity to 19 controls, researchers discovered that after 2 weeks of treatment, the hyperthermia group had significantly less pain and faster hematoma resolution.

The presence of fever has long been associated with better survival and shorter duration of disease in cases of infection. Although the concept of modulating fevers in acute illness using sponging rather than antipyretics was discussed previously, hydrotherapy can also be used to enhance or induce a fever in acute or chronic infections to mimic or increase the body's natural infection fighting capacity. Many studies have demonstrated the causes of that beneficial response. Four studies reviewed for this chapter[26-29] demonstrated the activation and mobilization of blood mononuclear cells with hyperthermia treatments. One of these studies[26] demonstrated significantly increased serum cortisol, plasma norepinephrine, and plasma epinephrine, and hypothesized that these elevated stress hormones were responsible for the rise in mononuclear cells. One study[28] concluded that "fever-induced Hsp70 expression may protect monocytes when confronted with cytotoxic inflammatory mediators, thereby improving the course of the disease."

GENERAL GUIDELINES FOR HYDROTHERAPY

1. The first rule of hydrotherapy is the same as for any therapy: treat the whole person. This involves considering all aspects, including medical history, current condition, current medications, and any other relevant information.
2. Use hydrotherapy treatments in a coordinated and integrated manner with any treatments or medications the individual is receiving.
3. To provide as precise a treatment as possible, grade the patient in terms of age, severity of problems, vitality, emotional state, circulatory condition, etc. A patient's body temperature, along with their subjective general feeling of warmth or chilliness, should be used as a guide as to how intense the hot or cold used in a treatment should be. Be especially careful with young

or elderly persons, and individuals who are chilly, have cardiac problems, are weak or debilitated, are obese, or have other severe physical compromises.
4. If a patient becomes chilled during a treatment, it may be necessary to stop the treatment and warm the person. Sometimes it may suffice to warm the person (by such means as hot drinks, friction rubs, additional blankets, or a hot water bottle to the feet) while continuing the treatment. If the person fails to warm after these attempts, then stop the treatments and warm him or her. Never allow a patient to become chilled to the point of shivering.
5. After a hydrotherapy treatment, avoid excessive heat or cold and/or drafts. The patient should be warmly dressed but not overly so.
6. It is best to do the treatment at an optimal time of day for that patient. It is best to do treatments before meals or at least one hour after a meal.

As with any therapy, it is important to practice hydrotherapy with a critical eye, noting unusual reactions and physiologic effects. Many physiologic parameters, such as urine chemistries and microscopic components, specific gravity, body temperature, and blood sugar levels, may be easily monitored and recorded during treatment. This information helps to optimize the treatment protocols, stimulates further research, and validates hydrotherapy as an effective and useful therapeutic modality.

Cautions and Contraindications

Although hydrotherapeutic procedures are generally low force and gentle treatments, they may in some situations produce unexpected or undesired effects. These effects may be the result of improperly applied treatments, but they may, in some cases, result simply from the individual's reaction to the treatment. They may, in the long term, be beneficial. Anytime an individual experiences an undesired effect after a treatment, the therapist should review the treatment's length, intensity, and appropriateness for the individual. If more treatments are considered, they may need to be adjusted to modulate the effects.

Some of the possible side effects of hydrotherapy treatments are headache, vertigo, nervousness, aches and pains, insomnia, hyperventilation, nausea, palpitations, lightheadedness, and chilliness. In most cases, these effects are self limiting and often respond well to simple intervention and/or rest.

If a patient has an adverse reaction, discontinue the treatment and assess the patient's needs. If the patients are chilled, warm them; if lightheaded or dizzy, make sure they are well hydrated, assess for low blood sugar, and allow them to rest. If complaining of headache or nausea, the patient could be detoxifying, so encourage plenty of water and rest. Coaching the person in deep, slow-breathing exercises for several minutes often relaxes them and decreases the reaction.[30] As with any treatment, use professional judgment as to the significance and cause of the patient's response and employ appropriate intervention. Although undesired effects may occur during or immediately after treatments, they may also occur as long as 24 hours later. Therefore, it is important for practitioners to be available to patients during off-duty hours.

Pregnancy

What to do or take in pregnancy is always a concern. Bathing in hot water is no exception. Ridge and Budd,[31] in a letter to the editor of the *New England Journal of Medicine*, summarized these concerns and concluded "that for pregnant (or potentially pregnant) women using a spa pool at a water temperature of 40° C (104° F), any immersion longer than 10 minutes may be too long."

Hypertension and Cardiovascular Disease

Two studies published in 1998[32,33] demonstrated no adverse cardiovascular effects from bathing in water above 40° C and a response to heat stress no different from normotensive subjects.

Cancer

A synergistic effect has been demonstrated with hyperthermia and radiation treatments given in cancer care. Any patient receiving radiation therapy should not be indiscriminately treated concurrently with hyperthermia.

Diabetes

For individuals with insulin-dependent diabetes, the application of heat to the extremities is to be approached with caution. As discussed previously, increased BF with hot application serves to conduct heat away from the area of application. In diabetics with poor circulation to the extremities, less heat is dissipated, and the local tissue temperature rises more than in tissues with normal circulation. It is safer to use less extreme temperatures in individuals with impaired circulation. Additionally, the application of heat increases tissue metabolism. With impaired circulation, tissue metabolic needs can quickly exceed the nutrients and oxygen available from the blood, and cells may die from oxygen depletion.[30] Therefore, very hot applications to the extremities are generally contraindicated in diabetics, whereas mild to moderately hot applications can be quite effective for improving circulation and increasing healing of diabetic ulcers.

For diabetics with conditions in which a hot application to the feet would normally be the treatment of choice but is contraindicated for the patient, a large hot compress to the lower abdomen, groin, and thighs can be used instead to get a reflex reaction in the lower extremities.

Diabetics may also display peripheral neuropathies that decrease their ability to sense heat, thereby increasing the possibility of causing a burn with hot applications. Likewise, individuals with neurologic injury or disease should also be treated with caution during hot applications and be guided to test the water with some part of their body that does not have decreased sensation.

HYDROTHERAPY TECHNIQUES

The various ways in which water may be applied to the human body therapeutically are only limited by the imagination of the practitioner. J.H. Kellogg, in his seemingly exhaustive treatise on hydrotherapy,[2] devoted 541 pages to describing the techniques of hydrotherapy.

Compresses

Compresses are of four basic types: hot, cold, warming, and alternating hot and cold. They are each applied using cloth or other compress material, which is wrung out to the desired amount of moisture and then applied to any surface of the body. A single compress consists only of layers of the wet material, whereas a double compress is one in which the wet cloth is completely covered by dry material, usually wool, which acts to prevent cooling by evaporation or radiation.

Compresses are commonly referred to by the area of the body to which they are applied, such as the throat, head, joint, trunk, or limb.

Cold Compresses and Packs

A cold compress consists of a cloth wrung from cold or ice water and then applied to the body. Some practitioners may add solutes to the water, such as salts. Herbs may also be used to create a more specific effect from the compress. Some commonly used herbs are hayflower, oatstraw, and fenugreek, made as teas into which the compress cloths are dipped. A cold pack is used if the goal is to cool the tissues more aggressively. Packs may be made from crushed ice or purchased as commercially available gel packs that are cooled in the freezer.

Cold compresses are renewed frequently (every one to five minutes) to maintain the primary cold effect, whereas packs remain cold longer. The temperature of a cold compress depends on the specific problem being treated, as well as the state of health of the patient. In general, the colder the application, the shorter the period of application.

The cold pack or compress has primarily a vasoconstrictive effect, both locally and distally. Due to this effect, it may be used to prevent or relieve congestion, reduce BF to an area, prevent edema after injury, inhibit inflammation, and relieve pain due to congestion. It may also be used to reduce body temperature when applied over a large area of the body. Cold compresses should not be used locally in a person who is chilly or who has pleuritis, sinusitis, or acute asthma, as these conditions may be seriously aggravated.

Hot Compresses and Fomentations

The hot compress is a prolonged application of moist heat to a local area of the body. A fomentation is a special type of hot compress that provides prolonged exposure at a higher temperature.

Hot compresses and fomentations have several therapeutic effects. In situations of pain resulting from spasm, they may create an analgesic effect, although this does not hold true for pain resulting from congestion. They also create a derivative effect, increasing BF to the periphery, thereby decreasing internal congestion. By applying short, intensely hot compresses, a stimulation effect may be obtained. This may be used to increase BF to a part, to stimulate certain organ functions, to decrease others, and to produce tissue warming and relaxation. Mildly hot compresses may be beneficial for their sedative effects in treating insomnia, nervous tension, and mild muscular spasms.

Fairly hot compresses may be applied directly to the skin surface, with care taken to not burn or startle the patient. When treating the elderly or those with impaired neurologic function, edema, or decreased circulation, special caution must be taken. Fomentations are commonly applied at temperatures that are not tolerated directly on the skin, and therefore must be applied over a bath towel.

Warming Compresses

The warming compress, also known as the cold double compress, consists of a cold compress covered completely by several layers of dry material, such as flannel or wool, which is allowed to remain on until warmed by the body. The layers of dry material prevent heat loss by evaporation, thereby permitting accumulation of heat. Warming compresses are used most commonly in upper respiratory infections, such as sore throats, bronchitis, influenza, pneumonia, and swollen lymph glands in the neck. They may also be applied over the trunk or abdomen, genital area, joints, limbs, or feet.

A classic example of the warming compress is the wet sock treatment, which is used for congestive headaches, sinusitis, and otitis media in young children. Thin cotton socks are wrung from cold water and pulled onto the feet. These are then covered with a pair of wool socks and left overnight to be warmed by the patient. Frequently, the socks are dry by morning.

The primary effect of the warming compress is to increase local circulation, thereby providing for increased nutrition and oxygenation of the tissues, as well as increased elimination of metabolic waste from the area. In the previous example of wet socks, it is the derivative effect of the treatment that is desired. As with cold compresses, the temperature of the initial application depends on the state of the patient and the condition being treated. In general, the colder the application, the stronger the secondary reaction to the cold. Since weak and debilitated patients are unable to generate a strong secondary reaction, a cool rather than a cold application may be indicated. The same general precautions as for a cold single compress should be followed.

Alternating Hot and Cold Compresses

One of the best ways to increase blood flow through an area is using the revulsive property of water via an alternation of hot and cold. Such treatment starts with a hot compress for 3 to 5 minutes, alternating with a cold compress for 30 to 90 seconds. This sequence is repeated three to five times, always ending with cold. This treatment is very effective for reducing swelling in a joint after an injury or surgery.

Baths

Baths are full or partial immersions of the body into water of various temperatures: cold, hot, neutral, or contrasting. Bath waters may contain additional substances such as salts, minerals, herbs, or medications and may be in an agitated state, as with a whirlpool. In addition to the thermal effects, upon immersion of the body in water, hydrostatic pressure is exerted on the body surface, which has the effect of increasing venous and lymph flow from the periphery and increasing urine output.

Hot Baths

Hot baths are given within a temperature range of 100° F to 106° F for 20 to 60 minutes or longer. They are indicated for rheumatoid arthritis, to aid in relief of muscular spasms, for cleansing the body, to stimulate the immune system, to induce sweating, and many other purposes, and are most useful for producing a hyperthermic response in the tissues or to raise core temperatures. As stated previously, hyperthermia treatments have been found useful in the treatment of infections and malignancies. Water immersions for hyperthermia have the benefit of low cost and more consistent heating of tissues.

When performing local immersions, the water temperature may be as high as is tolerable. The duration of treatment is typically 15 to 20 minutes. Treatment frequency depends upon the status of the patient and the condition being treated.

Whole body immersion at home should be limited to a water temperature of approximately 104° F and not longer than 30 minutes. Patients should have assistance when performing hyperthermia treatments at home.

When hyperthermia treatments are given in the office, close supervision may allow more aggressive treatment. The water temperature may be increased to 106° F, and the duration of treatment may exceed 60 minutes. Patient tolerance is the key to performing safe and effective hyperthermia.

When performing hyperthermia treatments, the following precautions should be observed regardless of whether the treatment is performed at home or in the office:

- Hypotension may result from hot immersions. When arising from the tub, patients may become lightheaded and lose their footing, so caution should be used in rising slowly and having assistance nearby.
- Patients should not take hyperthermia treatments on either an empty or full stomach. Too little food may result in a hypoglycemic episode, and too much food may result in nausea and vomiting.
- Hyperventilation sometimes occurs. On rare occasions patients may go into early tetany from respiratory alkalosis. Being present with the patient and coaching his or her breathing can prevent this.
- Headaches can and often do occur. These can be prevented by the early and frequent use of cold compresses to the head, face, and ears.

The sauna or steam bath can often be used interchangeably with the immersion bath. Immersion, sauna, and steam are most similar with respect to their immune stimulant and detoxification benefits.

In most instances, hot immersions are best followed by a brief cool bath, shower, or spray. Prolonged hot tub baths are never appropriate in the very old or very young, weak or anemic persons, individuals with severe organic disease, or in anyone with a tendency to hemorrhage.

Given for brief periods, they may help to reduce fevers by creating peripheral vasodilation, thereby promoting an increased heat loss.

Neutral Baths

The neutral bath is a full immersion bath given at the average temperature of the skin in which the recipient has neither the sensation of being warmed nor that of being cooled. A minor variation in temperature of as little as 2° F may create a totally different therapeutic effect. Since the ideal temperature depends on the patient's condition and reaction to the water, it is often better to use his or her sensation, rather than a thermometer, as a guide to adjusting the temperature. The duration of a neutral bath may vary from 15 minutes to 4 hours. If the bath lasts longer than 20 minutes, it is necessary to add warm water to maintain the temperature.

The primary effect of a neutral bath is to create a state of decreased excitation. This sedative effect, similar to that produced in deprivation tanks, calms the nervous system. A second effect is activation of the kidneys, creating increased urinary output due to the absorption of water into the body during periods of prolonged immersion.[34] This is aided by the neutral temperature, which provides no stimulus for water loss through sweating. Nephrotic patients display increased phosphate excretion after prolonged immersion; therefore, they warrant special care when given prolonged immersion baths.[35]

Lastly, the neutral bath causes a decrease in the surface temperature of the body due to the lack of the normal heat-producing stimulus of cool air on the skin. As a result, the surface may be cooled as much as 6° F, creating a tendency to chill after the bath. This effect necessitates special care in keeping the patient warm. When prescribed for home treatment, a neutral bath is best taken just before getting into bed to avoid chilling.

Therapeutically, neutral baths are most commonly used for their calming effects in cases of insomnia, anxiety, nervous irritability, exhaustion, or chronic pain. By increasing kidney output, they may be appropriate in detoxification programs for substances such as alcohol, tobacco, or coffee, or as an adjunct treatment for peripheral edema. They also serve a valuable role in the control of fevers in individuals who would not be able to react to stronger measures, such as the very young, very old, feeble, or exhausted.

Cold and Contrast Baths

A local cold immersion bath is an effective treatment for reducing swelling or pain in an area. Rather than a cold compress or ice pack, immersion in a cold bath may be preferable. Full body cold immersion is most often used in combination with hot immersion, since cold alone can be tolerated by only the most robust individuals.

Contrast baths are an excellent treatment for facilitating blood flow and decreasing congestion in any area of the body. As with any contrast therapy, treatment begins with immersion in hot and always ends with cold. With a local bath to the hand, arm, or foot, 3 to 5 minutes in hot and 30 to 90 seconds in cold works well. In the case of full body immersion, the patient often needs at least 10 minutes of immersion in hot, but 30 to 90 seconds in cold is still usually adequate. Local contrast baths can be used much like contrast compresses, increasing BF and decreasing swelling in a local area. Full body immersion improves BF and should be considered in any congested or stagnant condition such as fibroids, dysmenorrhea, amenorrhea, fibromyalgia, hemorrhoids, depression, constipation, edema, benign prostatic hypertrophy, and infertility, to name a few. Local contrast baths are a simple home treatment requiring only two bowls or buckets and water. Contrast full immersion is often done at a spa or clinic, since it requires two large tubs to accommodate both hot and cold water.

Another option for contrast therapy is a shower or affusion. Having patients end their daily hot shower with a full body cold rinse is tonifying to the circulation and immune system. Ernst et al[36] performed a long-term prospective study called "Prevention of Common Colds by Hydrotherapy." The researchers compared 25 volunteers to 25 controls. Volunteers were asked to work up to a 5-minute hot shower followed by a 2-minute cold rinse. The study demonstrated a decrease in both the frequency and intensity of common colds in the treatment group compared with the control group.

Sitz Bath

The sitz bath is a partial immersion bath of the pelvic region. It is more easily given in a specially constructed tub, but may also be effectively done in a regular bath tub. Often it is taken with the feet immersed in a separate tub of hot water before or during the bath. A sitz bath may be taken hot, neutral, cold, or contrasting hot and cold.

The primary effect of the hot sitz bath is analgesic. It may be helpful in cramps of the uterus or ureters, pain from hemorrhoids, ovaries or testicles, sciatica, urinary retention, and after cystoscopy or hemorrhoidectomy. It is followed by cool sponging or affusion of the area. Hot sitz baths are not indicated in cases of acute inflammation but may be appropriate for chronic pelvic inflammatory disease (PID). Hot applications to the pelvis are also contraindicated during menses in most instances.

Neutral sitz baths are more appropriate for situations of acute inflammation, such as cystitis and acute PID, as well as being effective for pruritus of the anus or vulva. The cold sitz bath is given immediately after a warm-to-hot sitz bath for 30 seconds to 8 minutes. It is important to ensure that the water level of the hot bath on the body is at least 1 inch above the level of the cold water. This ensures adequate warming of the area, thereby preventing chilling. Friction rubs to the hips during the cold sitz bath promote an increased reaction. The cold sitz bath is used mainly for

its tonifying effects. It may be used for subinvolution of the uterus, metrorrhagia, atonic constipation, enuresis, atony of the bladder, and chronic prostatic congestion. Because it increases the tone of the smooth muscles of the uterus, bladder, and colon, it lessens the tendency to bleed from the uterus, the lower bowel, and rectum. It is necessary to provide adequate coverings during neutral and cold sitz baths to avoid chilling.

Contrast sitz baths are much like immersion contrast baths but with only the pelvic region submerged in water. As an alternative, the cold application can be performed with a towel wrung from cold water, with the patient standing in the hot bath and pulling the cold towel into the groin, holding it like a diaper for the time prescribed. Care should obviously be taken when standing in a tub of water, especially when standing up from a hot bath. The contrast sitz bath increases pelvic circulation and tone of the smooth muscles of the region. It is indicated in chronic PID, chronic prostatitis, atonic constipation, and other atonic conditions of the pelvis. The strong revulsive effect created increases the BF in the pelvic region dramatically.

Cold Friction Rubs

Cold friction rubs, or ablutions, consist of frictioning the body in a predetermined sequence with cold water. They differ from sponging in that they are more tonifying and are done more vigorously with rougher materials. A woolen bath mitt works well, but if this is not available, a coarse washcloth or loofa may also be used.

The primary effect of a cold ablution is tonic. Therefore, it may be used for any condition in which tonification is desired, such as fatigue after illness or surgery or after hot applications, such as saunas, whirlpools, or hot baths. It is an excellent prophylactic hydrotherapy technique when used regularly along with saunas, hot tubs, and massage.

A whole body ablution is carried out with the patient lying supine, covered completely and not chilly. Using cool to cold water, the therapist dips the mitt into the water and vigorously causes friction on a portion of the body. Depending on the cooling effect desired, the mitt may either be saturated or wrung dry before the friction occurs. The body part is treated until reddening occurs. If the patient is weak, it is best to dry the areas as one proceeds using a coarse dry towel. If the patient is strong and vigorous, one can wait and dry all areas at the end of the treatment.

One sequence for an ablution treatment would be to proceed from the chest to the arms and then the legs, then, turning the patient prone, to do the back of the legs and feet, the buttocks, and finally the back. Only the part being treated is exposed at any time.

Constitutional Hydrotherapy

Constitutional hydrotherapy was, as stated previously, developed by O.G. Carroll as an application of first hot, then cold, to the trunk, both front and back, along with low volt electrical stimulation to tonify the digestive organs and enhance the effects of the water applications. This therapy utilizes both contrast hydrotherapy and warming compress effects. Apart from contrast hydrotherapy applications, it is the most generally useful of the various hydrotherapy treatments and is commonly used to balance body functions, strengthen the immune system, and promote healing, as well as being a useful adjunct to detoxification. A pilot study[37] completed in 2008 at the Bastyr Center for Natural Health on human immunodeficiency virus positive patients showed a statistically significant increase in energy and decrease in body fat and a trend toward increased physical function along with a decrease in pain after a course of treatment with constitutional hydrotherapy. Fifty-eight percent of participants showed a decrease in systolic blood pressure. There was also a sizable decrease in C-reactive protein levels.

Constitutional hydrotherapy may be used as an adjunct to the treatment of any condition. It may be used to treat acute conditions such as upper respiratory infections, bronchitis, asthma, and gastrointestinal infections, and chronic conditions such as irritable bowel, ulcerative colitis, pre-menstrual syndrome, and arthritis, as well as conditions related to nervous system dysregulation such as insomnia or anxiety. (As a general rule of thumb "when in doubt, try constitutional hydrotherapy.") Boyle and Saine's *Lectures in Naturopathic Hydrotherapy* contains an excellent write-up on the constitutional hydrotherapy procedure.[38]

Wet Sheet Pack

The wet sheet pack is one of the most useful of all hydrotherapy procedures. It may be done either in the office or as a home treatment, if adequate direction is provided. It requires from 1 to 3 hours, depending on the patient's condition. Understanding the process completely before using this treatment is important. *Lectures in Naturopathic Hydrotherapy* by Boyle and Saine outlines the wet sheet pack procedure in detail for practitioners.[38]

The wet sheet pack proceeds through four stages: tonic or cooling, neutral, heating, and eliminative. Depending on the desired effect, the therapist may wish to prolong any one specific stage:

- *Tonic stage.* This stage may last from 2 to 15 minutes and is finished when the patient no longer perceives the sheet as being cold. This phase is intensely alterative to the body due to the intense thermic reaction induced. The length of this stage is directly dependent on the amount of water left in the sheet. For weak or exhausted patients, the sheet should be wrung out as completely as possible. For young, strong individuals for whom a more tonifying treatment is desired, more water may be left in the sheet.
- *Neutral stage.* Once the sheet reaches body temperature, the person no longer feels cold. At this time, the neutral phase begins. It may last from 15 minutes to an hour or longer, depending on the vitality of the patient. During this phase, there is a sense of calm that is similar to that experienced during a neutral bath. Often the patient falls asleep during this phase. This stage is indicated in cases of insomnia, anxiety, and delirium. To prolong the neutral phase, provide only adequate covering to prevent the patient feeling cool. Greater amounts of blankets trap more heat, and the neutral phase finishes sooner.
- *Heating stage.* As heat accumulates beneath the blankets, the patient gradually senses the warming and eventually begins to show light perspiration on the forehead. The time between the patient feeling warm and the beginning of perspiration is known as the heating phase. This may last from 15 minutes to an hour.
- *Elimination stage.* The final stage begins when the body begins to perspire. In a febrile patient, this stage is reached sooner. This stage is especially beneficial for those patients in a detoxification process, such as from alcohol, tobacco, coffee, or other toxins. It may also be used with acute infections, such as colds, flu, or bronchitis. Certain conditions that affect the skin, such as jaundice, may also benefit from this stage, as well as acute inflammatory conditions, such as arthritis.

During the elimination phase, it is important to provide adequate fluid to the patient. Herbal teas, used for either their diaphoretic or therapeutic effects, are most appropriate. This phase may last up to an hour. The treatment should be ended quickly if the patient begins to feel chilled or becomes uncomfortable.

The treatment is ended by quickly removing the patient from the pack, frictioning the skin briskly with a dry towel, and having the patient dress. As this is often an intensive treatment, it should be followed with rest or appropriate activity. Lying in a warm room for an hour is an ideal follow-up to this treatment. If done at home, it is best done in the evening just before retiring.

Colonic Irrigation

Colon hydrotherapy utilizes warm water moved through the colon to aid in waste elimination. Colonics are primarily utilized in cases of chronic constipation to both eliminate waste and improve colonic action, or as part of a detoxification protocol supporting excretion of toxins through the gastrointestinal system. The therapy requires a colonic irrigation unit and some training on proper use. Ulcerative colitis, diverticulitis, inflamed hemorrhoids, intestinal bleeding, colon cancer, pregnancy, and hypertension are contraindications to colonic irrigation.

Sauna

Saunas can be wet or dry depending on their heat source. Steam saunas use water as their source of heat and are an excellent general hyperthermic treatment. Saunas have also shown efficacy in detoxification protocols supporting excretion of toxins through the skin. A recent review of the benefits and risks of sauna bathing[39,40] concluded the following:

- It is well tolerated by most healthy adults and children.
- It is safe during uncomplicated pregnancy.
- It may help lower blood pressure and increase left ventricular ejection in patients with congestive heart failure.
- It produces transient improvement in pulmonary function, which may be helpful for patients with asthma and chronic bronchitis.
- It decreases pain and increases mobility in patients with rheumatic diseases.
- It may be contraindicated in patients with unstable angina pectoris, recent myocardial infarction, and severe aortic stenosis.
- It is safe for patients with stable angina pectoris and old myocardial infarction.
- Krop[40] published a case study in 1998 demonstrating the usefulness of sauna in the detoxification of a patient with 20 years' duration chemical sensitivity resulting from low-level exposure to solvents.

SUMMARY

Hydrotherapy provides naturopathic physicians and the general public alike with an effective and inexpensive form of treatment for many conditions, as well as a time-tested method for stimulating the vital force and maintaining health. This chapter has touched on only a few of the many techniques developed over the years. Naturopathic students, patients, and physicians wishing to learn more about the uses and techniques of hydrotherapy are encouraged to read Father Sebastian Kneipp's *My Water Cure* and Boyle and Saine's *Lectures in Naturopathic Hydrotherapy.*[38] Both resources contain instruction in how to use a wide variety of hydrotherapy techniques to regain and maintain health.

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CHAPTER 41

Manipulation

Robert M. Martinez, DC, ND

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THERAPEUTIC KEYS

- Manipulation is a passive manual maneuver that introduces movement beyond the passive range of motion (ROM) through the elastic barrier, but does not exceed the anatomic barrier.[1] Mobilizations are passive stretches with or without oscillations over which the patient can exert control.[2] Chiropractic adjustments are techniques that range in force from a near imperceptible force to high-velocity thrusts causing joint cavitation (popping noise).
- As a prudent starting point, initial evaluation should determine if manipulation of the patient is appropriate, seeking out "red flags" that contraindicate manipulation, such as fracture, infection, neoplasm, progressive neurologic deficit, cord pressure, or cauda equina syndrome.[3,4]
- A correct differential diagnosis is key to selection of patients, and the functional assessment is key to the selection of appropriate manual medicine techniques.[5]
- If gross signs of inflammation are present in a joint (heat, swelling, redness, and pain), and repeated movement to end range (ER) worsens the signs, manipulation in that direction would most likely aggravate the condition.
- When bringing the joint complex to tension, if the pain peripheralizes, it is a relative contraindication to manipulation.
- The practitioner should be alerted that an adverse outcome is likely from manipulation when repetitive motion with progressive force in the direction of the manipulation peripheralizes pain and reduces function.
- Relaxation techniques (heat, muscle work, and calming environment) are helpful to patients complaining of anxiety, muscle tension, stiffness, and aching before manipulation.[6]
- If pain is the chief complaint, icing the area for 5 minutes causes surface anesthesia and 20 minutes causes sedation of the actions of the muscle spindle cells. Sedation of a muscle reflex arc before manipulation of a fixated painful joint may facilitate treatment.[2]
- If the patient reports an increase in pain or stiffness after manipulation, ice the area of treatment for 10 to 30 minutes to reduce spasm and pain.[7,8] The patient should be placed into a position that centralizes pain when icing.
- "The goal of manipulation is to restore maximal pain-free movement of the musculoskeletal system and postural balance."[9]
- Do not treat muscle spasm as a primary condition. Muscle spasm is almost always a response of the body to a noxious stimulus. Find the cause and treat it.[10]
- Trigger points are myofascial irritations that are frequently caused by underlying joint fixations. Manipulation can irritate a trigger point and can precipitate a muscle spasm later that day.[11]

HISTORICAL PERSPECTIVE

Manipulations are depicted in prehistoric cave drawings and Chinese statues, circa 2700 BC,[12] but Hippocrates is credited with the earliest recorded written physician's prescription of manipulative treatment methods, which changed little until the sixth century. He advocated key principles of judicious use of force, direction of thrust, and proper levering of joints.[13]

During the Dark Ages, priests provided medical treatment at their monasteries. Kessler stated: "Friar Moultan, of the order of St. Augustine, wrote The Complete Bonesetter. The text, which was revised by John Turner in 1656, suggests that

manipulation was practiced in medical settings throughout the Middle Ages and Renaissance."[14]

Three main concepts developed during the 1700s still have a major influence on manipulation today. The first held that "vertebral luxation" (bone out of place) was responsible for spinal deformity. The second, the mainstream medical opinion, maintained that "caries of the spine" caused spinal deformity, which was treated with bloodletting and rest, while condemning extension and manipulation as both useless and dangerous and citing concerns about the potentially disastrous effects of manipulating tuberculous, neoplastic, rheumatic, or fractured joints. The third held that muscles were the main cause of problems, and treatment should be complete rest or active exercise, as the case warranted.[13]

More recently, questions of vertebral disc herniation, precipitation of cerebral vascular accidents, controversial issues of cost-effectiveness and efficacy of manipulative treatment, and the lack of a differential diagnosis by many nonallopathic manipulators have become the cause célèbre.

It is interesting to note the following:

- Hippocrates railed against the abuse of manipulative therapy by physicians and others of his time.
- Physicians of the late 1700s assailed one another's methods of treatment (e.g., in *The Lancet*, December 16, 1826, the banner on page 347 appropriately read "THE YELLOW JOURNAL").
- Surgeons held "bonesetters" in great contempt "when they condescend[ed] to speak at all of bonesetters and their works."[12]
- Bonesetters held their secrets and passed them from father to son.
- Financial competition was noted early in the literature. "It is known to most practitioners of surgery, and has been made known to many to their great cost and loss, that a large portion of the cases of impaired mobility or usefulness of limbs after injury fall into the hands of a class of men called 'bonesetters'."[15]
- Although there has been a great deal of animosity, and claims of superiority made by the various practitioners of manipulative treatment even to this day, "specific conclusions cannot be derived from the scientific literature for or against either the efficacy of spinal manipulative therapy or the pathophysiologic foundations from which it is derived."[16]

SCHOOLS OF THOUGHT IN MANIPULATION

Bonesetters of England

Bonesetters of England generally held that a bone was out of place and had a "feel" for what was wrong. Hutton described the information gained from a bonesetter as "bring[ing] some spoils out of the camp of the Philistines."[15]

Chiropractic

D.D. Palmer, "the founder," of chiropractic "rediscovered" the principle of "lost nerve tone" in a revelation from a deceased friend, Dr. Atkinson, and reestablished this method of healing. D.D. Palmer, and his son, B.J. Palmer, "the developer," of chiropractic added one of the most colorful pages to the history of manipulative treatment.

D.D. performed the first chiropractic manipulation on a deaf janitor whose hearing had been lost when he stooped over and felt something give in his back. D.D. reasoned that if the deafness occurred from something slipping out, restoring the vertebra to its correct position should cure the condition: "With this new objective in view, a half-hour's talk persuaded Mr. Lillard to allow me to replace it and his hearing was restored."[17]

Although there are multiple schools of thought in chiropractic, each with its own strengths and weaknesses, the literature supports the need to combine therapeutic exercise with manipulation. *Rehabilitation of the Spine, A Practitioner's Manual,* 2nd ed. edited by Craig Liebenson,[4] is considered a landmark publication by many in the field and addresses this topic at length.

Naturopathic

All naturopathic techniques result from the blending of thoughts of the other schools of medicine. This is appropriate when one realizes there is little new in manipulation, only refining and relabeling. It is also appropriate that naturopathy does not lay claim to originating a school of thought on manipulation but uses this method of treatment, when indicated, not exclusively, but as part of a therapeutic regimen.

Several naturopathic schools in the past were associated with chiropractic and eclectic schools of medicine. The genesis of the naturopathic profession is well documented in Chapter 4, History of Naturopathic Medicine.

Osteopathic

Andrew Still left the practice of allopathic medicine and started a school of osteopathy in Kirksville, Missouri. It is highly probable that the first chiropractor, D.D. Palmer, went to this school and learned some of the techniques, but it is not well documented. The famed "equal but separate" movement of the osteopaths led to a 1921 resolution, submitted at the American Osteopathic Association convention, that allowed entrance of chiropractors with advanced standing into their schools. Still, before his death, saw the defection of his osteopathic profession into the ranks of medical orthodoxy.[18-20] Interestingly, manipulation is now only an elective segment in some American osteopathic schools, whereas in England, where osteopathy is not part of the medical establishment, manipulation is still the mainstay of osteopathic practice.

The resurgence of interest in manual medicine has been brought to the forefront by the Osteopathic College at Michigan State University. This school teaches manual medicine to physical therapists, Doctors of Medicine, and Doctors of Osteopathy. Greenman's[1] *Principles of Manual Medicine* adds a useful text to the field of manual medicine.

Allopathic

James Cyriax, James Mennell, and John Mennell were brilliant physicians who worked to reintegrate manipulation into medical practice. They wrote valuable texts on manipulative therapy, although they did not totally agree on the effects they achieved with manipulation. Mennell held to the correction of lost joint play and denied the effect on the intervertebral disc,[21] whereas Cyriax claimed reduction of a protruding disc.[10]

"Controversy and contention" best describe the higher levels of the respective schools of medical thought. The impression one gets in reading through the literature is intolerance of others' ideas expressed in ad hominem attacks. The mistake "lay" manipulators and "nonphysicians" make is not ineffectiveness, but in their willingness to seek training outside the fraternal order of the "medical" brotherhood; to address the public directly rather than communicating exclusively within the order; and, worst of all, to openly compete, economically and politically, against the fraternal order.[13,15]

Donald B. Tower, in the chairman's summary at the National Institute of Neurological and Communicative Diseases and Stroke

conference in 1975,[22] noted a physician who received little credit for his early contribution to the field: J. Evans Riadore, a London physician who wrote a treatise on the irritation of spinal nerves in 1843. He attributed many diseases to this condition, stating: "If any organ is deficiently supplied with nervous energy of blood, its functions immediately, and sooner or later its structure, become deranged." This was a viewpoint subsequently echoed by osteopaths and chiropractors.[22]

The fifth edition of *Spinal Manipulation* by Bourdillion et al,[23] the first authors who were medical manipulators, has been largely reworked from previous editions and heavily influenced by osteopathic methods.

Awareness of manual medicine has been fostered by Calliet, McNabb, Maigne, Maitland, Kaltenborn, Williams, Jirout, Lewit, Janda, Bogduk, McKenzie, and many others.

Physical Therapy

James Cryiax influenced Robin McKenzie, a New Zealand physical therapist who subsequently developed a systematic approach called mechanical diagnosis and treatment (MDT) of musculoskeletal conditions. It is a process of evaluation and treatment of musculoskeletal disorders based on a mechanical history and the patient's symptomatic and mechanical response to movement, positions, and loading.[4] McKenzie's approach is often prejudicially dismissed as "extension exercises for the low back." He proposed a new tack in the approach to back pain that was found to be highly effective in populations with acute and chronic back pain as well as low in cost.[24] MDT includes McKenzie's observations that most conditions are self-resolving and that focus should be on prevention and recovery of function by teaching patients proper posture and self management. After years of studying, performing, and researching manipulation, he felt that only 20% of patients needed manipulative therapy, and 80% could self-treat using ER loading strategies learned from books or practitioners.[25]

IS MANUAL MEDICINE THE RIGHT TREATMENT?

Patients with somatic pain caused by psychosocial factors often seek a physical cause and treatment for their pain. If the presenting complaints do not seem to follow a mechanical pattern and the pain diagram is nonanatomic, consider the possibility of psychosocial factors. Psychosocial workplace factors associated with risk of spinal injury include job dissatisfaction, stressful working conditions as perceived by the employee, employer practices reported as being unfair, poor coping skills, lack of recognition at work, low supervisor support, a high frequency of job problems, and negative beliefs of or attitudes toward the consequences of having "low back trouble."[26,27] A major factor in identifying the incidence of future pain is the patient's perception of being disabled.[28] If the patient's history and records include previous evaluation by multiple providers with conflicting and confusing reports from the patient, caution is advised in approaching the management of the patient. If in doubt, seek a consultation with an astute colleague, physiatrist, or appropriate specialist.

Is It Safe to Move?

A clinician must answer the question, "Is it safe to 'move the patient' using conservative therapies, exercise, mobilizations, and manipulations?" Red flags have been shown to have many false positives, resulting in unnecessary additional diagnostic testing. Recent studies showed less than 1% of patients presenting to general practitioners with conditions that warranted further diagnostic evaluation. Red flags are a source of unnecessary medical interventions. When the medical history and examination indicate a serious disease, neurologic compromise, or progressive neurologic deficit, further evaluation or consultation is warranted. Although the question of safety is usually answered by the provider's clinical training, a general outline of triage is presented as a starting point to help determine if further evaluation is indicated before initiating or continuing care.[29]

Signs of Neoplasm

The combination of age over 50 years, a history of cancer, unexplained weight loss of more than 10 kg within 6 months, failure to improve after 1 month of conservative care, and an elevated erythrocyte sedimentation rate (ESR) have a sensitivity of 100% in identifying patients with a neoplasm. Night pain, especially pain that prevents the patient from getting sleep or "drives them from the bed" also generates a high degree of suspicion.[30,31]

Signs of Infection/Inflammation/Illness

Heat, swelling, pain, redness, and loss of function are the cardinal signs of inflammation. Acute inflammation lasts from 1 to 3 days and chronic inflammation usually is considered from 7 days to 7 weeks, but may last up to 12 months. The stages between acute and chronic inflammation overlap, and a continuum exists.[32] The clinical picture may be confused by chronic pain.

Laboratory tests may show signs such as an elevated C-reactive protein, ESR, or other tests for inflammatory arthritides. Signs of infection may be as simple as a low grade fever, chills, a shift to the left in the white blood cell count, signs of a worsening chronic illness, or frank presentation of an acute illness.[33] Clinical signs are pain that is constant 24 hours a day, described as aching, throbbing, or burning, and aggravated by movement with no position that gives relief.

Manipulation is contraindicated over an area of acute inflammation, but acute pain may be the result of mechanical pain. Treatment of the tissues should be guided by the level of inflammation and the response of the tissue to mechanical testing, according to MDT methodology, to determine if the patient should rest or pursue specific therapeutic movements. Observe the post-treatment results to see if signs of inflammation worsen, indicating incorrect application or inappropriate therapy.

Signs of Neurologic Disorder or Progressive Neurologic Deficit

A loss of sensation, decreased or absent deep tendon reflex, loss of muscle strength, and positive nerve root tension are signs of nerve root involvement. If only these neurologic findings are present and do not become progressively worse, appropriate conservative care may be effective.[34] Dizziness, drop attacks, diplopia, dysarthria, dysphagia, numbness, nystagmus, and nausea are more concerning signs of central nervous system involvement. Loss of bladder or bowel control or saddle anesthesia requires urgent evaluation with magnetic resonance imaging of the lumbar spine. If progressive neurologic deficit of weakness, loss of sensation, and loss of function, or the previously mentioned signs and symptoms are present, a consultation with a competent colleague, physiatrist, or neurosurgeon is indicated.

Signs of Fracture

A fracture typically has an obvious traumatic cause when the patient is young or middle-aged. In older patients, pathologic fractures are a concern, especially if there is a history of prolonged or repeated steroid use. Be wary of occult fracture after motor

vehicle accidents or athletic injuries and nontraumatic fractures in the elderly. The red flags suggesting vertebral fracture are age more than 50 years, female sex, major trauma, pain and tenderness, and a distracting painful injury. In particular, look above and below the site of injury, as the force of trauma may be transmitted and cause a fracture some distance from the site of impact.[35] In a pelvic fracture, there is always a fracture in two places in the ring.[36]

Is the Best Treatment Movement or Rest?

Pain can be confusing and lead one to conclude that inflammation is present. If pain is constant aching, throbbing, or burning, it suggests that the pain has a chemical cause, and it is inflammation. When the pain goes away, even for 30 minutes in a day, it suggests that the pain is due to mechanical pressure on tissue. To illustrate this point, bend your finger backward until you feel strain and hold it. At first you may only feel discomfort, but after an extended period of time, it will become painful. Next, try bending the finger backward beyond strain until it hurts. The pain you feel is due to abnormal stresses on a normal tissue; there is nothing wrong with your finger! You do not need drugs, modalities, or manual therapy. Simply stop overstraining the soft tissues. Robin McKenzie used this seemingly simple example to teach the consequences of sustained ER loading as a common cause of pain—mechanical pain rather than pain from inflammation.[25,37]

If the pain is caused by inflammation, it is best to rest until the inflammation has been reduced. If the pain is mechanical, it is often best to move, but how far should one move and in which direction?

Which Direction to Move?

Common approaches to determine which direction to move the patient are orthopedic tests, selective tissue tension tests, and McKenzie's MDT. Each can inform the practitioner of which tissues are involved and help formulate an appropriate treatment program.

Orthopedic Tests

Orthopedic tests are designed to stress the damaged tissue and reproduce the pain of the primary complaint. The examiner is not looking merely for pain to be reported as a result of the maneuver, but rather pain that is specific for the test and reproduces the pain of the primary complaint. Therefore, the following should be remembered:

- The examiner can make the patient worse by forcing tests or performing them incorrectly.
- The least stressful tests should be done first. If the first test causes severe pain, most of the other motions will be painful afterward and confuse the findings.
- The test by definition has a positive response, which correlates to a specific condition that must be produced when the test is performed for the test to be positive (e.g., Lindner's test and Soto Hall's test are performed in the same way, but the findings to report a positive test are different).
- The test must reproduce the pain of the primary complaint and be positive by the test's definition.
- Tests are centered in allopathic medicine to diagnose pathology, fracture, moderate to severe sprain/strain, and dislocation. Although the patient feels pain from the movements of these tests, these are not true positive tests just because the patient reports the movement hurts.

When multiple orthopedic tests are indiscriminately performed on one visit, without an understanding of the mechanism of action of the stress these maneuvers put on the tissues, the unwitting examiner merely subjects the patient to the trauma of a series of painful maneuvers that only serve to confuse the practitioner and aggravate the patient's condition. Detailed texts that cover this area include those by Magee[38] or Evans[39]; such texts are helpful and should be referred to for additional information. It is even more helpful to attend programs in which experienced practitioners teach skills and knowledge to inexperienced practitioners.

Selective Tissue Tension Tests

This is an introduction to the differential diagnosis of soft tissue injuries by means of active and passive movements using the selective tissue tension tests of James Cryiax[10]; this topic is covered in depth in Kessler[14] and Magee.[38]

Active Movements. First, active ranges of motion (ROM) are performed to determine voluntary ROM and patient status. Measuring active ROMs cannot differentiate whether the loss of function is due to pain, weakness, stiffness, and/or lesion, but it is helpful to determine patient tolerance to motion and how guarded the patient is when moving.

Resisted Isometric Tests. Next, isometric muscle tests are performed to test the contractile tissue (muscle and tendons) with the joint in neutral to avoid involving the noncontractile tissues. The following results may be noted:

- Normal—painless and full strength
- Minor tear—pain with full strength
- Moderate tear—pain with little strength
- Neurologic deficit—no pain and little strength

Passive Movements. When the joint is put through passive motion, it reaches an end point, which has an "end-feel" that helps to determine the status of the soft tissue around the joint. The end-feel of a joint may be one of the following:

- Normal—the amount of motion and feel of the tissues are appropriate for age
- Abnormal—normal end-feels that are not normal for the joint and ROM that are being tested (e.g., the feeling of bone on bone is the normal end-feel at the elbow when extended but is abnormal when it occurs at the ER of knee extension)
- Pathologic—these end-feels are only present in joints that have undergone pathologic changes

Normal End-Feels

Capsular end-feel. This is a firm, "leathery" feeling, felt, for example, when the normal shoulder is at full external rotation. When felt in conjunction with a capsular pattern of restriction, and in the absence of significant inflammation or effusion, it indicates capsular fibrosis.

Bony end-feel. This feels abrupt, as when moving the normal elbow into full extension. When accompanying a restriction of movement, it may suggest hypertrophic bony changes, such as those that occur with degenerative joint disease, or possible malunion of bony segments after healing of a fracture.

Soft tissue approximation end-feel. This is a soft end-feel, as when fully flexing the normal elbow or knee. It may accompany joint restriction in the presence of significant muscular hypertrophy.

Muscular end-feel. This more rubbery feel resembles what is felt at the extremes of straight-leg raising (SLR) from tension on the hamstrings. It is less abrupt than a capsular end-feel.

Abnormal End-Feels. The tissue involved is determined by the response to the passive ROMs and by moving the joint to ER and into closed pack position.

Muscle or tendon. Active and passive movements are limited or painful, or both. Pain is caused by active contraction or passive stretching of the inflamed or torn muscle-tendon unit.

Ligaments. Both active and passive movements are limited or painful, or both, in the same direction due to stretch of the inflamed or torn ligament.

Capsular pattern. Only joints that are controlled by muscles have a capsular pattern. Pain is caused with both active and passive motions, and the limitation of motion is in a specific proportion that is listed in tables in Kessler's text.[14]

Pathologic Joint End-Feels. Pathologic joint end-feels indicate a disease process; they are limited and are never normal:

- Empty—bursitis, space-occupying lesion, neoplasm
- Boggy—joint effusion
- Spasm—guarding from inflammation
- Internal derangement—loose body/torn meniscus

McKenzie's Mechanical Diagnosis and Therapy (MDT)

MDT is an invaluable system for practitioners who perform manual therapy. Rather than a technique, it is a method of diagnosis determined by response to repeated movement and pressure to joints and soft tissue that, once mastered, allows rapid assessment and selection of patients for treatment. It also identifies those not likely to respond to manual therapy so the provider's treatment program can be altered, or the patient can quickly receive an appropriate referral. Resources available are classes from the McKenzie Institute on MDT, McKenzie's textbooks,[40,41] and a chapter in Liebenson's text.[4] Only a few of the many helpful concepts from the McKenzie method are discussed in the following. Keep in mind that McKenzie asserted that only 20% of patients needed manipulative therapy, and prevention is key to success in his model.

Centralization and Peripheralization

A cervical spine problem can refer pain to the shoulder blade, arm, forearm, and hand. A low back problem can refer pain to the sacroiliac joint (SIJ), buttock, thigh, leg, and foot. When the referred pain from the spine is brought closer to the midline in response to movements, position, or load, and remains reduced, it is called "centralization."[24] When the pain moves out from the spine in response to movements, position, or load, it is called "peripheralization." When a movement produces centralization, it is a motion to pursue for treatment. When a movement causes peripheralization, it is a motion to avoid, as it will likely worsen the condition. If no movement or position centralizes the pain, it is a poorer prognosis for response to the treatment method being used. Although this phenomenon is typically associated with vertebral disc problems, it can be observed in many musculoskeletal problems.

End-Range Pain and Pain During Motion

End-range pain (ERP) is felt only when the joint is moved to ER. It is a sign of deranged or adaptively shortened soft tissues around the joint complex. The importance is that this is an indication that stretching and mobilizing techniques should be used before manipulation. If the joint is not mobilized to ER repeatedly, the manipulation may cause aggravation of the complaint. When the joint is fully stretched, after a progression of forces described in the "Performing Manipulation" section, the practitioner can determine if and in which direction the mobilization or manipulation is indicated.

Pain during motion (PDM) is pain that is felt during joint movement, as well as at the ER. The joint ROM may be restricted as well. PDM is a sign of soft tissue derangement, often thought of as a vertebral disc problem. Movements or positions that increase the PDM and cause increased restriction of movement after the movement is performed should be avoided. When a mobilization or manipulation increases PDM or restriction, it is important to find a motion or position that will reduce the PDM and restore the motion as soon as possible to reduce the irritation of the tissues. Application of ice, analgesic, and/or anti-inflammatory medications may be indicated as well.

PRETREATMENT ASSESSMENT

Functional Assessment

Often the focus is on injury, pathology, and disease, but the majority of musculoskeletal pain is from pathomechanics due to postural and repetitive strain, disuse, deconditioning, fatigue, and nutritional factors that must be addressed if treatment is to be successful. Once the portion of the patient's condition that is a musculoskeletal problem has been established, the mechanical fault should be determined. Manipulative treatment without correction of the mechanical fault results in prolonged treatment and recurrence. Detecting this is sometimes easy, whereas at other times it is a mystery that takes careful investigation, as discussed in McKenzie,[37a] Greenman,[1] Lewit,[5] and Liebenson.[4]

Observe the posture of the patient. If he or she is tilted and antalgic to the side and/or forward, due to an episode of neck or back pain, it indicates a large space-occupying mass, which is most often the disc, but it could be other soft tissue or pathology. Proceed slowly and carefully, avoiding any movements that cause peripheralization, increase PDM, or increase the obstruction of motion.

Establish the baseline of the location of the complaint and its response to motion and then repeat motions to ER. In the cervical spine, test flexion, extension, rotation, and lateral bending. In the lumbar spine, test flexion, extension, and lateral translation. The testing procedures are described in detail with photos in Liebenson's text.[4]

Note the ROM. If there are complaints at or below the shoulder blade or buttock, it is important to test reflexes, muscle strength, sensation, and nerve root tension signs to assess if the nerve root is affected. Additional tests can be added as indicated.

Cervical Spine

The cervical spine presents a diagnostic challenge. Although the mechanism of the tests in the lumbar spine are similar, the area is much more delicate and thus requires more careful application.

There is considerable discussion of the topic of vertebrobasilar stroke (VBS) after manipulation of the cervical spine. Tests done in the office have not proved effective, but the history should alert the practitioner to the possibility of VBS insult, and manipulation is contraindicated. The presence of the signs listed in the section on "Signs of Neurologic Disorder" are important signs that indicate not to use mobilization or manipulation. The most important risk factors identified by Terrett[42] were dizziness, unsteadiness, giddiness, vertigo, and sudden severe pain in the side of the head or neck, which is different from any pain the patient has had before. If the practitioner elects to follow the pattern of the progression of force, the occurrence of these symptoms in the early mobilizations contraindicate progressing the force and manipulation. However, VBS has occurred during an examination simply by having the patient turning his or her head. The incidence is small, but missing this clinical presentation is devastating, though not clearly caused by the evaluation or manipulative treatment.[43]

If there is compression of the nerve root or cervical instability, the patient may present holding the head, lifting it cephalically to decompress the spine and root, which is a clear indication to stabilize and transport immediately. Any such presentation is best handled by emergency department staff because even passive ROM assessment may cause permanent injury.

If there is irritation of the brachial plexus or a nerve root, the patient may support the arm in abduction and flexion, often resting the hand on the top of his or her head. This is a sign to proceed cautiously. Any movements that cause peripheralization must be avoided, and movements that produce centralization should be pursued. In cases where there are no deficits and all signs and symptoms are relieved by elevation of the arm, this may be the only treatment needed. If overt signs of nerve root compression are present, mobilization and manipulation must be performed with caution.

Cervical Distraction

If distraction of the head from the shoulders causes aggravation of the patient's complaints at 12 lbs of traction (the average weight of the head), stabilization and relaxation techniques are indicated. If distraction of the head from the shoulders causes relief of the radiating pain at 12 lbs of traction, slowly increase the traction to 25 lbs. If this relieves the complaint of neck pain, it is an indication that mobilization and traction are indicated therapies. If it aggravates the complaint, it is an indication of inflammation or instability and suggests caution in using mobilization or traction.

Cervical compression that causes radiating pain to the arms is a sign that indicates nerve root irritation from the disc and is treated by symptom response that centralizes the arm complaint.

Maximum Cervical Rotation, Lateral Bending, and Compression

If maximum cervical rotation, lateral bending, and compression cause radiating arm pain, it is a sign of nerve root compression and only a skilled practitioner should attempt manipulation in that direction.

Spurling's Maneuver

When combined cervical rotation, lateral bending, and extension with overpressure (Spurling's maneuver) aggravate or reproduce the complaint or radiating pain to the midback or arm, this indicates nerve root irritation, and manipulation in that direction places the patient at risk for aggravation of this condition. If the pain is local, it is a sign of facet irritation that often responds well to manipulation. The practitioner can test the response with repeat mobilization to the ER; if only ERP is produced, then increased force can judiciously be used.

After determining that the lesion is not a "hard" orthopedic or neurologic lesion, differential tissue tension tests are used to determine the involved tissue. Appropriate repeated movements to ER and skilled mobilization and/or manipulations are identified by centralization of the symptoms and improved function.

Upper Limb Tension Signs

Butler[44] described, in detail, the identification of cervical root tension signs using upper limb tension tests developed by Elvy in 1979. The tests are useful to help guide treatment.

Lumbar Spine and Sacroiliac Joint

During supine SLR, the lumbar nerve roots begin to develop tension at about 35 degrees. If SLR causes leg pain below 30 degrees, it is likely due to stretching of the lumbar nerve root in the presence of a space-occupying lesion or significant hip pathology. SLR above 35 degrees causes increasing ipsilateral nerve root tension, ipsilateral hamstring tightness, and may expose lumbar dysfunction or derangement as the straight leg moves toward ER. Once the painful ER is found, one lowers the limb to the pain-free range and then performs internal rotation and dorsiflexion of the foot and great toe. If this maneuver causes return of the leg pain, there is likely tension on the lumbar nerve roots. Because the SLR maneuver stresses multiple tissues, the test can be misleading, and it can be somewhat difficult to determine what a positive finding is until the practitioner's skills develop, but the positive result should be described to help clarify the findings.

Assessing Radiating Leg Symptoms

Following the principle of "Do no harm," one should test reflexes and sensation first, then proceed to active tests such as the Valsalva maneuver to test for increased intrathecal pressure. If radiating pain results from the Valsalva maneuver, it is a sign of a space-occupying lesion. Next, the practitioner should do SLR, adding dorsiflexion of the foot with extension of the great toe to determine if the root tension reproduces or aggravates the radiating leg symptoms. Assessment with MDT protocols is recommended and is superior to standard orthopedic protocols for functional assessment. Commonly used tests are compression tests (Milgram's bilateral leg raising and Lindner's test [forcefully flexing the trunk while the patient is supine]); this forces the disc posteriorly (if herniated) and causes increased intraabdominal pressure, resulting in increased intrathecal pressure (Valsalva effect).

Some additional ideas to finding the area of lesion in the lumbar spine are as follows:

- Support Adams (the belt test)—With the patient standing, the doctor has him or her bend forward and notes the level of pain. The doctor then secures the patient's pelvis by hugging the anterior superior iliac spines with the arms, pressing the patient's sacrum into the doctor's hip. If the patient's pain is decreased, it indicates the lesion is in the pelvis (probably the SIJ or hip); if pain increases, it is in the lumbar spine.
- Patrick's test—Flexion, abduction, and external rotation of the hip are blocked; this causes pain over the inguinal fossa and into the thigh when a hip lesion is present.

This is only an introduction to one common problem that may present with many variations. Careful study of the mechanism of action of the tests used can confirm, rather than confuse, a diagnostic impression.

Assessing the Sacroiliac Joint

The SIJ is the "dumping ground" for pain from the lumbar spine, just as the shoulder blade is the "dumping ground" for pain from the cervical spine. The key to determining if the problem is in the SIJ is to rule out all lumbar problems first. Second, Laslett[45] determined that when two or more of the following SIJ tests produce concordant pain, it is highly likely that the SIJ is the pain generator.

1. Gapping test—patient is supine. The examiner crosses his or her arms, placing heels of the hands on the anterior superior iliac spine, forcefully pressing laterally and down into the table to "gap" the SIJ, attempting to stretch the anterior SIJ ligaments.
2. Compression test—The patient is lying on his or her side with the painful SIJ up. The pressure is directed to the opposite iliac crest, attempting to compress the anterior SIJ and stretch the posterior SIJ ligaments.
3. Posterior shear or "thigh thrust"—The patient is supine. The practitioner's hand, a small block, or sand bag is placed under

the patient's sacrum. The hip is flexed to 90 degrees (perpendicular to the floor), the knee is maximally flexed, and a thrust is applied down the shaft of the femur. One should avoid adduction of the hip, as this will cause pain in normal patients.
4. Pelvic torsion (Gaenslen's test)—The patient is supine at the edge of the table with one thigh extended over the edge of the table. On the other side, the hip and knee are flexed to the chest. Overpressure is applied to the extended thigh to accentuate the posterior rotation of the opposite side. This should be performed on both sides.
5. Sacral thrust—With the patient lying prone, the examiner thrusts down on the sacrum.
6. Cranial shear—With the patient prone, cranial pressure is applied to the apex of the sacrum with the examiner's hands, whereas the painful side ankle is placed between the examiner's knees and is tractioned caudally.

Techniques for correction of these fixations are described in Maigne,[46] Bourdillion,[23] and Maitland.[2]

TREATMENT CONCEPTS

Notes on the Art of Manipulation

Manipulation is an art. Assuming a proper differential diagnosis, one acquires a "feel" that allows recognition of the differences among the types of joint fixations and knowledge of when to manipulate.

When a movement causes pain, it should not be performed unless the diagnosis of the patient's condition is sure and the motion will cause no harm.[46]

Joint Motion

Joint motion descriptions can become elaborate, or one may simply say that there are six degrees of freedom of motion (plus long-axis extension): flexion, extension, left and right rotation, and left and right lateral bending. Not all joints have all six degrees of motion. The normal degrees and ROMs of joints are listed in anatomy and kinesiology texts. If a degree of motion is lost or blocked, the type of fixation and which form of manual medicine is indicated should be determined.

Barrier Concepts

Joint motion is described from neutral to an ER that is ultimately limited by the anatomic barrier, which, if exceeded, causes tissue trauma. The extent of the active ROM can be increased by passive motion to a point at which all of the tissues around the joint have been brought to tension, called the elastic barrier.[1] Beyond the elastic barrier is a small ROM referred to as the paraphysiologic space.[47] It is within the paraphysiologic space that joint cavitation, the "popping" sound, occurs. When joints and soft tissues are dysfunctional, alterations of ROM may occur both within the ROM and at the end of it. If one focuses only on working in the paraphysiologic space, one severely limits the effects that can be made on dysfunction.

Before using manipulation, think about the joint end-feel (the way the joint feels at the end of its ROM) and determine which pattern is present:

- Edematous and boggy end-feel—indicates joint effusion and possibly inflammation. Muscle spasms should not be treated as a primary condition, since they are almost always the body's response to a noxious stimulus or pathophysiologic fault. Cryotherapy, positive galvanism, pulsed ultrasound, and gentle, frequently repeated movements within the active ROM are indicated.
- Springy and taut end-feel—ligamentous fixations (as felt in the normal knee in lateral bending stress tests and drawer tests). Manipulation works well on these types of fixations. Surging sinusoidal and interferential current, ultrasound, and moist hot packs facilitate the treatment. One can follow with cryotherapy in the subacute stages.
- Bone-on-bone end-feel—usually indicative of degenerative joint disease (as felt in the normal elbow in extension). If there is fine crepitus, mild degenerative joint disease (DJD) may be present; coarse crepitus indicates moderate DJD, and joint creaking may be advanced DJD. Diathermy, contrast baths, and other naturopathic therapies indicated in osteoarthritis are helpful.

Preparation for the Manipulation

The room should be at a comfortable ambient temperature, and the physician should wear no watches or jewelry that might catch the patient's hair or skin.

The physician must be comfortable and relaxed. Manipulation is an art, but in general, side-posture manipulation of the pelvis and lumbar spine is easiest on a table that is at knee height; prone and supine thoracic manipulation are easiest at midthigh height; and cervical manipulation is easiest when seated, kneeling, or on a table at waist height. One may either change the height of the table or simply bend at the knees. Manipulation of the joints of the extremities can be performed in any position that allows the physician control over the joint and body parts.

The patient should be comfortable and relaxed on a firm but well-padded table. For a manipulative treatment, the patient should be in a position that relieves symptoms.

Performing Manipulation

Manipulation of a joint is performed to correct joint fixation. Once the area to be manipulated has been appropriately assessed:

1. Test the direction of manipulative thrust with repeat mobilization to ER to ascertain that the pain does not peripheralize, the movement does not increase PDM, and the movement does not result in increased obstruction to motion from mobilization, using a progression of force to determine the effect of the direction and force applied.

This is a logical stepwise progression of the force generated first by the patient, then by the practitioner. The advantages are increased patient comfort, ability to "test the waters," and decreased risk of harm from the procedure. The steps are as follows:

Patient-generated force—the patient does all the motion actively.

Patient-generated overpressure—the patient uses a strap, fulcrum, etc., to increase the movement to ER.

Practitioner-generated force—the practitioner mobilizes the joint to ER repeatedly.

Practitioner uses manipulative thrust if positive responses occur that include centralization, reduction of antalgic postures, increased ROM, and decreased PDM. It is a relative contraindication to continuing to step 4 if there is no positive response in steps 1 to 3.

2. Stabilize the area to be manipulated: A point of stabilization is created by one hand and the physician's body weight, while the other hand performs the manipulation. Minor corrections of the position of the stabilized part or hand, or both, are frequently interpreted by an observer as twisting or wrenching motions. Twisting and wrenching are difficult to control and may injure the patient.

3. Bring the joint to tension, removing the periarticular tissue slack. Mobilization with tissue slack not taken up is safe, but manipulation when tissue slack is present invites injury.
4. Thrust only when the patient is relaxed and the fixation is felt.

The manipulative thrust can be described according to the following:

- Direction of line of thrust—through the joint space, parallel to joint surfaces, or tangential to the point of fixation.
- Velocity—slow for mobilizations. High velocity can correct joint fixations and the speed must be faster than the patient's reaction time or a strain injury will result if the patient's muscular resistance occurs at the time of the manipulative thrust.
- Amplitude—governed by the quality of the health of the tissue, the quality of the fixation, and the location of the condition on the spectrum of the inflammation response.

After the elastic barrier has been stretched, repeated manipulation in the same direction is complicated because the end-feel tension normally felt before a manipulation is reduced or absent for at least 20 minutes. The same phenomenon occurs when one "pops" knuckles. The risk of injury is much greater, and changing to mobilization or active muscular relaxation techniques is recommended rather than repeated manipulation.

Reassess

The condition of the joint fixation should be reassessed after each treatment to determine if the therapy has been successful.

A single manipulation rarely corrects a problem completely. Learning a joint-scanning technique shows where the problems are that need further evaluation. The goal is to alleviate acute conditions or, if unsuccessful, to turn them into subacute conditions and resolve subacute and chronic conditions before they cause a chronic fatigue response, joint fixation, degeneration, or chronic myositis.

Troubleshooting Technique

Common problems blocking successful manipulation can be overcome by the following:

- Learning joint play analysis on the peripheral joints and practicing manipulations of those joints before attempting to manipulate the spinal joints.
- Practicing the manipulative procedure with repeated light oscillatory movements while modifying the direction to feel the changes in joint tension, thus gaining experience, confidence, and knowledge without inflicting injury.
- Being sure of the procedure; otherwise, the patient may sense the physician's hesitation and guard, preventing the manipulation and increasing the risk of a poor outcome.
- Feeling the fixation of the joint as it is brought to tension; otherwise, the manipulation traumatizes the tissues unnecessarily or does not gain the desired result.
- Learning the arthrology of the joint to be manipulated so as not to put the joint in a "locked" or jammed position that will cause the force of the manipulation to be dispersed to the surrounding tissues and joints.

Personal instruction is invaluable, but unless the rationales of joint mechanics, pathomechanics, and pathophysiology are the basis of the teacher's approach, it can be confusing and lead to erroneous conclusions. The Further Reading list includes texts by Bourdillion, Greenman, Liebenson, and Maitland; these are good sources for learning the basics of the art.

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An in depth look at the prevalence of red flags in primary care practice and how some red flags are positive for patients without serious pathology.

CHAPTER 42

Nonpharmacologic Control of Pain

Richard Kitaeff, MA, MD, DiplAc, LAc

CHAPTER CONTENTS

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INTRODUCTION

Pain in its myriad forms is one of the most common symptoms for which patients seek relief. Acute pain is an unpleasant experience primarily associated with tissue injury, and the protective response patients have to pain provides the clinician with valuable diagnostic information.

The reaction to pain is highly subjective and, as a function of higher centers, is extremely variable. It is influenced by many factors, depending on the individual patient and his or her situation. When pain becomes chronic, the multifactorial influences (e.g., anxiety; depression; social, cultural, and economic factors; secondary gain) play an even larger role.

When treating a patient for pain, the clinician must first determine the primary cause, the pathogenesis, and the secondary or contributing factors. The relief of pain may then be achieved by removal of the primary cause (e.g., cure of an infection), neutralization of the effect of the stimulus (e.g., emollients for an ulcer), relief of discomfort (e.g., biofeedback), suppression of the disease process (e.g., anti-inflammatory agents), and dulling or obliteration of the sense of pain (e.g., analgesics or acupuncture).[1]

Although the medical profession has chosen to emphasize the pharmacologic methods of pain control, many nonpharmacologic options are available. Their applicability and efficacy are documented here. (Although this chapter liberally utilizes pain control in childbirth, the examples and concepts can be generalized to any situation involving acute and/or chronic pain.)

THE EXPERIENCE OF PAIN

A Psychological Model

Pain is generally acknowledged to be a complex physiologic and/or psychological phenomenon. It involves motivational and emotional components and conceptual interpretation, which may or may not have their basis in actual nociception. Verbal reports of pain and associated behavioral responses are controlled, at least in part, by psychological, cultural, and situational factors.

For acute pain, such as that of childbirth, in which the painful experience can be directly related to nociceptive input, a multiprocess feedback model can be considered. However, one must keep in mind the complexity of the psychological processes intervening between sensory event and observable response, ranging from the physiologic to the social aspects of personality. These include elements of the following:

- Information processing
- Performance ability
- Attention
- Memory
- Expectancy
- Attitudes and beliefs
- Secondary gain
- Self-concept
- Designated sick roles

In the psychological model, the brain infers information from bodily signs and integrates it with existing personal and situational variables to direct behavior.

When consideration must also be given to the interactions with interested observers, such as physicians, family members, and birth attendants, who influence the interpretation with their own experiences and attitudes about pain, the complexity becomes even greater.

According to this model, which does not differ in essence from a general model of stress, a primary appraisal of the personal danger or threat posed by the painful stressor is followed by a secondary appraisal of one's ability to cope, based on emotional feedback and contributions of situational and sociocultural response factors. On this basis, a woman in labor could choose to regard pain as "positive," "functional," or "creative"; "pain with a purpose"; or, alternatively, "part of a process involving injury."[2] In the course of a pain management program carried out in 84 patients with low back pain, those who more strongly endorsed "organic" concepts about the nature and treatment of pain reported higher levels of disability, whereas reductions in reported "organic" pain beliefs improved reported disability, and endorsement of "psychological" concepts about the nature and treatment of pain was not associated with disability.[3] Several studies indicated that "catastrophizing" predicted pain or was associated with lower pain tolerance.[4,5] This conceptualization of painful stress suggests that intervention could be successful at several levels: cognitive patterning, physiologic arousal associated with emotional stress, and control of environmental stimuli. Examples of appropriate strategies are cognitive coping skills such as restructuring and utilization of preparatory information and attention shifts; muscular relaxation, physical or electrical stimulation, and biofeedback techniques; and structuring of the environment in a way conducive to effective coping (such as by making it nonthreatening and comfortable).[6]

Neuropsychological Mechanisms of Pain

According to research on the mechanisms of pain, pain can be treated not only by anesthetic blocks, surgical intervention, and the like, but also by influencing the motivational, affective, and cognitive factors.[7] The traditional specificity theory of pain, first enunciated by Descartes in the seventeenth century, holds that pain messages are conducted from specific pain receptors at the periphery through discrete pathways to pain centers in the brain. However, there are individual differences in pain responses; pain is not consistently stopped by cutting or blocking of the "pain pathway," and it is now known that nonpainful types of stimulation activate the A-δ and C fibers (see next paragraph) that are associated with pain. Therefore, later modifications of pain theory took into account patterning of nerve impulses over time to reflect differences in degree and intensity of stimuli and summation of signals from an extended area.[8]

The currently accepted view of pain is the gate control theory, which Melzack and Wall[9] formulated in 1965. Based on neurologic data and a categorization of the words used to describe pain, this theory conceptualizes the pain experience as having sensory discriminative, motivational affective, and cognitive evaluative components or modalities, corresponding to different patterns of nervous impulses. Neurologically, a specialized cluster of nerve cells in the substantia gelatinosa of the spinal column is thought to operate like a valve or gate, controlling nerve signals before they evoke the perception of, and response to, pain. Besides this monitoring of sensory data in the central nervous system, gating is also influenced by the relative amount of activity in large (A-β) and small diameter (A-δ and C) nerve fibers. The large fibers tend to inhibit transmission, or close the gate, preventing pain, and the small fibers tend to facilitate transmission, or open the gate, resulting in pain. The fact that large fibers are activated by pressure, touch, massage, and vibration suggests a mechanism for such pain control techniques as acupressure, acupuncture, and transcutaneous electrical nerve stimulation (TENS). Such stimulation apparently closes the spinal gate via the large fiber system. Melzack and Casey[7] expanded this theory by proposing the possibility of a higher level gate, in the reticular or limbic structures of the brain, that probably mediates the drive to escape from unpleasant stimuli. At central nervous system levels, the biochemical mechanisms of gate control may involve the endorphins, natural morphine-like substances that have been implicated in the pain controlling effects produced by acupuncture.[10]

Pain in Childbirth

A psychological and/or social learning approach to pain emphasizes control of motivation, expectation, focus of attention, stress, and feelings of anxiety, depression, and helplessness. Factors specifically operative in labor pain involve these as well as social support and the physiologic factors of hunger, rest, and muscular tension.[11]All of these factors can contribute to the interpretation of pain being placed on the nociceptive message provided by uterine contractions. The influence of motivation on labor pain was effectively demonstrated in a prospective study of maternal attitudes toward pregnancy in 8000 American women. One of the factors found to be strongly related to maternal attitude toward having a baby was the need for analgesics in labor.[12]

Cultural conditioning may also be fundamental to the labeling of childbirth as painful. Throughout most of the world, analgesics are not required for labor; a Japanese anesthesiologist suggested that the idea of "painless delivery" is a strange one to his culture.[13] American women, in contrast, "live through a largely self-fulfilling prophecy of birth as a painful, terrifying ordeal, and/or as a medical, drugged process over which they have no control."[11] This idea relates to body fantasies of injury, brought about in a hospital environment where distress is an expected response to the expulsive reflex.[2]

PAIN CONTROL

Moderating Variables and Psychological Techniques

Psychological Strategies

The psychological strategies recommended for control of labor pain, many of them part of prepared childbirth programs, generally aim to provide control, communication, relaxation, attention focus, and support, as well as physical counterstimuli. Considerable psychological research supports the use of these strategies in the development of pain tolerance.

The significance of various characteristics of an individual's psychological profile has been studied by evaluating the effects on pain perception of such parameters as the following:

- Introversion–extroversion[14-16]
- Augmenters–reducers[17]
- Field dependence[18,19]
- Repression–sensitization[20-22]

For example, on the repression–sensitization axis, repressors may be characterized as people who avoid having to cope with pain. Sensitizers, however, have an obsessive need to cope; they like to be informed in advance about the situation and to have control over it. The superior initial tolerance exhibited by repressors in response to heat and pressure stimuli disappeared in

repeated trials, showing that the sensitizers' predilection for challenge enabled them to endure long-term pain better.

The importance of individual difference variables is also illustrated by the observation that one third of patients undergoing surgical operations do not request pain-killing medication.[23] This common ability to suppress pain indicates that not all surgical patients consider themselves passive victims. During the postoperative period, pain persists longer for those who accept medication.

Cognitive Strategies

The impetus for devising cognitive strategies to promote tolerance of pain has been particularly supported by investigations showing that pain tolerance increases with greater predictability and perception of control.[24-28] Similarly, preparatory communications and information received before the onset of experimental or surgical pain consistently decreases the subjects' perception of pain.[29-31] Animal studies have demonstrated higher rates of instrumental responses when painful shocks are signaled than when they are unsignaled.[32] Kanfer and Seidner[33] found that subjects who could advance slides of travel pictures at their own rate tolerated ice water immersion of the hand longer than yoked subjects whose slides were changed by the experimenter.

When surgical patients were given a sense of control by being provided with preparatory information about postoperative discomforts and operative care, in combination with training in rehearsal of realistic, positive aspects of the surgical experience, they showed a significant reduction in postoperative anxiety (as indicated by nurses' observations), requests for sedatives, and length of hospital stay.[34]

A typical cognitive behavioral procedure utilizes "stress inoculation," beginning with an educational phase (in which the client is given a conceptual framework for understanding the nature of his or her stressful reactions), followed by rehearsal of behavioral and cognitive coping skills, based on a set of coping self-statements generated by the client in collaboration with the therapist. Such cognitive-behavioral techniques, sometimes in combination with electromyographic biofeedback control, have been found successful in treatment of chronic low back pain.[35-37] Also, cognitive-behavioral strategies have been effective in alleviating the pain of irritable bowel syndrome,[38] temporomandibular joint syndrome,[39,40] cancer,[41] migraine headaches,[42] rheumatic conditions,[43-45] fibromyalgia,[46] and complex regional pain syndrome.[47] This emphasis on conceptualization, preparatory information, and cognitive transformation seems to have been incorporated into the Read method of natural childbirth, which replaces fear with knowledge about birth.[12] Sheila Kitzinger,[2] in her method of prepared childbirth, similarly emphasizes the necessity of "acquiring knowledge and understanding of what labor involves, the terminology used by obstetricians and midwives, and information about what happens in hospitals."

A study by Stevens and Heide[48] conducted at the University of Wisconsin used iced water to test perception and endurance of pain in subjects who had been taught methods used in childbirth education classes. Control subjects for this training and an additional control group were offered only distraction during the tests. Those who had been taught the techniques reported only about half the pain of that reported by control subjects and endured it 2.5 times longer. The prepared childbirth strategies improved with practice, were effective for pain lasting longer than most contractions in labor, and were more effective than distraction techniques.[48]

Attention-Focusing

Distraction or focused attention, mostly utilizing the rhythms of the breath, is essential to the Lamaze method, the most popular prepared childbirth program in America, and is important in the Bradley and other methods. Sheila Kitzinger[2] described the controlled attention focusing as:

> …concentration on what is happening, one's response to it as a task, and visualization of what is being achieved by the work of the uterus during contractions. The focus may be on the fantasy of the contractions as a shape provided by actual objects (furniture, architectural details, flowers, a painting) in the room, or a combination of these factors.

Stevens and Heide[48] found that attention-focusing functions effectively as an analgesia for labor pain. Such strategies are strongly supported by much psychological research. Hospitalized children with chronic illnesses who were taught distraction techniques were able to reduce measures of distress before and during medical procedures such as intramuscular and intravenous injections.[49] In a study of patients with burn pain, sensory-focusing techniques were more successful than distraction techniques in controlling pain, and both were more successful than standard care.[50] The focus may be on a competing response, as in a study by Kanfer and Goldfoot,[51] which showed that when attention was directed to self-presented external slides, individuals were able to increase their tolerance of the pain of cold water. Focus on a competing response was also shown in the use of hypnosis as an analgesic and in the meditative states of Raj yogis, who pinpointed attention on the tip of the nose or a point on the back of the skull, and then did not react physiologically to cold water, bright lights, or sudden sounds.[52,53] Other adepts in unusual feats of pain tolerance, such as having spikes stuck through the skin, either maintained an unfocused attitude, without evaluation, or pinpointed attention totally on the pain, but without evaluation.[54] In such cases, the attitude of detachment from the pain can be reflected by an undisturbed electroencephalography (EEG) pattern of α- or β-waves throughout performance of the feat.

Relaxation Training

Relaxation training, another essential element of pain control, is found in all childbirth training programs. A considerable body of literature supports its importance in pain control, because a state of lowered autonomic arousal is incompatible with anxiety. Although progressive muscular relaxation, systematic desensitization, and autogenic training are all well-established physiologic approaches to muscular relaxation, meditation traditions provide quicker methods to achieve what Benson[55] called the "relaxation response." One of the simplest meditation practices—maintaining a focal awareness of the flow of the breath—is taught by Rahima Baldwin[11] in *Special Delivery* and is identical to the ancient Buddhist practice of vipassana, or insight meditation.

Hypnosis

Hypnosis or autohypnosis is another method utilized to induce deep relaxation for pain control. It incorporates many of the therapeutic elements already referred to—focused attention, positive expectation, and a supportive or permissive attitude—in making suggestions that alleviate anxiety. Thus, its success in pain management may be viewed from a cognitive-behavioral perspective.[56] In one technique, "glove anesthesia" is induced in one hand and the "numb, heavy wooden feeling" so produced is transferred to the other hand, the face, and eventually to the abdomen to "relieve the discomfort" of uterine contractions (the word "pain" is never used, because its use would be countersuggestive).[57] Pain modulation in "highly hypnotizable" subjects has been confirmed through brain measurement of somatosensory event-related potentials to noxious stimuli, with highest amplitudes for these subjects recorded at frontal and temporal scalp sites.[58]

Counterstimulus Methods: Massage, Acupuncture, Transcutaneous Electrical Nerve Stimulation

The hand reflexology method of grasping combs during labor to activate points on the fingertips and balls of the hand that relate to uterine functioning is one example of counterstimulus strategy.[11] Foot reflexology, acupressure, acupuncture, and TENS might also share a common autonomic nervous mode of operation.

Transcutaneous Electrical Nerve Stimulation

In a controlled study of experimentally induced cold-pressor pain, the effect of electrical stimulation with TENS electrodes at two traditional acupoints in 20 subjects had an analgesic effect with statistical significance comparable to that of morphine, and the combined effect of TENS with morphine was stronger than TENS alone.[59] A series of controlled randomized double-blind studies on carpal tunnel syndrome pain found that the combination of low-level laser and microcurrent TENS on distant and local points significantly decreased McGill Pain Questionnaire Score, sensory and motor latencies, and Phalen and Tinel signs, compared with sham treatment.[60] A British study, investigating the relative hypoalgesic effects of different TENS parameters upon experimentally induced mechanical pain, found that low-frequency, high-intensity, extrasegmental stimulation (i.e., over an acupuncture point rather than over a nerve distribution) produced a rapid-onset hypoalgesic effect, which increased during the stimulation period and was sustained for 30 minutes after stimulation.[61]

Generally in TENS, the electrodes are placed over the painful area to stimulate the cutaneous nerves in that area. For use in labor, four electrodes are placed on either side of the midline of the spine to stimulate the posterior primary rami of the spinal segments (T11-L1 and S2-S4) receiving the painful stimuli during labor. It is interesting to note that these are the loci of acupuncture points (BL-20, BL-27, and BL-28) that are traditionally thought to reflect female reproductive function.

The selection of this area for stimulation is based on Bonica's account of the neurologic mechanism of delivery pain.[62] During the first stage, pain receptors are assumed to be activated by contractions of the uterus and dilation of the cervix. The evoked impulses are mediated in afferents that run in the hypogastric nerves and reach the spinal cord via the dorsal roots T10-L1. The pain is referred to large areas of the abdomen and back. During the second stage, pain is also caused by distention and stretching of the delivery canal, the pelvic floor, the vulva, and the perineum. The pain is localized, and the impulses reach the spinal cord mainly via the pudendal nerves and the dorsal roots S2-S4. The pain during the first stage is characterized as an ache considered to be mediated in small-diameter C fibers. During the second stage, the pain has the more localized intensive nature usually identified with the δ-afferent fibers.[62,63]

In the typical application of this technique for control of pain during labor, low-intensity stimulation is given continuously and a high-intensity stimulation can be initiated by the parturient herself whenever pain increases. Stimulation via the thoracic electrodes is maintained throughout the delivery at an amplitude that is maximal for a pleasant sensation, whereas sacral stimulation is added from the later part of the first stage. Table 42-1 summarizes the uniformly good results that have been reported.

Those patients who complained of backache have especially appreciated it. An Austrian study compared the analgesic effects of TENS, pethidine, and placebos on labor pain in 30 parturient women during the first stage of labor. Patients who received pethidine and those who were given TENS experienced considerable relief of pain.[69] A 1996 review of 30 studies on TENS stimulation of acupuncture points in labor substantiated the conclusions of earlier research.[70]

TABLE 42-1 **The Results of the Use of Transcutaneous Electrical Nerve Stimulation for Pain Control in Labor**

STUDY	NO. OF PATIENTS	Results (%)		
		GOOD	MODERATE	NONE
Augustinsson et al[64]	147	44	44	12
Andersson et al[65]	27	48	37	15
Kanfer and Goldfoot[51]	35	20	62	18
Stewart[66]	67	31	56	13
Kubista et al[67]	102	55	24	21
Bundsen et al[68]	347	47	42	11

In view of the relatively good results and lack of complications, the consensus of all the preceding studies is that the TENS method is recommended as a primary pain-relieving measure, to which conventional methods can be added as needed. Robson[71] commented that TENS is noninvasive and is believed to be safe for both mother and baby. It is easy to apply and can be operated throughout labor by the doctor, midwife, father, or mother. Augustinsson et al[64] were most impressed by the lack of complications, because the conventional methods, including analgesic and sedative drugs, nitrous oxide inhalation, epidural anesthesia, and local blockades, all possess a varying level of potential risk.[64] Another advantage is that TENS, because it does not give complete analgesia, does not eliminate pain as a diagnostic tool; it can be interrupted whenever needed for clinical evaluation. More important, perhaps, from the point of view of the woman in labor is the fact that her consciousness is not altered to the point of excluding her own active participation in and experience of the delivery.

Acupuncture

Hundreds of studies have investigated the efficacy and mechanisms of acupuncture analgesia for acute and chronic pain in surgical operations and in childbirth. In a review article of 24 studies, Lewith and Machin[72] found that the typical clinical trial showed a 70% efficacy of acupuncture compared with placebo treatment. Reichmanis and Becker[73] found similar results in a review of 17 studies of acupuncture analgesia in experimentally induced pain. On the basis of a thorough review of the clinical and experimental research on acupuncture pain control, Stux and Pomerantz[74] concluded that acupuncture analgesia helped from 55% to 85% of patients with chronic pain, comparing favorably with the effects of potent pain medication (such as morphine, which is 70% effective), and clearly distinct from the placebo effect, which helped 30% to 35%. At the same time, somatosensory EEG–evoked potential studies provided objective evidence of the analgesic effect of acupuncture.[75-77]

Recent randomized and double-blinded controlled studies demonstrated clinical effectiveness of acupuncture in treating chronic lateral epicondylitis[78] and chronic neck pain.[79] In the neck pain study, stimulation at distant points of the neck-related meridians were more effective than sham acupuncture points and "dry needle" injections of local myofascial trigger points, reducing motion-related pain by one third after a single treatment. A single-blind randomized controlled trial showed that electroacupuncture (EAP) was superior to manual acupuncture in treating patients

with tennis elbow.[80] A review article on treatment of fibromyalgia pain for patients at a hospital in Brazil showed improvement with traditional acupuncture, measured on subjective scales and number of tender points.[81] Preoperative EAP led to reduction in intraoperative and postoperative requirement of analgesic medications (alfentanil and morphine) in patients receiving gynecologic lower abdomen surgery.[82] Surgery that requires general anesthesia in Western countries is routinely performed in Chinese hospitals with the combination of acupuncture and local anesthesia for pain control, providing a considerable decrease in risk for surgical patients.

In their own study of acupuncture analgesia for normal delivery, Hyodo and Gega[13] tested 32 patients, equally divided between primaparas and multiparas. Low-frequency electrical current was introduced through needles at LI-4, ST-36, and SP-6, a standard therapeutic repertory for sedation of the reproductive organs. The results were assessed from relief noted by the patient (subjective scale) as well as from the obstetrician's observation (objective scale); among the primiparas, 62.5% found good or excellent effect on the subjective scale, and 62.6% good or excellent on the objective scale; and among the multiparas, 93.8% subjective relief and 93.7% objective relief were seen. Overall, 90% of the patients experienced relief of pain within 20 minutes of initiation of acupuncture anesthesia. These researchers noted the considerable disparity in reports of effectiveness of acupuncture from Japan and America, explaining it as a novelty effect. It is natural that in Japan, where no analgesic methods are normally used, the scoring in favor of acupuncture would be high compared with that in America.

Hyodo and Gega[13] concluded that acupuncture analgesia is useful for delivery, especially because of its safety, although its results are more erratic and less potent than those of conventional anesthetic techniques. More recently, a randomized controlled trial investigating acupuncture treatment as a complement or an alternative to conventional analgesia for labor in a Swedish hospital found that acupuncture significantly reduced the need for epidural analgesia, and parturients receiving acupuncture achieved a better extent of relaxation than the control group.[83]

One of the most influential and controversial studies of acupuncture over the past decade has been the so-called "German Acupuncture Trials "(GERAC) for chronic low back pain. This double-blind, randomized controlled trial involved 340 outpatient practices and included 1162 patients. Treatment according to principles of traditional Chinese medicine was compared with "sham" acupuncture, consisting of superficial needling at nonacupuncture points, and with conventional therapy (combining drugs, physical therapy, and exercise). After 6 months, effectiveness of acupuncture, whether true (47.6%) or sham (44.2%), measured on scales grading pain and functional ability, was almost twice that of conventional therapy (27.4%). Statistical significance level was $P < 0.001$. The controversial issue in this study was whether the method of "sham" acupuncture applied was an adequate control, considering that insertion of acupuncture needles at nontraditional points apparently produced acupuncture effects, including the possible mechanism of stimulation of endogenous opiates.[84]

A considerable amount of research has focused on determining a mechanism for acupuncture analgesia. A 1995 review of studies on acupuncture effects in pain and disease pointed out that, like exercise, acupuncture produces rhythmic discharges in nerve fibers and causes the release of endogenous opioids and oxytocin. Furthermore, "experimental and clinical evidence suggests that acupuncture may affect the sympathetic system via mechanisms of the hypothalamic and brain-stem levels."[85] Animal studies continue to demonstrate that acupuncture analgesia is mediated in the central and peripheral nervous systems by opioid peptides.[86-88] The cortex and hippocampus appear to participate in the modulation of chronic pain, and the analgesic action of EAP seems to operate along this pathway.[89] A study carried out on dogs seemed to verify the traditional theory of points of tonification and sedation, through differential production of sympathomimetic and parasympathomimetic effects on the cardiovascular system upon stimulation of different points. Carlsson,[88] a Swedish researcher, concluded that a mechanism for therapeutic acupuncture must include peripheral events that release neuropeptides, spinal mechanisms such as gate control, and supraspinal mechanisms through the descending pain inhibitory system, the sympathetic nervous system, and the hypothalamic-pituitary-adrenal axis. He cautioned that much of animal and human experimental acupuncture research shows only short-term hypoalgesia; that almost all such experimental research has been performed with EAP rather than the more gentle manual style of therapeutic acupuncture; and that pain threshold elevation in human experimental research does not necessarily predict the clinical outcome.

In a study of labor induction and inhibition by EAP, Tsuei et al[89] utilized SP-6 and SP-4 points, which are located in the territory of the L4 dermatome. The spleen meridian, to which these loci belong, runs across the dermatomes of L4, L5, L2, and L1, and then upward from T12 to T5. Because the sympathetic nerve controlling the uterus through the pelvic plexus receives preganglionic fibers from T5 to L4, Tsuei et al[89] concluded that it is highly possible that stimulation of the electropermeable loci within this area may alter the physiologic function of the uterus. The LI-4 points of the upper extremities, often added to the spleen meridian points in the acupuncture control of labor pain, perhaps represent the central approach to the autonomic nervous system, because these loci control pain to the head and neck. It should be noted, however, that Motoyama,[90] who attempted to verify the traditional subtle anatomy of meridian pathways through tests of electrocutaneous resistance at meridian points, claimed that these effects could not be adequately explained in terms of the conventional sympathetic dermatomes but instead imply an alternative bioelectric transmission system.

The discovery of the head McKenzie sensory zones showed the possible mediation of the invisible meridians and points of traditional Eastern medicine between internal organs and corresponding skin areas. Nakatani[91] was able to detect the electropermeable line as an apparent viscerocutaneous autonomic nerve reflex when organic diseases were involved. Hyodo[92] explained acupuncture stimulation as the transmission of impulses centrally from the reactive electropermeable loci via a sympathetic afferent fiber, and that the autonomic nerve in the viscera is stimulated to response by the reverse of the McKenzie theory. An exciting recent development in acupuncture research has been the finding by functional neuroimagery of neuronal correlates of acupuncture stimulation in the human brain. In a controlled study of EAP stimulation of GB-34 on the left leg, real EAP elicited significantly higher activation over the hypothalamus and primary somatosensory motor cortex than mock and minimal EAP, showing that the hypothalamic-limbic system was significantly modulated by EAP at acupoints.[93]

Other Methods

The scope of this chapter does not permit detailed discussion of other promising methods of pain control, but mention can be made of massage, biofeedback, and nutritional and botanical agents for

treatment of pain. A literature search led to the conclusion that massage, particularly acupressure, is effective for low back pain, especially when it is combined with exercises and education, with beneficial effects lasting at least 1 year after the end of treatment.[94] A vast amount of literature is available on biofeedback training for pain. An article suggesting a future direction in pain medicine described the use of "off-the shelf," low-cost, and low-bandwidth telemedicine equipment to deliver clinical biofeedback treatment when the patient and provider are in two different locations.[95] In a randomized double-blind trial of 30 patients with chronic maxillofacial pain, significant reduction in pain scores and improvement in tolerance of experimentally induced dental pain were achieved with administration of 3 g daily of the amino acid tryptophan and a high-carbohydrate, low-fat, low-protein diet in comparison with placebo.[96] Among botanical agents for pain, corydalis rhizome or tuber (yanhusuo) is well known in the Chinese materia medica for its analgesic effect, containing combined alkaloids found to be 40% as effective as morphine. Acting probably through inhibition of the reticular activating system, corydaline was shown in one clinical study to decrease or relieve pain in 32 of 44 patients with dysmenorrhea.[97]

SUMMARY

This chapter has presented many of the current nonpharmacologic strategies for control of pain. Because the mechanism of pain perception has been shown to involve both physiologic and psychological components, the optimal treatment might combine psychological factors, such as preparatory information, attention focus, relaxation, and supportive communication, with the physical stimuli of TENS or acupuncture. Such a multidisciplinary approach to patients with chronic back pain was evaluated after a 4-week program that included back schooling, psychological intervention, and treatment by acupuncture, chiropractic, the Alexander technique, and a pain specialist. Significant improvement was maintained for a period of 6 months.[98]

Dental researchers of the Pediatric Pain Program of the University of California at Los Angeles School of Medicine searched several databases for reports of randomized, controlled clinical trials of complementary and alternative medical modalities used to treat chronic facial pain. Three acupuncture trials, eight biofeedback trials, and three relaxation trials met the researchers' inclusion criteria, suggesting that these modalities were comparable to conventional treatment such as an intraoral appliance.[99]

Increasingly, the multidisciplinary pain management team, incorporating a variety of nonpharmacologic treatment modalities, is being considered "the optimal method for delivery of comprehensive treatment to patients in pain."[100] The incorporation of "alternative" forms of pain management, including acupuncture, relaxation techniques, hypnosis, biofeedback, and guided imagery, is acknowledged by the Children's Hospital of the Medical College of Wisconsin to complement pharmacologic management of children's pain.[101] The selection, balance, and application of these treatment components should be based on consideration of an individual's coping styles. Such a treatment program could be developed to provide a more consistently effective analgesia than the individual components can provide separately. Relieving the pain of childbirth, for example, without diminishing or distorting the full consciousness of the experience for the mother, would be consistent with the goals of the contemporary physician of natural medicine.

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CHAPTER 43

Nontransfusion Significance of ABO and ABO-Associated Polymorphisms

Peter J. D'Adamo, ND, MIFHI, and Barbara Siminovich-Blok, ND, LAc

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INTRODUCTION

Concepts without percepts are empty; percepts without concepts are blind.
—Immanuel Kant (1724-1804)

Since Landsteiner first described the ABO typing system in 1900, the preeminent clinical role of this red cell antigen–serum antibody system has been the prediction of reactions involving transfused blood and, to a lesser degree, transplanted organs. Despite this exceedingly important role, however, no rational individual should conclude that the proper exchange of blood or other tissues constitutes their primary biological role.

It can be argued that the overwhelming and revolutionizing influence of the ABO system on the history and practice of transfusion medicine and the general reluctance of allopathic medicine to find a workable niche for the nonreducible have had the effect of precluding interest in the nontransfusion significance of ABO polymorphism and, attendant to that, of a lack of any meaningful medical applications.

This chapter examines the biological significance of the ABO blood grouping and the ABH secretor system, with special attention to the effects of ABO expression as a "tipping point" for a variety of physiologic and pathologic manifestations that may be of interest to the practitioner of natural medicine.

BACKGROUND

Although a comprehensive review of the glycobiology of the ABO system is beyond the scope of this work, the brief overview given here should allow the reader to understand the basic mechanics and nomenclature of the system.

All humans can be typed for ABO blood group. There are four basic blood types: A, B, AB, and O. The system is composed of two antigens and two antibodies. The specific combination of these four components determines that individual's type. Table 43-1 shows the possible permutations of antigens and antibodies with the corresponding ABO types.

ABH Antigens

The ABO blood group antigens are not primary gene products but instead enzymatic reaction products catalyzed by enzymes called glycosyltransferases. As depicted in Figure 43-1, they are synthesized from an oligosaccharide intermediate, "H substance", which is produced by the monosaccharide fucose. Group A or B activity is produced by the addition of a single sugar on the nonreducing end of the H chain. Adding the glycoprotein *N*-acetyl galactosamine (GalNAc) to the end of the chain results in blood group A antigenicity. The terminal carbohydrate and the B group antigen is the monosaccharide galactose. There is no true O antigen: the terminal carbohydrate of O (H) antigen is the monosaccharide fucose. We identify the blood types as "ABO" but typically refer to the actual antigen system as "ABH."

ABH substances manifest quite early in life processes.[1] They are detected in the cell membranes and secretions of human embryos at about 5 weeks' gestational age in the epithelium and virtually all vascular endothelium. In fetal organs' endothelial cells, the expression of ABH antigen is ubiquitously upregulated. This is considered suggestive evidence that blood group antigens serve as early immunomorphologic

TABLE 43-1 **Possible Combinations of Antibodies and Antigens in the ABO Blood Grouping System**

ABO BLOOD TYPE	A ANTIGEN	B ANTIGEN	ANTI-A ANTIBODY	ANTI-B ANTIBODY
A	Yes	No	No	Yes (IgM)
B	No	Yes	Yes (IgM)	No
O	No	No	Yes (IgM, IgG)	Yes (IgM, IgG)
AB	Yes	Yes	No	No

Ig, immunoglobulin.

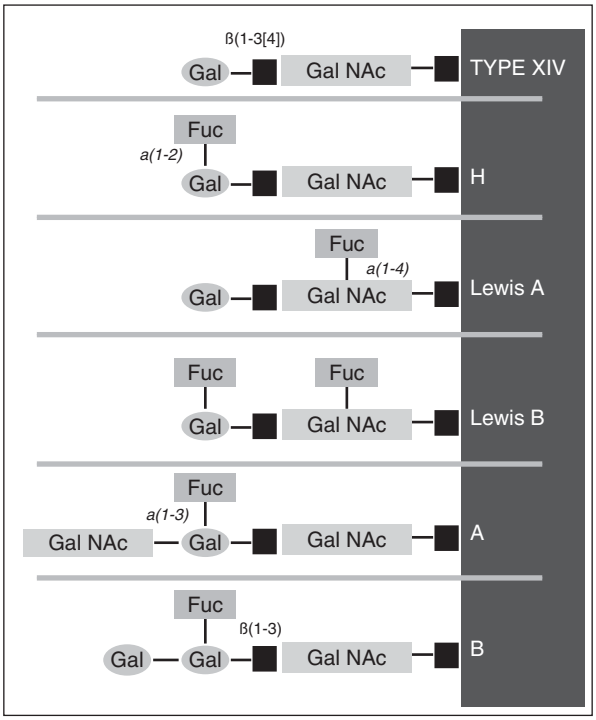


FIGURE 43-1 Structures of the nonreducing end of the ABH and Lewis blood group antigen determinants.

markers of the endothelial differentiation of mesenchymal cells, specifying the location of future blood vessels.[2]

All embryonic epithelia contain the ABH antigen, except those of the nervous system, adrenal glands, and liver. The antigens subsequently disappear from epithelia in an orderly and predictable manner as evidence of morphologic differentiation appears. By about the end of the third intrauterine month, the adult pattern of distribution is achieved.

The embryonic expression of ABH antigens may be an important aspect in the pathogenesis of certain diseases: a scrutiny of 2557 medical records for children with type 1 diabetes and controls showed ABO blood group incompatibility in close to 90% of children with diabetes,[3] indicating that maternal–fetal ABO incompatibility may have acted to inhibit normal pancreatic islet formation in the fetus.

The expression of ABH antigens in the adult is tightly regulated, and their reappearance in adult tissue—normally devoid of them—is virtually always a sign of disease. Inappropriate ABH expression is one of the prime manifestations of the aberrant glycosylation state that is a hallmark of malignancy. Instances have been observed indicating that aberrant ABH expression may be paralleled in entirely different organ systems. A link has been demonstrated between ABH antigen expression in normal and neoplastic colonic epithelia and consequent alterations of ABH expression in the thyroid.[4]

ABH Secretors and Nonsecretors

By 1930 it had been shown that some people do and others do not secrete antigens corresponding to their ABO blood group into their saliva. Persons with these substances in saliva (secretors) have more ABH substances in their tissues than those lacking the substance in their saliva (nonsecretors). The ability to secrete behaved as a simple Mendelian function dominant to nonsecretion. Persons with blood groups A, B, and AB who are secretors secrete the antigens corresponding to their blood groups. Group H persons secrete the H substance, as do all other secretors, to a somewhat lesser extent.

ABH substances are secreted by mucous glands in many organs, including the upper respiratory tract, the gastrointestinal tract from the esophagus through the colon, and the uterine cervix. ABH secretor status is a major conditioner of the gut mucosa. ABH secretors have greater quantities of free ABH antigens in the makeup of their intestinal secretions, which has significant effects on bacterial and lectin adherence to the gut microvilli. The secretor gene regulates the synthesis of blood group substances in superficial glands of the gastric and small intestine mucosa. Large amounts of ABH material are found in all secretors,[5-8] characterized by a uniform distribution of blood type antigens in the gastric pits. ABH expression is independent of secretor status: glands situated deep in the mucosa of the pylorus and small intestine (Brunner glands) and gastric parietal glands both produce A and B substances without regard to secretor status.[9]

For a more detailed discussion of the metabolic consequences of ABH secretor status, the reader should refer to the author's article specifically on the subject.[10]

Brush-Border Hydrolases

ABO blood group determines much of the enzyme activity in the tissue (brush border) of the intestine. At least six intestinal hydrolases have ABO blood group antigenic determinants directly related to ABO blood group. The expression of ABH antigens secreted by intestinal glycoproteins is under the control of the secretor gene; therefore, these antigens are not detected in the hydrolases of nonsecretor subjects.[11]

Intestinal Alkaline Phosphatase Activity

Intestinal alkaline phosphatase (IAP) is involved with both the breakdown of dietary cholesterol and the absorption of calcium. The activity of IAP and serum alkaline phosphatase (SAP) is strongly correlated with ABH secretor phenotypes. It has been estimated that the SAP activity of nonsecretors is only about 20% of the activity in the secretor groups.[11-15]

ABO polymorphism is linked to the levels and persistence of IAP.[16] Numerous studies have associated group O individuals with the highest alkaline phosphatase activity, and group A with the lowest.[17] In addition, one study implied that the group A antigen itself might inactivate IAP.[18]

Bacterial Flora

The role of the ABO blood group in determining the bacteria making up a healthy gastrointestinal ecosystem is particularly strong in ABH secretors. Because ABH secretor status and ABO

blood group dictate the presence and specificity of A, B, and H blood group antigens in human gut mucin glycoproteins, their status can influence the populations of bacteria capable of taking up local residence. This occurs because some of the bacteria in the digestive tract are actually capable of producing enzymes that allow them to degrade the terminal sugar of the ABH blood type antigens for a constant food supply.[19] Bacteria capable of degrading blood group B antigen can detach the terminal α-D-galactose. Group A–degrading bacteria can detach the GalNAc. These bacteria have a competitive advantage and can thrive in the environment created by the preconditioning of ABH secretions. Although comparatively small populations of bacteria produce blood group–degrading enzymes (estimated populations are 10^8 bacteria per gram), the quantity of these bacteria are several orders of magnitude greater in different blood types, and they are much more stable residents. For example, B-degrading bacteria have a population density about 50,000-fold greater in blood group B secretors than in other subjects. Similar bacterial specificity and enzyme activity are found in other blood types.[20]

Evidence suggests that ABH nonsecretors have lower levels of immunoglobulin-G (Ig-G)[21,22] and secretory IgA concentrations than secretors.[23,24] ABH nonsecretors appear to have a higher prevalence of a variety of autoimmune diseases, including ankylosing spondylitis, reactive arthritis, psoriatic arthropathy, Sjögren's syndrome, multiple sclerosis, and Graves' disease.[22,25-27]

Blood Group as Self-Declaration and Adhesion Molecules

In the larger world of glycoproteins, ABH antigens are characterized as O-linked glycans (glycosylation at serine or threonine residues by GalNAc). Many proteins in nature carry these dense and complex arrays of covalently attached sugar chains. Their biological roles are particularly important in construction of complex multicellular organisms and organs.

Glycans are typically on the cellular outer surfaces and outside of secreted macromolecules; therefore, they can mediate interactions between organisms. They are also involved in cell-to-cell and cell-to-matrix interactions that are crucial to the development and function of complex multicellular organisms.

Glycans can have a significant effect on fungal, viral, and bacterial pathogenicity.[28] ABH antigens are ubiquitous in nature, found abundantly in foodstuffs (where they are thought to play a role in the induction of opposing blood group antibodies early in life) and in a host of microorganisms.

A 1995 study showed that of 833 fungi harvested from 1977 to 1994, 422 extracts (47.8%) produced agglutination of human red blood cells (RBCs), equally distributed against type O, A, and B cells. The fungal agglutinins, in this case, are desirous of attaching and infecting seeds or other microbes that possess some "ABO blood type" activity of their own.[29]

ABH antigens appear in secretions by 8 to 9 weeks of age, first in the salivary glands and stomach, then throughout the gastrointestinal and vaginal tracts. The ABH variation of blood group antigen expression on vaginal epithelial cells and mucus has a significant role in susceptibility to urinary tract infections in women.[30]

Infertility and Spontaneous Abortion

ABO blood type incompatibility may be a critical factor in infertility. ABO-incompatible mating couples (a type A male fertilizing a type O female) are a common occurrence in miscarriages, especially very early in the gestational term. One study of 288 miscarriages showed that there was an excess of blood type A and type B in otherwise normal fetuses. The researchers concluded that the ABO incompatibility between mother and fetus was likely a cause of early miscarriages, but almost exclusively in chromosomally normal fetuses.[31-34]

In a study of 102 infertile couples, Solish[35] found that 87% were blood type incompatible. This researcher suggested that the infertility was due to the presence of antibodies in the secretions of the mother's genital tract or incompatible sperm from the father. In another study, a total of 589 compatible mating couples were compared with 432 incompatible mating couples. The mean number of living children presented a significant difference. There was a 21% deficiency of type A children in the two groups. Similarly, there was a 16% deficiency of type B children in the two groups. It appears that a 31.9% rate of miscarriage is associated with incompatible matings, compared with 17.15% in compatible matings. This finding has led some researchers to theorize that ABO incompatibility results in "cervical hostility" between the man's blood type antigens, which are present in his sperm, and the woman's opposing antibodies, present in her cervical mucus.[36]

Besides infertility, habitual abortion is also related to ABH secretor status as shown in 2010. Secretor status of 66 couples with recurrent spontaneous abortion (RSA) was obtained and compared with couples with successful term pregnancies. It was found that a secretor phenotype of couples with RSA, especially of the husband, could facilitate "reproductive success" and that couples in which both parents were secretors, the RSA probability was extremely diminished.[37] A previous study showed the interaction between ABO blood groups and adenosine deaminase genetic polymorphism during intrauterine life, providing results that could not be explained by strictly conventional immunologic mechanisms. The authors concluded that cell-to-cell interactions involving ABO antigens might have an important role at implantation, and that adenosine deaminase, through control of local adenosine concentration, could modulate these interactions, influencing the probability of successful implantation.[38] A third and most recent study comparing secretor status compatibility between mother and child suggested an intrauterine selection against Se- (nonsecretor) of the embryo carried by an Se+ (secretor) mother. The selection was dependent on factors influencing the maternal environment.[39]

To measure women's fertility below age 45, follicle-stimulating hormone (FSH) levels are measured. Women with an FSH level greater than 10 are considered to have diminished ovarian reserve. In an ongoing study at Yale University and the Albert Einstein College of Medicine, it was observed that women with types A or AB blood were significantly less likely to have an FSH greater than 10 than were women with types O or B blood. They concluded that type O blood might affect fertility.[40]

Other Immune Correlates

In 1991, D'Adamo reported that individuals of group O blood reporting previous urticaria or anaphylaxis showed high residual titers of anti-A isoagglutinins. A score value was assigned to each agglutination reaction. Individuals with these disorders showed remarkably high titration scores compared with controls of the same blood group, up to three times higher. Mild increase was noted for group O subjects with severe eczema or asthma, but total scores in these subjects were only marginally greater than those of controls. A striking association was shown for group O women experiencing endometriosis.[41]

ABO and Secretor Blood Group Genetics

ABO System

In 1910 Epstein and Ottenberg suggested that the ABO blood group system could be inherited.[42] The determination of ABO status is the result of two co-dominant alleles and one recessive allele found on chromosome 9q band 34.

A and B blood group genes are dominant over the O blood group, and the A and B group genes are themselves co-dominant. The ABH antigens are not primary and direct gene products; they are the reaction products catalyzed by glycosyltransferases type of enzymes.

ABO genes consist of at least seven exons, and the coding sequence in the seven coding exons spans more than 18 kb of the genomic DNA. The single nucleotide deletion found in most (but not all) of the O alleles that is responsible for the loss of the activity of the enzyme is located in exon 6.[43]

ABH Secretor System

The secretor gene (*FUT2* at 19q13.3) codes for the activity of glycosyltransferases needed to assemble (secrete) free ABH antigen in body fluids like saliva, semen, vaginal fluid goblet cells, and mucous gland cells. This is accomplished in concert with the gene for group O or H *(FUT1)*. Secretor status is determined by two alleles on *FUT2*, *Se* (dominant) and *se* (recessive), with approximately 80% of the population typing as secretors (*SeSe* or *Sese*).

Lewis Blood Groups and Their Association with the ABH Secretor System

The ABH secretor system is a major determinant of the Lewis (Le) blood grouping system. This is due to the fact that, in addition to ABH, *FUT1* and *FUT2* provide the glycans necessary for conversion of Le antigens as well.

Two broad categories of Le blood type exist. These are the "Lewis positive" (either Le^{a+b-} or Le^{a-b+}) and "Lewis negative" (Le^{a-b-}) phenotypes. Depending on race, between 1% and 8% of the population are Lewis negative.

In Lewis-positive phenotypes, Le^a is formed initially, and in the case of nonsecretors (lacking the *Se* gene, *FUT2*), Le^a glycan is attached to the red cell, and they type as Le^a. In the case of secretors, the *Se* gene activates the H gene, which causes an additional sugar to be added to Le^a, converting it to Le^b (see Figure 43-1).

Among Le-positive individuals, ABH secretors are always Le^{a-b+} because they convert all their Le^a antigen into Le^b. Conversely, among Lewis-positive people, ABH nonsecretors are always Le^{a+b-} because they lack the *FUT2*-dependent glycosyltransferase to accomplish this conversion.

Thus, it is often possible (and quite handy) to use the Lewis groups to infer ABH secretor status, because Lewis typing is fairly quick to perform and easy to master compared with the traditionally used salivary inhibition test. However, using Lewis typing to infer ABH secretor status works only in those individuals who are Lewis-positive (about 9 of every 10 patients). Lewis-negative individuals can either be secretors or nonsecretors. Lewis-negative patients carry important metabolic consequences of their own, worthy of much attention.[10] Table 43-2 shows Lewis blood types and their relationship to ABH secretor and/or nonsecretor status.

Sialylated forms of several Lewis variations (sialyl Lewis A, sialyl Lewis X) are oligosaccharide ligands now considered crucial to the initial adhesion of white blood cells to a site of injury mediated by E-selectins. Large quantities of sialyl Lewis X have also been found on the surfaces of certain tumor and cancer cells, and one of its variants (sialyl 6-sulfo Lewis X) appears to be involved in routine homing processes involving a variety of chemokines.

TABLE 43-2 **Lewis (Le) Blood Types and their Relationship to ABH Secretor and/or Nonsecretor Status**

LEWIS TYPE	CATEGORY	ABH SECRETOR STATUS
Le^{a+b-} Le^a antigen but not Le^b	Lewis positive	ABH nonsecretor
Le^{a-b+} Le^b antigen but not Le^a	Lewis positive	ABH secretor
Le^{a-b-} Neither Le^a nor Le^b	Lewis negative	Lewis outcome cannot determine ABH secretor status

Individuals of blood group O phenotype run an approximate 1.5- to 2-fold higher risk for development of peptic ulcer disease,[44] although there is no direct correlation between ABO blood group phenotypes and the prevalence of *Helicobacter pylori* infection. However, in addition to H type 1, the Le^b antigen is also a binding receptor for *H. pylori,* and in this capacity, it can best be described as a "virulence promoting factor." For virulent strains, Le^b antigen binding activity targets the microbes to the epithelial cell surfaces and potentiates the effect of secretion of virulence factors, such as the vacuolating cytotoxin and/or neutrophil activating–recruiting factors.[45]

Linkage and Pleiotropism

Linked genes occur on the same chromosome and are inherited as a single unit. Gene linkage analysis shows several genes linked to the ABO locus. For example, there are strong indications that a gene regulating dopamine β-hydroxylase activity is linked to the ABO blood group locus.[46] Dopamine β-hydroxylase is a key enzyme in the conversion of dopamine to norepinephrine.

This linkage may help explain the continued significance of ABO group as a discreet and significant genetic marker for a variety of affective disorders, including type A behavior in men subsequent to myocardial infarction[47] and bipolar depression,[48,49] each of which has been associated with blood group O. The ABO locus shows putative linkage with platelet monoamine oxidase activity,[50] reduced levels of which have been noted in group O healthy men.[51]

Additional evidence implies that there is a linkage between the ABO gene and the gene that regulates the activity of the enzyme argininosuccinate synthetase, which recycles arginine from citrulline in the production of nitric oxide.[52] A letter to the editor in the journal *Lancet* reported differences between ABO groups in their responsiveness to inhaled nitric oxide therapy: types with a B antigen (B and AB) had less success with this therapy.[53]

Elevated factor VIII (FVIII) levels contribute to venous thrombotic risk. FVIII levels are determined to a large extent by levels of von Willebrand factor (vWF), a protein that protects FVIII against proteolysis.[54] ABO polymorphism is one of the best-characterized genetic modifiers of plasma FVIII; it accounts for approximately 30% of the total genetic effect.[55] Subjects with blood group non-O have higher vWF and FVIII levels than individuals with blood group O.[56]

Digit ratio, a marker of assessing the levels of prenatal exposure to androgens, has yielded mixed results[57,58] as a predictor of androgen stimulation in individuals with polycystic ovarian syndrome. However, preliminary evidence suggests that genes contributing to

the expression of 2D:4D reside in the vicinity of the gene loci (chromosomal locations: 9q34.2 and 1p36.11) of the blood groups or that there may be pleiotropic effects on digit ratio as a result of the blood group genes. Associations using digit ratios may require incorporation of ABO blood group in their interpretation.[59]

Additional Physiologic Correlations

In addition to the previously described variations in IAP and brush border hydrolase activity, several additional circumstances where ABO polymorphism exerts a significant influence on physiology have been reported.

Gastric Acidity

Because the prevalence of both pernicious anemia and gastric cancer is higher in individuals of blood group A and that of duodenal ulcer higher in those of group O, a hypothesis relating blood group effects on acid secretion was inevitable.[60] Early work confirmed that acid output tended to be greater in group O than in group A subjects.[61,62]

Gastrin and Pepsinogen

In one study, serum pepsinogen A (pepsinogen I) levels were studied in relation to ABO blood group, age, and sex in 700 healthy blood donors. Serum pepsinogen A levels were higher in males than in females and rose with increasing age. Blood group O individuals showed higher serum pepsinogen A levels than blood group A individuals.[63] There is also evidence that the type A antigen in gastric juice binds to pepsin and possibly inactivates it.[64] A study using serum pepsinogen levels as a marker for gastric atrophy showed a high association with blood groups A and B.[65] However, possibly owing to the polygenic nature of pepsinogen activity, one study failed to find any significant difference in pepsinogen levels between ABO groups.[66]

Another study looking at ABO polymorphism and serum gastrin concentration after stimulation by a glycine drink could find no correlation with ABO blood group.[67] However, the study had a simple preprandial and postprandial methodology. In a separate study, the concentrations of gastrin were measured in the blood of 121 fasting healthy Greek volunteers of both sexes and different ABO blood types, between ages 20 and 70 years. The testing took place immediately after a test meal was eaten by subjects who had fasted for 8 hours; the measurement was repeated at 10 and 40 minutes post meal. The researchers found that gastrin levels took 40 minutes to increase after the meal in the blood type A and B subjects, but that a significant increase appeared 10 minutes after the meal in the blood type O subjects.[68]

Cholesterol

Although several studies on highly select populations have yielded conflicting results,[69,70] the general consensus is that blood group A individuals have a significantly higher basal cholesterol level than those in other blood groups. The relationship between ABO blood phenotype and total serum cholesterol level was examined in a specific Japanese population. The results showed that cholesterol levels were very significantly elevated in the blood type A compared with non-A.[71]

ABO blood group and coronary risk factor levels were measured in a nationwide sample of more than 6000 black and white adolescents aged 12 to 17 years. Blood group A was associated with significantly higher serum total cholesterol levels in white females independent of all other risk factors, in white males independent of age and weight, and in southern black females independent of age and weight.[72] A separate study (the Bogalusa Heart Study) looked at 656 white and 371 black adolescents and found the same results with regard to total cholesterol; even higher levels of low-density lipoprotein cholesterol were found in type A adolescents than in other blood types.[73]

Stress

Several studies have identified differences between ABO group and possible chemical responses to stress. Interestingly, individuals of blood group A appeared to have a lower incidence of "type A personality."[74]

One study evaluated the influence of blood type A versus O coupled with a mirror-drawing stressor on very-low-density lipoprotein toxicity-preventing activity (TxPA). Plasma cortisol levels showed significant ABO variation. Exposure to the stressor significantly decreased TxPA and increased cortisol for the total group of 25 older men. The stress response patterns of the 15 blood type A men were different from those of the 10 type O subjects. The blood type A group had higher initial levels of TxPA and cortisol as well as quicker stress recovery rates than the type O group.[75] Another study showed that blood group A individuals responded to a stressful situation (venipuncture) with higher levels of cortisol and, possibly, of adrenaline.[76]

Rheology

For purposes of this discussion, rheology is used to describe the dynamics between blood clotting (moving toward a solid state) and blood thinning (moving toward a liquid state). It might be tempting to substitute the word viscosity for rheology when talking about blood types and clotting. Viscosity, however, does not cover the "dynamics" of how, when, and why blood can change texture; it only distinguishes one texture state from another.

There is evidence that the rheology of blood may play a role in a variety of chronic anxiety states. Compared with normal subjects, chronic depressive and schizoid patients had very significant differences in their blood rheology and in the ability of their RBCs to aggregate. When patients with schizoid anxiety were compared to those with depressive anxiety, their ratio of albumin to globulin was increased. When patients were divided according to their ABO blood groups, significant differences were found in their albumin/fibrinogen ratio and their blood viscosity. This was particularly true for women who had blood type A and who had depressive anxiety; their blood tended to be substantially "thicker" and to have higher amounts of serum proteins in it than women with similar depression who had blood type O.[77]

Associations between the ABO phenotype and variations in blood rheology have also been reported in high blood pressure[78]; stress[79]; diabetes[80]; heart attack, cancer, and thyroid disease[81]; kidney failure[82]; and malignant melanoma.[83]

Soluble Endothelial Cell Markers

Selectins are cell–cell adhesion molecules that are involved in leukocyte–endothelial cell adhesive interaction, which is required for extravasation at target tissue sites. Three types of selectins have been discovered: L-selectins are generally expressed on almost all leukocytes; E-selectins are inducible on vascular endothelium upon stimulation with cytokines; and P-selectins are found on activated platelets.

The role of thrombomodulin as a C-type lectin is less known. It has a domain that interferes with neutrophil adhesion to endothelial cells. Elevated levels of E-selectin (P <0.001) and thrombomodulin (P <0.001) are linked with blood type A individuals.[84]

PATHOLOGIC PROCESS AND ABO BLOOD GROUPS

Mental Disease

There are several reports exploring the relationship of ABO groups, ABH and Lewis secretor type, and mental disease like obsessional illness,[85] bipolar disorder,[86,87] depression,[88] and schizophrenia.[87] A significant part of that research was done in the 1970s and 1980s and does not seem to have been updated or explored much further. Most of the articles reviewed and not discussed here were not conclusive about blood group associations.

Cardiovascular Disease

Stroke

A European study compared 50 patients with stroke. The standard expected frequency of ABO blood types in the surrounding population showed that the frequency of the blood group A in the patients with stroke was 120% greater than would normally be expected. The percentage of blood type B was even higher (159% of expected rate of occurrence). Patients with blood type O were only 85% as likely to experience stroke.[89]

A 1979 study of 220 patients with stroke looked at the viscosity of their blood a few hours after the stroke event. About 80% of the patients had blood cells that easily aggregated. What was especially interesting was the discovery by the researchers that the clotting of blood in patients with A and B blood types was mostly due to fibrinogen, whereas in blood types O and AB it was caused by other clotting factors.[90]

Individuals with blood types A and AB have a generalized tendency toward problems associated with blood clotting, whereas problems in those with blood types B and O appear to be linked to excessive bleeding and poor clotting. This observation was verified in several studies, the largest being performed in 1460 patients with "stroke" and reported in the *Lancet*. In 329 cases, the cause of death was certified as cerebral thrombosis (brain clot). In the thrombosis cases, there was an excess of patients of blood types A and AB and a deficiency of those with blood types O and B. In the 482 "strokes" that were due to cranial bleeding, the reverse was true: there was a significantly higher proportion of patients with blood types O and B than of those with blood types A and AB.[91]

A 2009 United Kingdom systematic review tried to assess whether the effects of non-O status on thrombosis risk were of the magnitude predicted by its effect on vWF/FVIII levels. They confirmed the historical impression of linkage between some vascular disorders and non-O blood group status. They concluded that the odds ratios were similar to those predicted by the effect of ABO(H) on vWF levels on thrombosis. They proposed further work to understand and refine the effect of reducing O(H) antigen expression and therefore a more widespread adoption of ABO(H) typing.[92]

Peripheral Artery Disease and Venous Thromboembolism

Peripheral artery disease (PAD) occurs in approximately 12% of the adult population. The prevalence of PAD rises with age: almost 20% of people older than 70 years have the disease. E-selectin and thrombomodulin levels are always elevated in intermittent claudication, a disorder almost always found with PAD and carrying a distinct association with blood type A.[93]

In 125 patients experiencing venous thrombosis in a Brazilian population, a higher than expected proportion of blood group A and a lower than expected proportion of blood group O were observed among the patients.[94] This is consistent with the previously discussed influence of ABO on a third soluble endothelial product, wWF, and its role in thromboembolism. Another study in 2007 confirmed than non-O blood type was independently associated with risk of venous thromboembolism, and added to the risk associated with FV Leiden.[95] Even in pregnancy, a nested case–control study within a cohort of 71,729 women who gave birth to 126,783 children in Denmark showed that blood groups A and AB might be associated with increased risk estimates for venous thromboembolism in pregnancy and the puerperium.[96]

Heart Disease

There is a clear-cut association with having A and AB phenotypes and an increased risk for heart disease. This association has been reported continuously in the scientific literature over the last 50 years. Individuals who have blood type A have higher rates of heart attack in all age groups, both genders, and all ethnic and national groups.

In 1962, the Framingham Heart Study typed the blood of the surviving 4125 members of the original study group of 5209 people first examined in 1948 to 1951. The most striking observance was the lower rates of nonfatal heart disease in men aged 39 to 72 years with blood type O than in those with blood type A.[97] A 1994 Polish study on patients who underwent coronary bypass surgery with highly advanced arteriosclerosis of the coronary arteries found a significantly higher number of cases with group AB and a lower number of those with group O.[98] A 1981 German study of 13,175 patients showed a prevalence of blood type A in all types of heart disease examined.[99]

In a study of 191 coronary artery bypass candidates, investigators paradoxically found an excess of type O over type A subjects. After examining the data more closely, they concluded that the tendency of type A subjects for more ready development of blood clots ("thrombotic proneness") led to a poorer prognosis. In essence, the blood type A subjects were missing from the study because they had already died in greater numbers, leaving a disproportionate number of type O subjects among the long-term survivors.[100] In a study of male survivors of heart disease, researchers found that there were fewer patients who were type A and younger than 55 years than would have been otherwise expected.[101]

A 1975 Italian study of 746 patients with high blood pressure, 3258 with congenital heart disease, and 4503 with a history of heart attack found a significant lack of patients with type O blood, and a significant excess of blood type A patients in the group with myocardial infarction. The study also showed an excess of blood type A patients with high blood pressure, and a lack of patients who were blood type B.[102] A 1983 study of 255 women originally investigating the effects of smoking on the rates of heart attack also found several other factors significantly associated with heart attacks in this group, including hypertension, angina pectoris, family history, diabetes mellitus, and blood type A.[103]

Platt et al[104] examined blood type and heart attacks in two different age groups. The patients were divided into two groups: 65 years or older and younger than 65 years. The predominance of blood type A in patients with cardiac infarction was "highly significant" in both age groups (P <0.005). This study was unique in that it excluded other risk factors, such as smoking, high blood pressure, diabetes, and high cholesterol levels. When the researchers looked specifically at the older group, the predominance of blood group A in those with cardiac infarction was even higher (P<0.001). The researchers concluded, "Our investigation strongly suggests the existence of a genetic factor associated with blood

group A and independent of the other risk factors, which is also responsible for a greater incidence of cardiac infarction."[104]

An 8-year study of 7662 British men found that blood type A was linked to the incidence of ischemic heart disease as well as higher total serum cholesterol concentrations.[105]

Cancer

> *"Some cancers contain an A-like substance even when they occur in persons who are not A or AB. These observations suggest that in the tissues, both normal and neoplastic, of all persons, there are blood group A-like antigens present at a biochemical level, which are usually inaccessible to the immune system." Mourant, AE (Blood Groups and Disease, 1977)*

Tumor development is usually associated with changes in cell surface carbohydrates. Cell glycosylation depends on the expression and function of various glycosyltransferases and glycosidases. These enzymes modify the carbohydrate core structure or the terminal carbohydrate structures, resulting in the incomplete synthesis or modification of existing carbohydrates. Numerous data demonstrate that malignant transformation is associated with various and complex alterations in the glycosylation process.

These and other changes provide a selective advantage for tumor cells during their progression to more invasive and metastatic forms. Some of the more studied glycoprotein modifications include:[106]

- Increase in *N*-glycation and O-glycation and fucosylation processes
- Increase in mucins
- Alteration in galectin levels and specificities
- Increase in cell surface sialylation
- Increase in chitinase-like proteins and proteoglycans
- Increase in glycosphingolipids

The blood group–related carbohydrate structures Le(x), sialyl-Le(x), ABH, and Le(y) are examples of terminal carbohydrate structures that are related to tumor prognosis. These structures are of increasing interest because they may function as adhesion molecules or motility factors.[107]

Thomsen-Friedenreich Antigen (Pancarcinoma Associated Antigen)

Many malignant cells develop a tumor marker called the Thomsen-Friedenreich (T) antigen (TFA). Tn and sialyl Tn (STn) appear to result from somatic mutations in the *Cosmc* (*C1GALT1C1*). Diverse neoplastic lesions, including colon cancer and melanoma-derived cell lines, express both Tn and STn antigen due to loss-of-function mutations in *Cosmc*.[108] This antigen is encrypted in normal healthy cells, much like a rock is covered over by water at high tide. T antigen becomes "unsuppressed" only as a cell moves toward malignancy, much like the example of the covered rock, which is uncovered as the tide moves out.

It has been estimated that T antigen (or its precursor, Tn antigen) is expressed in about 90% of all cancers, earning it the appellation "pancarcinoma associated antigen."[109] As a general rule, an orderly expression of T antigens on a cancer cell usually indicates a relatively favorable outlook. However, a prevalence of Tn antigens on a cancer cell usually denotes a highly aggressive, metastatic cancer, irrespective of the form of cancer or organ involved.[110]

Tn antigen is rarely found in healthy tissue; most people produce TFA agglutinins antibodies to it, probably in response to cross-induction by the gut flora. ABO blood group appears to influence the amount and activity of these antibodies against T and Tn antigens. Although derived from the MN blood type antigen, Tn antigen shows structural homology to the A antigen because they share terminal GalNAc. Because antibodies against Tn antigen cross-react with A glycolipids, Tn antigen was concluded to be an A-like antigen in a broad sense. Blood group A patients with gastric cancer have the greatest and most uniform suppression of TFA agglutinins levels, irrespective of age, cancer stage, or tumor morphology.

Inadvertent Elaboration of Blood Group Antigens

Deletion, reduction, or inappropriate expression of blood group A or B antigen in tumors of blood type A or B individuals is clearly correlated with the level of malignancy and metastatic potential.[111] The most significant variations are summarized in Table 43-3.

A and B blood group antigens are present on carcinoma cells at the early stages of carcinogenesis and tend to disappear at later stages. The blood group A antigen may render malignant cells resistant to apoptosis.[112]

Lewis blood groups can modulate the expression of several tumor-associated antigens, including DU-PAN9 and CA19-9. Some researchers have suggested that taking into account Lewis secretor status to establish reference ranges for the tumor antigen measurements might actually be a way to improve their clinical utility. This relationship is shown in Table 43-4.

The association of blood groups with cancer was first demonstrated by Aird et al[113] in 1953, pointing to group A with gastric carcinoma. One hypothetical mechanism is that the carcinoma cells produce an antigen immunologically related to blood group A, which may have a protective effect, particularly in blood group O individuals, by prevention of the growth and spread of the tumor.[114] It appears that the progression of stomach cells to stomach cancer involves a necessary mutation at the ABO gene, the result of which is the production of A antigen, even if this is not the person's blood type. This "A-like" antigen may not be the true A antigen but rather, what one researcher called "tumor-associated, A cross-reacting antigens occurring in a wide variety of human adenocarcinomas of hosts belonging to all ABO blood groups."[115] There is also a B-like antigen noted in colon or rectal carcinoma and other malignant processes.[110] More data needs to be collected about different malignant processes. A 2009 study in Italy that retrieved tumor data on 15,359 patients was able to show that

TABLE 43-3 **Variation in Blood Group Antigen (BGA) Expression in Normal and Neoplastic Tissues**

TISSUE, ORGAN	NORMAL EXPRESSION OF BGAs	EXPRESSION OF BGAs IN MALIGNANCY	REFERENCE
Colon*	Present	Absent	152
Bladder†	Absent	Present	153
Prostate	Present	Absent	154
Liver‡	Absent	Present	155
Squamous	Present	Absent	156
Endometrium§	Absent	Present	157
Stomach	Present	Absent	158
Thyroid*	Absent	Present	159
Esophagus	Present	Absent	160

*Inversely correlated.
†BGAs better than all other tumor markers.
‡BGAs effective at predicting hepatitis transformation to malignancy.
§Vast majority of BGAs secreted are H antigen.

TABLE 43-4 **Correlation of CA19-9 and DU-PAN-9 Expression in Colorectal Cancer with Lewis (Le) Type**

LEWIS PHENOTYPE	CA19-9 EXPRESSION*	DU-PAN-9 EXPRESSION
Le^{a+b-}	Highest levels	Lower levels
Le^{a-b+}	High levels	Lower levels
Le^{a-b-}	Zero to very low levels	Highest levels

*Individuals having homozygous inactive Se alleles *(sese)* and homozygous active Le alleles (*LeLe*), exhibited the highest mean CA19-9 value. All of the Lewis-negative individuals (lele genotype) had complete absence of CA19-9, irrespective of the Se genotype.[10]

exocrine pancreatic malignancy was associated with ABO blood group, but no other probabilistically significant correlations were made or discarded about other malignancies associations.[116]

Epidermal Growth Factor

The epidermal growth factor receptor (EGF-R) bears an antigenic determinant that is closely related to the human blood group A carbohydrate structure. A higher number of high-affinity EGF binding sites was observed in donors with blood group A1 erythrocytes than in donors with blood groups O and B.[117]

That the blood group A antigen can also bind to EGF-Rs is now well documented, so it is not unlikely that free A antigen in individuals with blood groups A and AB (especially if they are secretors) can find their way onto these excess EGF-Rs and act to stimulate cell growth. As with vWF and FVIII, excessive activation of the EGF-R results in cancer cells that become more mobile and better able to develop new and additional blood supplies (angiogenesis).[118]

One reason that low stomach acid is linked to type A blood may have to do with the role of EGF discussed in the previous section on saliva, "ABH Secretors and Nonsecretors". As described, the EGF-R has a high affinity for the type A antigen, and although the major action of EGF is to stimulate repair of the digestive lining, it has also been shown to decrease acid production in the stomach.

Pancreatic Cancer

The state of the art in the field of pancreatic cancer research continues to prove the relationship of malignancy to ABO blood group. A clinical trial for pancreatic ductal adenocarcinoma that involved 3000 people from the Han population showed that higher risk, higher state of malignancy, and less survival after surgery was associated with non-O blood groups.[119] Analyzing ABO genotype alleles with a genome-wide association study (PanScan) identified significant associations at the ABO gene locus with risk of pancreatic cancer. An increase in risk was noted with the addition of each non-O allele. Compared with OO genotype, AA presented a higher risk than AO in the 3000 patients analyzed.[120]

To help identify what aspect of the O allele is involved in lowering the pancreatic cancer risk in 2009, 558,542 single-nucleotide polymorphisms (SNPs) were genotyped in 1900 cancer patients and an equal number of control patients. A link was found between a locus on 9q34 and pancreatic cancer marked by the SNP rs505922. This SNP maps to the first intron of the ABO blood group gene, corroborating the epidemiologic fact that people with blood group O may have a lower risk of pancreatic cancer than those with groups A or B.[121]

The enzyme glycosyltransferase is associated with increased pancreatic cancer risk impact rather than actions of other nearby genes on chromosome 9q34. Glycosyltransferase activity is greater for the A1 versus A2 variant. In a 2010 cancer cohort study, an increased risk in participants with A1, but not A2 alleles, was observed. The same study showed that the protective effect of the O allele would be equivalent for O01 and O02 variants. Secretor status was not an effect modifier.[122]

Having a non-O ABO blood group and colonization by *Helicobacter pylori* are risk factors for pancreatic cancer. In a study at the Yale School of Medicine in 2010, an association between pancreatic cancer risk and CagA-negative *H. pylori* seropositivity was found among individuals with non-O blood type but not among those with O blood type, proving that there is an association between pancreatic cancer and *H. pylori* colonization, particularly for individuals with non-O blood types.[123]

Breast and Other Gynecologic Cancers

The following articles represent a sampler of the advances in understanding relationships between ABH antigens, secretor status, and incidence and prognosis of different gynecologic related cancers. In 2009, a correlation between breast cancer in Greek women and ABO blood group was published. One hundred sixty-six female patients with breast cancer were examined. They revealed that blood group A is more often associated with ductal breast cancer (49.6%), in contrast to the other blood groups, and particularly to blood group AB (3.6%). The relative risk of metastasis in Rh (–) patients was 4.2 times higher than that in Rh (+) patients. Consequentially, blood group A and, particularly, A (–) has the worst prognosis of all.[124]

Breast cancer researchers have given the aberrant glycosylation moiety T/Tn antigen the moniker "ligand-like complex" (LLC). By virtue of altered antigenicity, LLC allows for both metastatic egress from the regional lymph nodes and detachment from the extracellular matrix, and thus is associated with cancers of poor prognosis.[125] We believe that LLC may well be the "A-like," pancarcinoma cross-reacting antigen. Observation of the GalNac binding lectin from the Roman snail, *Helix pomatia* agglutinin, appears to identify this oligosaccharide[126]; there have been separate reports that "Springer's vaccine" (human group O RBC membrane–derived T/Tn antigen containing traces of phosphoglycolipid A hyperantigen) has had significant effect as an immune modulator in breast carcinoma of even advanced stage.[127]

A study of epithelial ovarian cancer incidence and its association to ABO blood groups and risk was performed in 2010, in Harvard, which analyzed data from 49,153 women in the Nurses' Health Study. Compared with women with blood group O, women with blood group AB or B had a nonsignificant 38% increase in ovarian cancer incidence, whereas blood group A was not associated with risk. Combining blood groups AB and B, they observed a statistically significant positive association with presence versus absence of the B antigen for the serous invasive subtype and overall. In this large, prospective cohort of women, presence of the B antigen was positively associated with ovarian cancer incidence, whereas blood group A was not associated with the same risk.[128]

Another interesting, yet not definitive association, is presented between invasive squamous cell carcinoma (SCC) of the vulva and ABO blood groups. The distribution of ABO blood group for 33 women diagnosed with invasive SCC of the vulva was determined. ABO blood group was also recorded for 100 female patients (controls) who underwent a gynecologic procedure for a non-neoplastic process during the same period. A trend was identified for women with invasive SCC of the vulva to have blood group type A, but this did not determine a definitive association between blood group type A, or any other blood group and vulvar SCC.[129]

TABLE 43-5 **Mechanisms of ABO Influence on Infectious Disease**[10]

CLASS	MECHANISM	DESCRIPTION	EXAMPLE
Selectivity	Adhesion kinetics	Adhesion or lectin specificities of the infectious agent based on particular ABH glycosylation	*Candida albicans* (group O)
	Humoral dynamics	Inadequate isoagglutinin production or activity	*Neisseria gonorrhoeae* (group B)
	Molecular mimicry	Infectious agent is antigenically similar to host's ABO group	*Giardia lamblia* (group A)
Response variability	Host response	Variation in severity of disease through unique biological response (examples: inappropriate inflammatory response; rosette formation)	Cholera (group O) Dengue fever (group B) Malaria (group A)
	Substrain susceptibility	Different ABO groups often show variations in susceptibility between individual bacterial, fungal, or parasitic species or viral strains	Influenza (all groups) Malaria (group O vs group A)

Other Cancers

In two large independent populations, non-O blood group was associated with a decreased risk of skin cancer. The association was statistically significant for nonmelanoma skin cancer. Additional studies are needed to confirm these associations and to define the mechanisms by which ABO blood type or closely linked genetic variants may influence skin cancer risk.[130]

In colorectal cancer, there is no specific association with blood group type, but there is a significant difference between the Rh(+) and Rh(–) groups. Further studies on blood group antigens are needed to elucidate the relationship between these antigens and colorectal cancer.[131]

Infection

To a great extent, infectious diseases, especially the worldwide epidemic diseases, have selective effects. This is demonstrated inter alia in the different "selection values" in the ABO blood group system. During the eons before antimicrobial intervention, selection variability via ABO polymorphism was the preeminent natural survival mechanism.

The previous section appears to imply a selection disadvantage for group A individuals, and it has been argued that under present day civilized living conditions, blood type O carriers have a preservation advantage over blood group A carriers.[132] This may be the result of the deletion of the selection factor "infectious disease," which may nevertheless regain importance if environmental changes occur.[133]

Historically, some of the most catastrophic epidemic and endemic diseases are ABO selective, and, in many instances, demonstrate ABO variation in morbidity, mortality, or microcharacteristics such as substrain preferentiality and level of inflammatory response. They include cholera (O), smallpox (A), malaria (A), and influenza (variable subsets depending on strain).

The influence of ABO polymorphism on infectious disease appears to stem from a multitude of unique factors. These are encapsulated in Table 43-5. A morbidity and mortality variation among the ABO and secretor groups is presented in Table 43-6. A special examination of polymorphic differences in uropathic infectious disease is presented in Table 43-7.

An interesting study done in Sudan about placental malaria showed that women of eastern Sudan are at risk for placental malaria infection irrespective to their age or parity, but that women with blood group O were at higher risk of past placental malaria infection.[134] A higher seroprevalence of IgG *H. pylori* specific antibodies was observed in gastric ulcer patients (90%) compared to the control group (60%). A significant increase of phenotypes O, A2 and Le^b in *H. pylori*-infected patients was observed. The expression of these antigens had progressive alterations in areas of ulcerous lesions and intestinal metaplasia; therefore, ABH and Lewis blood group antigens appear to be a good indicator for cellular alterations in the gastric epithelium.[135]

For a more detailed examination of particular infectious scenarios, the reader is referred to the author's comprehensive survey.[136]

Periodontal Disease and Oral Malignancy

A recent study segregated populations (1220 subjects aged between 20 and 55) into three groups according to Ramfjord's periodontal disease index: healthy, gingivitis, and periodontitis. Blood types were confirmed for each of the participants. Effectively, blood group A showed a significantly higher percentage in the gingivitis group and blood group O showed a higher percentage in the periodontitis group. The blood group AB showed the least percentage of periodontal diseases. The distribution of Rh factor in all groups showed a significantly higher distribution of Rh-positive.[137]

In most human carcinomas, including oral carcinoma, a significant event is decreased expression of histo-blood-group antigens A and B. A relative downregulation of the glycosyltransferase that is involved in the biosynthesis of A and B antigens is seen in oral carcinomas in association with tumor development. As reviewed previously, the events leading to loss of A transferase activity are related, in some instances, to loss of heterozygosity involving chromosome 9q34, which is the locus for the ABO gene, and in other cases, to a hypermethylation of the ABO gene promoter. Altered blood group antigens in malignant oral tissues may indicate increased cell migration. Some studies showed that normal migrating oral epithelial cells, like malignant cells, show lack of expression of A/B antigens and, therefore, lack of ABH antigens to key receptors controlling adhesion and motility, such as integrins, cadherins, and CD-44.[138]

BLOOD GROUPS AND DIETARY LECTINS

ABO polymorphism is one of the prime determinants of the glycosylation variability of gut mucin. As such, it affords insight into the actions of a class of carbohydrate-binding dietary proteins called lectins, which are increasingly the subject of interest for nutritional researchers.

Historical Perspective

Stillmark at the University of Dorpat in Estonia first identified lectins in 1888. While investigating the toxic effects on blood of castor bean extract *(Ricinus communis)*, he noticed that the RBCs were being agglutinated. He isolated the material responsible for the agglutination and called it ricin.

TABLE 43-6 **Influence of ABO Polymorphism on Susceptibility to Various Infectious Agents**[10]

STRAIN	SUSCEPTIBLE PHENOTYPE	COMMENTS
Amoebic dysentery	O, A	• Blood groups B and AB have a degree of resistance against developing severe or acute dysentery, especially the amoebic forms.
Candida carriage	O, NS	• *Candida* carriage was associated with blood group O ($P<0.001$) and, independently, with nonsecretion of blood group antigens ($P<0.01$). • *Candida albicans* extracellular polymeric material contains a mannoprotein adhesion with a lectin-like affinity for H (type 2) blood group antigen. • There were a significantly higher number of nonsecretors (48.9%) among 174 patients with either oral or vaginal *Candida* infections compared with the proportion of nonsecretors in the local population (26.6%). Nonsecretor saliva actually seemed to enhance *Candida* attachment.
Cholera	O, AB	• Blood group O individuals have a greater risk of infection with cholera and develop the most severe and life-threatening forms of this illness. This has been documented in several studies. • In contrast, type ABs appear to have the highest degree of protection from cholera infections. • Type O had more diarrhea-like stools per day than persons of other blood groups and were more likely to report vomiting and muscle cramps.
Coccidioidomycosis	B	• Blood group B individuals are more prone to disseminated disease after exposure.
Dengue fever	B	• According to researchers, blood group B was strongly associated with the severe form of dengue fever known as dengue hemorrhagic fever.
Dermatophytosis	A	• The fungus *Trichophyton rubrum*, isolated from 54.5% of the patients tested, was more frequent in individuals belonging to blood group A.
Escherichia coli	Variable subsets	• It appears that many forms of *E. coli* capable of causing diarrhea are immunologically "B-like." This results in a substantially higher number of cases of diarrhea among individuals of blood group B and AB people. • However, when it comes to the overall severity of infection with *E. coli*, types B and AB are not alone; type Os also are more likely to get a severe form of diarrhea.
Giardia	A	• Blood group A is more susceptible to giardiasis, especially the asymptomatic form, whereas blood group B is less susceptible to giardiasis.
Helicobacter pylori	O, nonsecretor	• *H. pylori* variants produce a variety of blood group antigens, including A, Lewis (a) and a variety of type 1 H like antigens (O). • Group O would be a moderate risk factor for infection by *H. pylori*, with more severe cases in men. • Group O has a more pronounced inflammatory reaction to *H. pylori*. Group O cells released significantly more IL-6 and TNF in response to *H. pylori* infection. • The Lewis^{a+b-} nonsecretor phenotype and blood group O are relevant genetic markers of peptic ulcer. • The Lewis$^{a+ b-}$ nonsecretor phenotype and blood group A were all positively associated with esophageal adenocarcinoma, with concurrent *H. pylori* infection.
Hookworm	O	• A 1972 Egyptian study correlated type O with higher incidence of hookworm and strongyloidiasis.
Influenza	Variable subsets	• Blood group A: Generate a quick and substantial antibody response against influenza type A(H1N1) and especially A(H3N2). The antibody response against influenza B is not quite as dramatic. • Blood group AB: Relatively poor ability to generate high antibody levels against any of the influenza viruses. • Blood group B: Reasonable, but not great ability to generate an antibody response against influenza A (H1N1). Slowest (3-5 months) and weakest ability to generate antibodies against influenza A (H3N2 "Hong Kong") of any blood group. Against influenza B virus, blood group B has a significant advantage and responds differently from either blood group A or O. The blood group B immune response happens much earlier and persists longer. • Blood group O: Moderate ability to generate antibody response against influenza A (H1N1) and A (H3N2) viruses. Antibody response against influenza B is not as dramatic as blood group B.
Malaria	A, AB	• The evidence suggests that blood group A individuals might have a higher predisposition to infection with the *Plasmodium vivax* species, whereas blood group B individuals tend toward higher infection rates with *P. falciparum.* • Malaria infected RBCs sometimes bind to uninfected red blood cells to form clumps, called rosettes. The rosettes can obstruct flow in small blood vessels and lead to tissue damage and severe malaria disease. The tendency for malaria to be worse among As and ABs is due primarily to a greater degree of rosette formation by RBCs with these antigens. • Von Willebrand Factor, always elevated type A, also enhances rosette formation.
Neisseria gonorrhoeae	B	• The relation of infection with *Neisseria gonorrhoeae* to the blood groups A, B, AB, and O was examined in 584 women attending a prenatal clinic. The occurrence of gonorrhea was significantly higher in black patients with blood group B than in those with blood groups A, AB, or O. Depending on the ABO blood group, gonorrhea may affect the titers of isohemagglutinins compared with those of uninfected controls. • The isohemagglutinin titers in group O patients were significantly increased ($P<0.001$) against erythrocytes A, B, and AB. In group A patients, only the titer against AB erythrocytes was significantly increased. • In group B patients, the titer against AB erythrocytes was significantly lower ($P<0.001$) compared with that in sera of healthy persons.

TABLE 43-6 **Influence of ABO Polymorphism on Susceptibility to Various Infectious Agents[10]—cont'd**

STRAIN	SUSCEPTIBLE PHENOTYPE	COMMENTS
Norwalk Virus (NV)	O	• It appears that group O RBCs are most easily bound by NV vs group B RBCs that are apparently little bound, if at all. Individuals with an O phenotype were more likely to be infected with NV. • The preferred binding sites are apparently the H type 2 antigen that functions as the viral receptor on human type O RBCs. • The Lewis B antigen (found in secretors) is also a binding site.
Schistosomiasis	A	• Group A tends to be more susceptible to infection, tends to get more intense symptoms after infection, and is much more likely to have damage to organs (like the liver) after infection.
Shigellosis	B, AB	• A strong association between blood group B (and AB to a slightly lesser degree) and shigellosis exists.
Smallpox	A	• Group A has higher mortality from smallpox infection. • Group A individuals also have more reactions from smallpox vaccination. • The leukocytes of peripheral blood of group A individuals showed a poorer binding capacity with respect to the smallpox vaccine virus. • Blood group A also exhibited a high rate of chromosomal aberration after vaccination, resulting to some extent from increased proliferative ability of the cells.
Staphylococcus aureus	A	• Blood group A is much more likely to be a chronic carrier of *S. aureus*. This is partly due to blood group A individuals having a decreased ability to mount an aggressive antibody (or immune) response against this organism.
Streptococcus (group B)	B	• A blood group connection with neonatal group B streptococci infection exists for blood group B. Maternal blood group B is associated with about a doubling of risk for infection among their infants.
Strongyloidiasis	O	• An 1972 Egyptian study correlated type O with higher incidence of hookworm and strongyloidiasis.
Tuberculosis	O	• Group O blood has a much higher rate of infection with tuberculosis (this is particularly true in individuals of European descent). • Tuberculosis runs a much more aggressive and detrimental course in blood group O, whereas type A are afforded the highest degree of protection. • Typically, during the first 2 y of infection with bacillary tuberculosis, there is a significant excess of infection among individuals with blood group O and AB.

IL-6, interleukin-6; NV, norovirus; RBCs, red blood cells; TNF, tumor necrosis factor.

TABLE 43-7 **Influence of ABO Polymorphism on Susceptibility to Various Uropathic Infectious Agents[10]**

BLOOD GROUP	UROPATHOGENIC STRAINS
A	• *Staphylococcus saprophyticus*
B	• *Klebsiella pneumoniae* • *Proteus* spp. • *Pseudomonas* spp.
AB	• *Klebsiella pneumonia* • *Proteus* spp. • *Pseudomonas* spp. • *Staphylococcus saprophyticus*
Nonsecretor	• Uropathogenic *Escherichia Coli*

As a general rule, blood group B is most plagued by chronic or recurrent urinary tract infections.
Type AB is next on the susceptibility list, followed by type A.
Type Os are the most protected.
Nonsecretors are much more prone to repeated and severe urinary tract infections.

In 1945, William Boyd of the Boston University School of Medicine discovered that lectins can be blood group specific, being able to agglutinate the RBCs of one type but not those of another. He discovered that lima bean lectin would agglutinate RBCs of human blood type A but not those of O or B. The seeds of *Lotus tetragonolobus* can agglutinate group O specifically, and *Bandeiraea simplicifolia* is specific to group B. The specificity of lectins is so sharply defined that they can differentiate among blood subgroups. *Dolichos biflorens* lectin reacts more vigorously with blood group A1 than with A2.

The word lectin was proposed by William Boyd in 1954 to describe a class of blood type–specific agglutinins found in certain plants. The word is allegorical to a degree, because it derives from a Latin word meaning "to choose."

Actions of Lectins

The surface epithelium of the gut is extensively glycosylated,[139] mainly because most membrane proteins, including hormone and growth factor receptors, transport proteins, and brush-border enzymes, are glycosylated before being embedded in the brush-border membrane. Membrane lipids and gangliosides are also glycosylated, and all secreted mucins are carbohydrate-rich glycoproteins. Thus, the scope of potential lectin–carbohydrate interactions is quite wide. However, not all lectins react with the epithelium, and even those that do react vary in their ability to recognize and bind to specific types of carbohydrate receptors. Because lectin reactions are quite specific, it is imperative that the correct carbohydrate structures be present on the surface of the gut mucosa. Factors that are known to influence lectin activity are summarized in Box 43-1.

Lectins can have a variety of biological effects, including induction of mitosis in lymphocytes, cellular agglutination via cross-linking of membrane sugars, preferential agglutination of malignant cells, precipitation of polysaccharides and glycoproteins, and activation of complement pathways. The variety of reported effects resulting from the ingestion of dietary lectins is summarized in Table 43-8.

Most lectins in the United States diet are resistant to breakdown during gut passage, so they are bound and endocytosed by epithelial cells. Endocytosed lectins act as powerful exogenous growth

factors for the small intestine, and they can induce dramatic shifts in its bacterial flora and interfere with its hormone secretion. In addition, lectins that are transported across the gut wall into the systemic circulation can modulate the body's hormone balance, metabolism, and health. In contrast to dietary proteins, lectins resist degradation in the small intestine and are also resistant to breakdown by most gut bacteria. Thus, most lectins survive, at least in part, the passage through the digestive tract in an immunologically and functionally intact form.[140]

BOX 43-1 Factors Influencing Glycosylation in the Intestines, Hence Activity of Dietary Lectins

- Animal species
- Blood group specificity
- Age
- Particular area of the small intestine
- Position along the villi
- State of cell maturation
- Diet
- Bacterial status
- Sickness or pathology

Data from Pusztai A, Bardocz S. Biological effects of plant lectins on the gastrointestinal tract: metabolic consequences and applications. Trends Glycosci Glycotechnol 1996;8:149-165.

Although lectin binding is most commonly studied in the small intestine, similar binding can occur throughout the entire digestive tract, from the stomach to the distal colon. However, surface glycosylation varies in the different functional parts of the gut, so lectin binding is not uniform in the digestive tract. Binding of lectins and their endocytosis by enterocytes is more extensive in the colon, where bacterial counts are high. Endocytosis in the small intestine becomes appreciable only in the presence of large numbers of commensal bacteria.[141]

How prevalent are lectins in the diet? A superficial survey done in the early 1980s implied that they are quite extensively distributed in our food supply.[142] In this study, the edible parts of 29 of 88 foods tested, including common salad ingredients, fresh fruits, roasted nuts, and processed cereals, were found to possess significant lectin-like activity as assessed with blood agglutination and bacterial agglutination assays.

Lectin content is a prime area of manipulation for the production of transgenic foods,[143] so they will probably continue to occupy the attention of nutritionally oriented physicians well into the future.

Role of ABO Blood Groups

Because ABO blood group is a prime determinant of glycosylation, it is not surprising that a substantial number of food lectins show ABO specificity. However, equally important, but not

TABLE 43-8 **Reported Effects of Dietary Lectins**

ACTION	DESCRIPTION
Induction of interleukins (ILs)	Dietary lectins are known to induce interleukins IL-4 and IL-13. Because lectins can enter the circulation after oral uptake, they might play a role in inducing the so-called early IL-4 required to switch the immune response toward a helper T cell type 2 response and type I allergy.[162]
Induction of autoimmunity	The interaction of dietary lectins with enterocytes and lymphocytes may facilitate the translocation of both dietary and gut-derived pathogenic antigens to peripheral tissues, which in turn causes persistent peripheral antigenic stimulation. In genetically susceptible individuals, this antigenic stimulation may ultimately result in the expression of autoimmune disease.[163]
Interference with protein digestion	Aminopeptidase activity (the enzyme that breaks down polypeptides into amino acids) is inhibited by several dietary lectins.[164]
Interaction with the brush-border membrane	Lectins, which bind avidly to the brush-border membrane, are potent hyperplastic growth factors for the gut.[165] Binding of lectins to the epithelium is obligatory for growth stimulation, and their growth factor activity is determined mainly by the strength and intensity of their binding.[166]
Antinutrient effects	Rats fed a diet composed principally of raw navy bean flour were smaller and had 50% less ability to absorb glucose and utilize dietary protein than a control group that was fed navy beans in which the lectin had been inactivated.[167]
Enhancement of gut permeability	In one study, rats fed on diets containing kidney beans showed greater intestinal permeability to serum proteins that had been injected into the blood stream. After challenge with kidney bean proteins, the protein injected into the blood stream was detected in both the lumen (open space) and the walls of the small intestine. The researchers suggested that dietary lectins may, at least in part, be responsible for loss of serum proteins and may contribute to other food intolerance secondary to the loss of gut integrity.[168]
Activation of gut hormones	Cholecystokinin is induced by several dietary lectins.[169]
Hormone and growth factor mimicry	Because surface membrane receptors of cells are glycosylated, lectins are good mimics of the effects of endogenous growth factors, hormones, and cytokines in all types of cells.[140] Lectins can mimic the effect of the natural ligands and induce similar physiologic reactions. It is also possible that bound lectin induces conformational changes in the receptor and/or physically blocks the active site of the receptor, thereby attenuating or completely abolishing the physiologic effect of the natural ligand.
Mucotractive effects	Many lectins stimulate the production of mucus. This is possibly a protective function or an allergic response and was for a time thought to be an action of lectins that promised some therapeutic benefit that could be applied in patients with cystic fibrosis.[141]
Mitogenic effects	Several foodstuffs and herbal medicines are known to contain lectins that are capable of inducing T- or B-cell blastogenesis.

typically recognized, is the author's observation that ABO status appears to influence variability in secondary glycosides, which are not integral to the ABO type of the hosts. These secondary glycosides appear to provide additional conditioning of the mucin manufactured by the particular ABO type, which can explain the apparent effects of panhemagglutinins and other non-ABO specific lectins on one particular ABO type over another. These effects are listed in Table 43-9.

The benefit of using the ABO groups as a predictive device in narrowing down potential food reactions in sensitive subjects lies in its low cost to the patient, and the clinician's ability to discern interactions that are not easily testable via standard food allergy isolation methods. A useful resource for clinicians seeking more information on lectins is *Lectser*, the world's most complete lectin characterization database, available at the principal website.[144]

CLINICAL APPLICATIONS OF ABO POLYMORPHISM

The "Blood Type Diet"

The advantage of a low-lectin diet can be exemplified by the best known application of the ABO polymorphisms, The Blood Type Diet (BTD), popularized by publication in 1997 of the author's New York Times bestseller *Eat Right 4 Your Type*.

Eat Right 4 Your Type was the first "diet book" that looked at foods as medicine tailored to the individual rather than simply as part of a generic single-purpose mechanism (i.e., weight loss, cholesterol control). Like the very antigens that it uses for its determination, BTD is "nonreducing," meaning that the food value system is essentially stateless: a food that might cause difficulties in one ABO phenotype may well possess therapeutic value in another, a concept that harkens back to the observation of the Roman philosopher, Lucretius, "What is food to one man may be fierce poison to others."

The BTD inventories a variety of parameters, including the physiologic and pathologic distinctions between the blood groups as reported in the literature, lectin and agglutinin characterizations (both from the author and from others), and variations in isoagglutinin titer and reactivity with regard to food challenge (both in vitro and in vivo). It also provides specific recommendations regarding foods that should be considered beneficial and should be emphasized and others that may be problematic and might better be avoided.

TABLE 43-9 **Primary and Secondary Mucin Glycosides Known to be Associated with ABO Polymorphism**

BLOOD GROUP	PRIMARY GLYCOSIDE	SECONDARY GLYCOSIDE(S)
A	*N*-Acetyl galactosamine	Mannose[170] Glycophorin A[171] Galactosyl-A glycolipids[172] "Band 3"[173]
B	Galactose	*N*-Neuraminic acid[174] Glycophorin B[171]
O	Fucose	*N*-Acetyl glucosamine[175-177]

One advantage conferred by the theory is the notion that certain individuals may be better suited to Paleolithic or vegetarian diets. Despite certain locutions and circumlocutions offered by proponents of one system or the other, most clinicians have ample experience with the simple fact that certain patients make better vegetarians or carnivores than others. Conversely, the ability to identify particular individuals at risk of an adverse reaction to high-protein and/or low-carbohydrate diets can lead to actions aimed at the prevention of such consequences.

For example, high-protein diets are known to upregulate soluble endothelial adhesion factors,[145] whereas a soy-based, lipid-lowering diet is known to decrease endothelial adhesion factors, including vWF, E-selectin, and the intercellular adhesion molecule.[146-148] Because individuals with blood group A have been reported to have increased levels of all three endothelial adhesion factors and, perhaps consequently, a higher incidence of cardiovascular disease, a modified Asian and/or Mediterranean plant-based diet would appear ideal for this phenotype.

Conversely, in 1998, we examined serum cholesterol levels in a small number of group O subjects after a minimum of 1 month of the BTD recommended for that phenotype.[149] Group O individuals following the "Type O Diet" (higher protein, lower carbohydrate) showed a consistent drop in serum cholesterol (n = 14; average 237.3 mg/dL before diet, 200.2 mg/dL with diet); in subjects with elevated serum triglyceride values, the results were more pronounced (n = 6; average 387.1 mg/dL before diet, 168.8 mg/dL with diet).

In 2009, D'Adamo reported that sequential breath hydrogen levels (BHL) after lactulose administration varied significantly by ABO blood group and secretor status. Breath hydrogen excretion was significantly higher in group A subjects (n = 35) versus group O (n = 31). Secretor status appeared to influence location and temporality of bacterial overgrowth and BHL, with secretors having significantly higher levels on earlier blows (B1: $P = 0.027$) and nonsecretors having significantly elevated BHLs on later blows (B3: $P = 0.014$, B4: $P = 0.013$). Adoption of blood group specific dietary recommendations significantly reduced mean BHLs (n = 40; $P = 0.007$).[150]

The BTD has produced an extensive library of works, at a various levels of information density. *Eat Right 4 Your Type* has been translated into more than 60 languages, and well over 6 million individuals follow the system.[151] Self-reported outcomes collected via the Internet appear to indicate wide consumer satisfaction with the system: in over 7,000 reports, the basic ABO based system generated a 85% level of satisfaction. Most interestingly, this percentage was essentially unchanged across the individual blood groups. In other words, 85% of the blood type A respondents reported satisfaction with a predominantly plant-based diet, whereas the same percentage of type O individuals reported satisfaction with a high protein, Paleo-type diet. What this portends for the future of reductionist, one-size-fits-all diet systems remains to be seen.[152]

Materia Medica

ABO polymorphism and its clinical expression have led to new or rediscovered applications and contraindications for several traditional naturopathic treatment modalities. The most significant are summarized in Table 43-10.

TABLE 43-10 **Modalities Known to Exert Effects at Least Partially Preferential to ABO Group**

AGENT/SPECIES	COMMON NAMES	ACTIONS	NOTES	REFERENCES
Fucus vesiculosus	Bladderwrack kelp	Antiadhesive Candicidal	Best suited for O, nonsecretors	178-180
Baptisia tinctoralis	Wild indigo	Induces anti-Tn or cross-reacting antibodies	Best suited for A, AB	181, 182
Urtica dioica rhizome	Stinging nettle root	"Superantigen" lectin T-cell mitogen (CD4+ and CD8+); Candicidal	Not useful in B or AB	183, 184
Helix pomatia agglutinin	Roman or escargot snail	Contains Tn-, LLC-, and "A-like"–specific lectins	Best suited for A, AB	125, 126
Agaricus bisporus	Domestic mushroom	Lectin stimulates insulin release by pancreatic islets. Lectin binds Tn antigen; stimulates differentiation of undifferentiated colon cancer cells; inhibits proliferation of epithelial cell lines	Best suited for A	185, 186
Marrubium spp.	Horehound	Contains Tn-specific lectins	Best suited for A, AB	187
Salvia spp.	Sage	Contains Tn-specific lectins; attenuates soluble endothelial adhesion factors	Best suited for A, AB	187, 188
Vicia faba	Fava bean	VFA stimulated an undifferentiated colon cancer cell line to differentiate into gland-like structures. The adhesion molecule epCAM is involved in this process. Dietary or therapeutic VFA may slow progression of colon cancer	Best suited for A; can be used by O, B	189
Griffonia (Bandeiraea simplicifolia)	African legume from which 5-HTP is extracted	Griffonia contains 5 isolectins, at least 3 of which are blood group agglutinating. GSA B4 is a serologically Lewis b(Le^b)–active binding lectin claimed to be blood group B specific as well. The "A"-rich lectin preferentially agglutinates blood group A, and the"B"-rich lectin preferentially agglutinates blood group B cells and is specific for alpha-galactose residues	Not useful in A, AB, B or secretors	190-192
Artocarpus integrifolia	Jackfruit seeds	Contains T- and Tn-specific lectin (jacalin)	Best suited for A, AB; can be used by O, B	193

epCAM, epithelial cell adhesion molecule; GSA, Griffonia simplicifolia agglutinin; LLC, ligand-like complex; VFA, Vicia faba agglutinin.

SUMMARY

It is our hope that this abbreviated survey proves sufficient information to persuade the reader that ABO and ABO-related polymorphisms, in both genotypic and phenotypic expression, exert biological significance far beyond the surface of an erythrocyte, and that this expression is worth factoring into the everyday algorithms of a nutritional practice. Perhaps the advent and acceptance of the newly emerging science of "nutrigenomics" might provide the conceptual framework needed to allow the nontransfusion significance of ABO and secretor polymorphism to parse into meaningful scientific dialogue. At that point, natural medicine could be considered to have the rational beginnings to delivering its long-awaited promise, "Treating the patient, not the disease."

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CHAPTER 44

Nutritional Medicine

Michael T. Murray, ND

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Let your food be your medicine and let your medicine be your food.

—Hippocrates

INTRODUCTION

Nutritional medicine, as described in this textbook, consists of the use of diet and nutritional supplementation as therapeutic modalities. The foundation of nutritional medicine is a health-promoting diet that focuses on the consumption of whole, natural foods. Nutritional supplements are used in the overall context of nutritional medicine as complementary agents, not as sole primary medicines. Diet is always primary, and supplementation secondary.

EVOLUTIONARY ASPECTS IN HUMAN NUTRITION

Although the human gastrointestinal tract is capable of digesting both animal and plant foods, a number of physical characteristics indicate that *Homo sapiens* evolved to primarily digest plant foods. Specifically, our teeth are composed of 20 molars, which are perfect for crushing and grinding plant foods, along with eight front incisors, which are well suited for biting into fruits and vegetables. Only our front four canine teeth are designed for meat eating. Our jaws swing both vertically to tear and laterally to crush, but carnivores' jaws swing only vertically. Additional evidence that supports the body's preference for plant foods is the long length of the human intestinal tract. Carnivores typically have a short bowel, and herbivores have a bowel length proportionally comparable to that of humans. Thus, the human bowel length favors plant foods.[1]

A Look at Our Closest Wild Relatives

To answer the question, "What should humans eat?" many researchers look to other primates, such as chimpanzees, monkeys, and gorillas. Nonhuman wild primates are also omnivores or, as often described, herbivores and opportunistic carnivores. They eat mainly fruits and vegetables, but may also eat small animals, lizards, and eggs if given the opportunity. Only 1% and 2%, respectively, of the total calories consumed by gorillas and orangutans are animal foods. The remainder of their diet is from plant foods. Because humans are between the weights of the gorilla and orangutan, it has been suggested that humans are designed to eat around 1.5% of their diet as animal foods.[2] Most Americans derive well over 50% of their calories from animal foods.

Although most primates eat a considerable amount of fruit, it is critical to point out that the cultivated fruit in American supermarkets is far different from the highly nutritious wild fruits these animals rely on. Wild fruits have slightly higher protein contents and a higher content of certain essential vitamins and minerals, but cultivated fruits tend to be higher in sugars. Cultivated fruits are therefore very tasty to humans, but because they have a higher sugar composition and also lack the fibrous pulp and multiple seeds found in wild fruit that slow down the digestion and absorption of sugars, cultivated fruits raise blood sugar levels much more quickly than their wild counterparts.

Wild primates fill up not only on fruit but also on other highly nutritious plant foods. As a result, wild primates weighing one tenth as much as a typical human

TABLE 44-1 **Estimated Mineral Intakes of Wild Monkeys and Humans**

MINERAL	TOTAL DAILY INTAKE OF 7-kg ADULT MONKEY (mg)	RECOMMENDED DAILY ALLOWANCE FOR 70-kg MAN (mg)
Calcium	4571	800
Phosphorus	728	800
Potassium	6419	1600-2000
Sodium	182	500
Magnesium	1323	350
Iron	38.5	10
Manganese	18.2	2.0-5.0
Copper	2.8	1.5-3.0

ingest nearly 10 times the level of vitamin C and much higher amounts of many other vitamins and minerals. Other differences in the wild primate diet are also important to point out, such as a higher ratio of α-linolenic acid, the essential ω-3 fatty acid, to linoleic acid, the essential ω-6 fatty acid[2] (Table 44-1).

Hunter–Gatherer Diets

Determining what foods are best suited for humans may not be as simple as looking at the diet of wild primates. There are some structural and physiologic differences between humans and apes. The key difference may be a larger, more metabolically active brain. It has been theorized that a shift in dietary intake to more animal foods may have produced the stimulus for brain growth. The shift itself was probably the result of limited food availability that forced early humans to hunt grazing mammals, such as antelope and gazelle. Archeological data supports this association: the brains of humans started to grow and become more developed at about the same time as evidence shows an increase in bones of animals butchered with stone tools at sites of early villages.

Improved dietary quality alone cannot fully explain why human brains grew, but it definitely appears to have played a critical role. With a bigger brain, early humans were able to engage in more complex social behavior, which led to improved foraging and hunting tactics, which in turn led to even higher quality food intake, fostering additional brain evolution.

Data from anthropologists looking at hunter–gatherer cultures provide much insight as to what humans are designed to eat; however, it is very important to point out that these groups were not entirely free to determine their diets. Instead, their diets were molded by what was available to them. For example, the diet of the Inuit Eskimos is far different from that of the Australian aborigines. It may not be appropriate to answer the question, "What should humans eat?" simply by looking at these studies. Nonetheless, it is important to point out that regardless of whether hunter–gatherer communities relied on animal or plant foods, the rate of diseases of civilization, such as heart disease and cancer, is extremely low in such communities.[3]

It should also be pointed out that the meat that our ancestors consumed was much different from the meat found in supermarkets today. Domesticated animals have always had higher fat levels than their wild counterparts, but the desire for tender meat has led to the breeding of cattle that produce meat with a fat content of 25% to 30% or more, compared with less than 4% for free-living animals and wild game. In addition, the type of fat is considerably different. Domestic beef contains primarily saturated fats and virtually undetectable amounts of ω-3 fatty acids. In contrast, the fat of wild animals contains more than five times more polyunsaturated fat per gram and has a good amount of beneficial ω-3 fatty acids (approximately 4%).[4]

Considerable evidence indicates that a high intake of red or processed meat increases the risk of mortality. For example, in a cohort study of half a million people aged 50 to 71 years at baseline, men and women in the highest versus lowest quintile of red and processed meat intake had elevated risks for overall mortality.[5]

In another prospective cohort study, subjects were followed from 1980 (women) or 1986 (men) until 2006. Low-carbohydrate diets, either animal-based (emphasizing animal sources of fat and protein) or vegetable-based (emphasizing vegetable sources of fat and protein), were computed from several validated food-frequency questionnaires assessed during follow-up.[6] A low-carbohydrate diet based on animal sources was associated with higher all-cause mortality in both men and women, whereas a vegetable-based, low-carbohydrate diet was associated with lower all-cause and cardiovascular disease mortality rates.

The Importance of a Plant-Based Diet

The evidence supporting diet's role in chronic degenerative diseases is substantial and overwhelming. There are two basic facts linking the diet–disease connection: (1) a diet rich in plant foods (i.e., whole grains, legumes, fruits, and vegetables) is protective against many diseases that are extremely common in so-called Western society, and (2) a diet providing a low intake of plant foods is a causative factor in the development of these diseases and provides conditions under which other causative factors are more active.

The Pioneering Work of Burkitt and Trowell

Much of the link between diet and chronic disease originated from the work of two medical pioneers, Denis Burkitt, MD, and Hugh Trowell, MD, authors of *Western Diseases: Their Emergence and Prevention*, first published in 1981.[7] Although now extremely well-recognized, their work is actually a continuation of the landmark work of Weston A. Price, a dentist and author of *Nutrition and Physical Degeneration*. In the early 1900s, Dr. Price traveled the world observing changes in teeth and palate (orthodontic) structure as various cultures discarded traditional dietary practices in favor of a more "civilized" diet. Price was able to follow individuals as well as cultures over 20 to 40 years and carefully documented the onset of degenerative diseases as their diets changed. On the basis of extensive studies examining the rate of diseases in various populations (epidemiologic data) and his own observations of primitive cultures, Burkitt formulated the following sequence of events:

First stage. In cultures consuming a traditional diet consisting of whole, unprocessed foods, the rate of chronic diseases like heart disease, diabetes, and cancer is quite low.

Second stage. Commencing with eating a more "Western" diet, there is a sharp rise in the number of individuals with obesity and diabetes.

Third stage. As more and more people abandon their traditional diet, conditions that were once quite rare become extremely common. Examples are constipation, hemorrhoids, varicose veins, and appendicitis.

Fourth stage. Finally, with full westernization of the diet, other chronic degenerative or potentially lethal diseases, such as heart disease, cancer, osteoarthritis, rheumatoid arthritis, and gout, become extremely common.

BOX 44-1 Diseases Highly Associated with a Low-Fiber Diet

Metabolic
Obesity, gout, diabetes, kidney stones, gallstones

Cardiovascular
High blood pressure, strokes, heart disease, varicose veins, deep vein thrombosis, pulmonary embolism

Colonic
Constipation, appendicitis, diverticulitis, diverticulosis, hemorrhoids, colon cancer, irritable bowel syndrome, ulcerative colitis, Crohn's disease

Other
Dental caries, autoimmune disorders, pernicious anemia, multiple sclerosis, thyrotoxicosis, psoriasis, acne

Since Burkitt and Trowell's pioneering research, a virtual landslide of data has continually verified the role of the Western diet as the key factor in virtually every chronic disease, especially obesity and diabetes. Box 44-1 lists diseases with convincing links to a diet low in plant foods. Many of these now common diseases were extremely rare before the twentieth century.

TRENDS IN U.S. FOOD CONSUMPTION

During the twentieth century, food consumption patterns changed dramatically (Table 44-2). Total dietary fat intake rose from 32% of the calories in 1909 to 43% by the end of the century. Overall carbohydrate intake dropped from 57% to 46%, and protein intake remained fairly stable at about 11%.

Compounding these detrimental changes are the individual food choices accounting for the changes. The biggest changes were in significant rises in the consumption of meat, fats and oils, and sugars and sweeteners in conjunction with the decreased consumption of noncitrus fruits, vegetables, and whole grain products. The absolutely greatest change in the last 100 years of human nutrition is the switch from a diet with a high level of complex carbohydrates, as found naturally occurring in grains and vegetables, to a tremendous and dramatic increase in the number of calories consumed from simple sugars. Currently, more than half of the carbohydrates being consumed are in the form of sugars (sucrose, corn syrup, etc.) being added to foods as sweetening agents. High consumption of refined sugars is linked to many chronic diseases, including obesity, diabetes, heart disease, and cancer.

THE GOVERNMENT AND NUTRITION EDUCATION

Throughout the years, various governmental organizations have published dietary guidelines, but the recommendations of the United States Department of Agriculture (USDA) have become the most widely known. In 1956, the USDA published *Food for Fitness—A Daily Food Guide*. This became popularly known as the Basic Four Food Groups. The Basic Four were composed of the following:

1. The Milk Group: milk, cheese, ice cream, and other milk-based foods
2. The Meat Group: meat, fish, poultry, eggs, with dried legumes and nuts as alternatives
3. The Fruit and Vegetable Group
4. The Breads and Cereals Group

TABLE 44-2 **Trends in Quantities of Foods Consumed Per Capita (Pounds Per Year)**

FOODS	1909	1967	1985	1999
Meat, Poultry, and Fish				
Beef	54	81	73	66
Pork	62	61	62	50
Poultry	18	46	70	68
Fish	12	15	19	15
Total	146	203	224	199
Eggs (each)	37	40	32	32
Dairy Products				
Whole milk	223	232	122	112
Low-fat milk	64	44	112	101
Cheese	5	15	26	30
Other	47	159	190	210
Total	339	450	450	453
Fats and Oils				
Butter	18	6	5	5
Margarine	1	10	11	8
Shortening	8	16	23	22
Lard and tallow	12	5	46	
Salad and cooking oil	2	16	25	29
Total	41	53	68	70
Fruits				
Citrus	17	60	72	79
Noncitrus				
Fresh	154	73	87	115
Processed	8	35	34	37
Total	179	168	193	231
Vegetables				
Tomatoes	46	36	38	55
Dark green and yellow	34	25	31	39
Other				
Fresh	136	87	96	126
Processed	8	35	34	39
Total	224	183	199	259
Potatoes, White				
Fresh	182	67	55	49
Processed	0	19	28	91
Total	182	86	83	140
Dry beans, peas, nuts, and soybeans	16	16	18	22
Grain Products				
Wheat products	216	116	122	150
Corn	56	15	17	28
Other grains	19	13	26	24
Total	291	144	165	202
Sugar and Sweeteners				
Refined sugar	77	100	63	68
Syrups and other sweeteners	14	22	90	91
Total	91	122	153	159

Modified from United States Department of Agriculture. Food Review 2000;23:8-15.

One of the major problems with the Basic Four Food Groups model was that it graphically suggested that the food groups were equal in health value. The result was overconsumption of animal products, dietary fat, and refined carbohydrates, and insufficient consumption of fiber-rich foods like fruits, vegetables, and legumes. This in turn resulted in diets being responsible for many premature deaths, chronic diseases, and increased health care costs.

As the Basic Four Food Groups became outdated, various other governmental as well as medical organizations developed guidelines of their own, designed to reduce the risk of either a specific chronic degenerative disease, such as cancer or heart disease, or of all chronic diseases.

In an attempt to create a new model in nutrition education, the USDA first published the "Eating Right Pyramid" in 1992. It received harsh criticisms from numerous experts and other organizations. One big question that should be asked is, "Is it appropriate to have the USDA making these recommendations?" After all, the USDA serves two somewhat conflicting roles: (1) it represents the food industry, and (2) it is in charge of educating consumers about nutrition. Many people believe that the pyramid was weighted more toward dairy products, red meat, and grains because of influence from the dairy, beef, and grain farming and processing industries. In other words, the pyramid was designed not to improve the health of Americans but rather to promote the USDA agenda of supporting multinational agrifoods giants (Figure 44-1).

One of the main criticisms of the Eating Right Pyramid is that is does not stress strongly enough the importance of quality food choices. For example, the bottom of the pyramid represents the foods that the USDA thinks should make up the bulk of a healthy diet: the Bread, Cereal, Rice, and Pasta Group. Eating 6 to 11 servings a day from this group is supposedly the path to a healthier life. In this way, the pyramid sets a person up for insulin resistance, obesity, and adult-onset diabetes if he or she consistently chooses refined rather than whole grain products in this important category. This is one example of how the Eating Right Pyramid does not take into consideration how quickly blood glucose levels rise after eating a certain type of food—an effect referred to as the food's glycemic index (GI). The GI is a numerical scale used to indicate how fast and how high a particular food raises blood glucose (blood sugar) levels. There are two versions of the GI, one based on a standard of comparison with glucose as 100, and the other based on white bread. Foods are tested against the results of the selected standard. Foods with a lower GI create a slower rise in blood sugar, whereas foods with a higher GI create a faster rise in blood sugar.

One of the major problems with the Eating Right Pyramid is that the GIs of some of the foods that the pyramid is directing Americans to eat more of, such as breads, cereals, rice, and pasta, can greatly stress blood sugar control, especially if derived from refined grains, and are now being linked to an increased risk for obesity, diabetes, and cancer. As a result, the goal of the Eating Right Pyramid was to improve the health of Americans and, hopefully, slow down the growing trend toward obesity and diet-related disease, but because of poor individual food choices within the categories, the pyramid has only worsened the problem.

On June 2, 2011 the USDA unveiled a new food icon, MyPlate, to replace the food pyramid (see Figure 44-2). This simplified illustration is designed to help Americans make healthier food choices. MyPlate is the first step in a multi-year effort to raise awareness and educate consumers of eating more healthfully. The initial launch came with some simple recommendations:

- Balancing Calories
- Enjoy your food, but eat less.
- Avoid oversized portions.

Foods to Increase

- Make half your plate fruits and vegetables.
- Make at least half your grains whole grains.
- Switch to fat-free or low-fat (1%) milk.

Foods to Reduce

- Compare sodium in foods like soup, bread, and frozen meals and choose the foods with lower numbers.
- Drink water instead of sugary drinks.

Hopefully, this new campaign will be more successful than prior efforts. And, hopefully, the program will not yield to political pressure, and focus on communicating important nutritional guidance (Figure 44-2).

THE OPTIMAL HEALTH FOOD PYRAMID

On the basis of existing evidence we have created The Optimal Health Food Pyramid (Figure 44-3). The major difference from the USDA pyramid is that the Optimal Health Food Pyramid

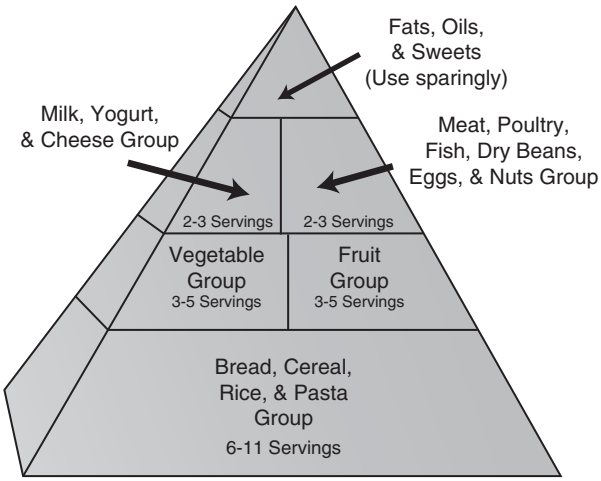


FIGURE 44-1 U.S. Department of Agriculture Food Pyramid.

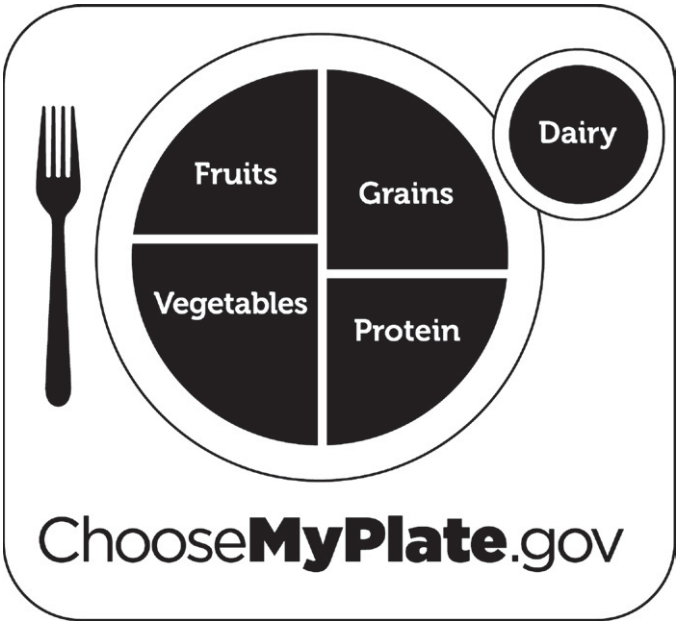


FIGURE 44-2 U.S. Department of Agriculture, MyPlate icon.

incorporates the best of two of the most healthful diets ever studied—the traditional Mediterranean diet (see later) and the traditional Asian diet. In addition, the Optimal Health Food Pyramid more clearly defines what the healthy components within the categories are and stresses the importance of vegetable oils and regular fish consumption as part of a healthful diet. Appendix 8 provides a patient handout that clearly defines the components of the Optimal Health Food Pyramid.

We based the Optimal Health Food Diet on the following nine principles:

1. Eat a "rainbow" assortment of fruits and vegetables.
2. Reduce exposure to pesticides.
3. Eat to support blood sugar control.
4. Do not over consume animal foods.
5. Eat the right types of fats.
6. Keep salt intake low, potassium intake high.
7. Avoid food additives.
8. Take measures to reduce foodborne illness.
9. Drink sufficient amounts of water each day.

1. Eat a "Rainbow" Assortment of Fruits and Vegetables

A diet rich in fruits and vegetables is the best bet for preventing virtually every chronic disease. That fact has been established time and again in scientific studies on large numbers of people. The evidence in support of this recommendation is so strong that it has been endorsed by U.S. government health agencies and by virtually every major medical organization, including the American Cancer Society. "Rainbow" simply means that selecting colorful foods—red, orange, yellow, green, blue, and purple—provides the body the full spectrum of pigments with powerful antioxidant effects as well as the nutrients it needs for optimal function and protection against disease (Box 44-2).

Fruits and vegetables are so important in the battle against cancer that some experts have said, and we believe, that cancer is a result of a "maladaptation" over time to a reduced level of intake of fruits and vegetables. As a study published in the medical journal *Cancer Causes and Control* put it, "Vegetables and fruit contain the anticarcinogenic cocktail to which we are adapted. We abandon it at our peril."[8] A vast number of substances found in fruits and vegetables are known to protect against cancer.[9-11] Some experts refer to these as "chemopreventers," but they are better known to many as phytochemicals (Table 44-3). Phytochemicals include pigments such as carotenes, chlorophyll, and flavonoids; dietary fiber; enzymes; vitamin-like compounds; and other minor dietary constituents. Although they work in harmony with antioxidants like vitamin C, vitamin E, and selenium, phytochemicals exert considerably greater protection against cancer than these simple nutrients. Among the most important groups of phytochemicals are pigments such as chlorophyll, carotenes, and flavonoids.

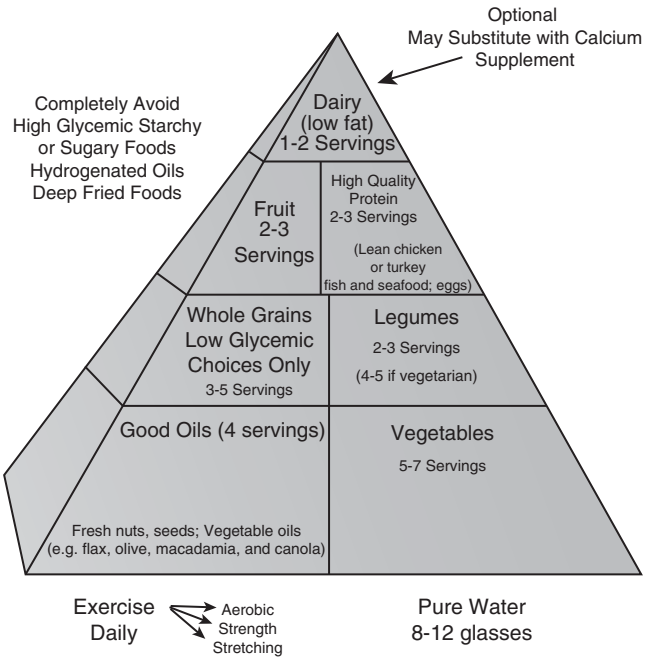


FIGURE 44-3 The Optimal Health Food Pyramid.

2. Reduce Exposure to Pesticides and Food Additives

In the United States, more than 1.2 billion pounds of pesticides and herbicides are sprayed on or added to food crops each year. That is roughly 5 lbs of pesticides for each man, woman, and

BOX 44-2 The "Rainbow" Assortment of Fruits and Vegetables

Red
Apples (red)
Bell peppers (red)
Cherries
Cranberries
Grapefruit
Grapes (red)
Plums (red)
Radishes
Raspberries
Strawberries
Tomatoes
Watermelon

Dark Green
Artichoke
Asparagus
Bell peppers (green)
Broccoli
Brussels sprouts
Chard
Collard greens
Cucumber
Grapes (green)
Green beans
Honeydew melons
Kale
Leeks
Lettuce (dark green types)
Mustard greens
Peas
Spinach
Turnip greens

Yellow and Light Green
Apples (green or yellow)
Avocado
Banana
Bell peppers (yellow)
Bok choy
Cabbage
Cauliflower
Celery
Fennel
Kiwi fruit
Lemons
Lettuce (light green types)
Limes
Onions
Pears (green or yellow)
Pineapple
Squash (yellow)
Zucchini (yellow)

Orange
Apricots
Bell peppers (orange)
Butternut squash
Cantaloupe
Carrots
Mangoes
Oranges
Papaya
Pumpkin
Sweet potatoes
Yams

Purple
Beets
Blackberries
Blueberries
Cabbage (purple)
Cherries
Currants
Eggplant
Grapes (purple)
Onions (red)
Pears (red)
Plums (purple)
Radishes

TABLE 44-3 **Examples of Anticancer Phytochemicals**

PHYTOCHEMICAL	ACTION(S)	SOURCES
Carotenes	Antioxidants Enhance immune functions	Dark-colored vegetables, such as carrots, squash, spinach, kale, tomatoes, yams, sweet potatoes; fruits such as cantaloupe, apricots, citrus fruits
Coumarin	Antitumor properties Enhances immune functions Stimulates antioxidant mechanisms	Carrots, celery, fennel, beets, citrus fruits
Dithiolthiones, glucosinolates, and thiocyanates	Block cancer-causing compounds from damaging cells Enhance detoxification	Cabbage-family vegetables—broccoli, brussels sprouts, kale, etc.
Flavonoids	Antioxidants Direct antitumor effects Immune-enhancing properties	Fruits, particularly darker fruits, such as berries, cherries, citrus fruits; also tomatoes, peppers, greens
Isoflavonoids	Block estrogen receptors	Soy and other legumes
Lignans	Antioxidants Modulate hormone receptors	Flax seed and flax seed oil; whole grains, nuts, seeds
Limonoids	Enhance detoxification Block carcinogens	Citrus fruits, celery
Polyphenols	Antioxidants Block carcinogen formation Modulate hormone receptors	Green tea, chocolate, red wine
Sterols	Block production of carcinogens Modulate hormone receptors	Soy, nuts, seeds

Modified from Steinmetz KA, Potter JD. J Am Diet Assoc 1996;96:1027-1039.

child. There is a growing concern that in addition to the significant number of cancers caused by the pesticides directly, exposure to these chemicals damages the body's detoxification mechanisms, thereby raising the risk of cancer and other diseases. To illustrate just how problematic pesticides can be, one can take a quick look at the health problems of the farmer. The lifestyle of farmers is generally healthy: compared with city dwellers, farmers have access to lots of fresh food; they breathe clean air, work hard, and have a lower rate of cigarette smoking and alcohol use. Yet studies show that farmers have a higher risk of lymphomas, leukemias, and cancers of the stomach, prostate, brain, and skin.[13-15] Exposure to pesticides may explain this occurrence.

Perhaps the most problematic pesticides are the family of halogenated hydrocarbons, such as 1,1-dichloro-2,2-bis(4-chlorophenyl) ethylene (DDE), polychlorinated biphenyl (PCB), pentachlorophenol (PCP), dieldrin, and chlordane. These chemicals persist almost indefinitely in the environment. A similar pesticide, dichlorodiphenyltrichloroethane (DDT), has been banned for nearly 30 years, yet it can still be found in soil and root vegetables such as carrots and potatoes. The human body also has a tough time detoxifying and eliminating these compounds. Instead, they end up being stored in fat cells. Moreover, inside the body these chemicals can act like the hormone estrogen. They are thus suspected as a major cause of the growing epidemic of estrogen-related health problems, including breast cancer.[12] Some evidence also suggests that these chemicals raise the risk of lymphomas, leukemia, and pancreatic cancer as well as play a role in low sperm counts and reduced fertility in men.[16]

Avoiding pesticides is especially important in children of preschool age. Children are at greater risk for two reasons: they eat more food relative to body mass, and they consume more foods higher in pesticide residues—such as juices, fresh fruits, and vegetables. A recent University of Washington study[17] that analyzed levels of breakdown products of organophosphorus pesticides (a class of insecticides that disrupt the nervous system) in the urine of 39 urban and suburban children aged 2 to 4 years found that concentrations of pesticide metabolites were six times lower in the children who ate organic fruits and vegetables than in those who ate conventional produce.

After conducting an analysis of USDA pesticide residue data for all pesticides for 1999 and 2000, Consumers Union[18] warned parents of small children to limit or avoid conventionally grown foods known to have high pesticide residues, such as cantaloupes, green beans (canned or frozen), pears, strawberries, tomatoes (Mexican grown), and winter squash. The University of Washington study added apples to this list.

Recommendations for Patients to Avoid Pesticides in the Diet

Patients can avoid consuming pesticides in their foods by following these recommended practices:

1. Do not over consume foods that have a tendency to concentrate pesticides, such as animal fat, meat, eggs, cheese, and milk.
2. Buy organic produce, which is grown without the aid of synthetic pesticides and fertilizers. Although less than 3% of the total produce in the United States is grown without pesticides, organic produce is widely available.
3. Develop a good relationship with your local grocery store produce manager. Explain your desire to reduce your exposure to pesticides and waxes. Ask what measures the store takes to ensure that pesticide residues are within approved limits. Ask where the store obtains its produce; make sure the store is aware that foreign produce is much more likely to contain excessive levels of pesticides as well as pesticides that have been banned in the United States.
4. Try to buy local produce in season.
5. Peeling off the skin or removing the outer layer of leaves of some produce may be all you need to do reduce pesticide levels. The downside is that many of the nutritional benefits of fruits and vegetables are concentrated in the skin and outer layers. An alternative measure is to remove surface pesticide residues, waxes, fungicides, and fertilizers by soaking the item in a mild solution of additive-free soap such as Ivory or pure castile soap. All-natural, biodegradable cleansers are also available at most health food stores. To use, spray the food with the cleanser, gently scrub, and rinse.

3. Eat to Support Blood Sugar Control

Refined sugars, white flour products, and other sources of simple sugars are quickly absorbed into the blood stream, causing a rapid rise in blood sugar. In response, the body boosts secretion of insulin

by the pancreas. High-sugar, "junk food" diets definitely lead to poor blood sugar regulation, obesity, and ultimately type 2 diabetes and heart disease.[19-21] The stress on the body that they cause, however, including secretion of too much insulin, can promote the growth of cancer and increases the risk of heart disease as well.

As already discussed, the GI of a food refers to how quickly blood sugar levels will rise after it is eaten. However, the GI does not tell how much of that carbohydrate is in a typical serving of a particular food, so another tool is needed. The glycemic load (GL) is a relatively new way to assess the effect of carbohydrate consumption that takes the GI into account but gives a fuller picture of the effect that a food has on blood sugar levels than GI alone. A GL of 20 or more is high, a GL of 11 to 19 inclusive is medium, and a GL of 10 or less is low. For example, beets have a high GI, but a low GL. Although the carbohydrate in beet root has a high GI, the amount of carbohydrate is low, so a typical serving of cooked beet root has a relatively low GI (about 5). Thus, as long as one eats a reasonable portion of a low GL food, the impact on blood sugar is acceptable, even if the food has a high GI. For example, a diabetic can enjoy some watermelon (GI 72) as long as he or she keeps the serving size reasonable; the GL for 120 g watermelon is only 4.

In essence, foods that are mostly water (e.g., apple, watermelon); fiber (e.g., beet root, carrot); or air (e.g., popcorn) will not cause a steep rise in blood sugar even if their GIs are high as long as portion sizes are moderate. To help design a healthy diet, we provide a list of the GI, fiber content, and GL of common foods in Appendix 6.

4. Reduce Intake of Meat and Other Animal Foods

Study after study seems to indicate that the higher the intake of meat and other animal products, the higher the risk of heart disease and cancer, especially the major cancers like those of the colon, breast, prostate, and lung, whereas a diet focusing on plant foods exerts the opposite effect.[5,6,22,23]

There are many reasons for this association. Meat lacks the antioxidants and phytochemicals that protect from cancer. At the same time, it contains lots of saturated fat and other potentially carcinogenic compounds—including pesticide residues, heterocyclic amines, and polycyclic aromatic hydrocarbons, which form when meat is grilled, fried, or broiled. The more well done the meat, the higher level of amines.[24]

Some proponents of a diet high in meats claim that people should eat the way their "caveman" ancestors did. That argument does not really hold up. As already discussed, the meat of wild animals that early humans consumed had a fat content of less than 4%. The demand for tender meat has led to the breeding of cattle whose meat contains 25% to 30% or more fat. Domestic beef contains primarily saturated fats and virtually no beneficial ω-3 fatty acids (discussed later), whereas the fat of wild animals contains more than five times the polyunsaturated fat per gram and has substantial amounts (about 4%) of ω-3 fatty acids.

Range-fed animals also contain ten times as much conjugated linoleic acid (CLA) as grain-fed animals. CLA is a slightly altered form of the essential fatty acid linoleic acid. It occurs naturally in meat and dairy products. CLA was discovered in 1978, when researchers at the University of Wisconsin were looking for cancer-causing compounds that result from cooking. Instead, they found CLA, which appears to be an anticancer compound. Preliminary studies show that CLA might reduce the risk of heart disease and cancer.[25]

Particularly harmful to human health are cured or smoked meats, such as ham, hot dogs, bacon, and jerky, that contain sodium nitrate and/or sodium nitrites—compounds that keep the food from spoiling but that dramatically raise the risk of cancer. These chemicals react with amino acids in foods in the stomach to form highly carcinogenic compounds known as nitrosamines.

Research in adults makes a convincing argument to avoid these foods. Even more compelling is the evidence linking consumption of nitrates to a significantly increased risk of the major childhood cancers (leukemias, lymphomas, and brain cancers), as follows:

- Children who eat 12 hot dogs per month have nearly ten times the risk of leukemia compared to children who do not eat hot dogs.[26]
- Children who eat hot dogs once a week double their chances of brain tumors; eating hot dogs twice a week triples the risk.[26]
- Pregnant women who eat two servings per day of any cured meat have more than double the risk of bearing children who have brain cancer.[27]
- Kids who eat the most ham, bacon, and sausage have three times the risk of lymphoma.[26]
- In addition, kids who eat ground meat once a week have twice the risk of acute lymphocytic leukemia compared with those who eat none; eating two or more hamburgers weekly triples the risk.[26]

Fortunately, vegetarian alternatives to these standard components of the American diet are now widely available, and many of them actually taste quite good. Consumers can find soy hot dogs, soy sausage, soy bacon, and even soy pastrami at their local health food stores as well as in many mainstream grocery stores.

5. Eat the Right Type of Fats

There is no room for debate: a diet high in fat, particularly saturated fat and cholesterol, has been linked to numerous cancers. Both the American Cancer Society and the National Cancer Institute recommend a diet that supplies less than 30% of calories as fat. However, just as important as the amount of fat is the type of fat consumed. The goal is to decrease total fat intake (especially intake of saturated fats, trans fatty acids, and ω-6 fats) while increasing intake of ω-3 fatty acids and monounsaturated fatty acids.

What makes a fat "bad" or "good" has a lot to do with the function of fats in the body's cellular membranes. Membranes are made mostly of fatty acids. What determines the type of fatty acid present in the cell membrane is the type of fat consumed. A diet composed mostly of saturated fat, animal fatty acids, and trans fatty acids (from margarine, shortening, and other sources of hydrogenated vegetable oils) and high in cholesterol results in membranes that are much less fluid in nature than a diet with optimal levels of unsaturated fatty acids. Modern pathology clearly indicates that an alteration in cell membrane function is the central factor in the development of virtually every disease. As it relates to diabetes, abnormal cell membrane structure due to eating the wrong types of fats leads to impaired action of insulin.

Without a healthy membrane, cells lose their ability to hold water, vital nutrients, and electrolytes. They also lose their ability to communicate with other cells and to be controlled by regulating hormones, including insulin. Without the right type of fats in cell membranes, cells simply do not function properly. Considerable evidence indicates that cell membrane dysfunction is a critical factor in the development of many diseases.

The type of dietary fat profile that is linked to many diseases is an abundance of saturated fat and trans fatty acids (hydrogenated vegetable oils) along with a relative insufficiency of monounsaturated and ω-3 fatty acids. One of the key reasons appears to be that because dietary fat determines cell membrane composition, such a dietary pattern leads to reduced membrane fluidity, which in turn causes reduced insulin binding to receptors on cellular

membranes and/or reduced insulin action. Particularly harmful to cell membrane function are margarine, vegetable oil shortening, and other foods containing trans fatty acids and partially hydrogenated oils. These "unnatural" forms of fatty acids interfere with the body's ability to utilize important essential fatty acids and are now linked to an increased risk for heart disease, diabetes, and cancer. Just the opposite effect has been shown for diets high in monounsaturated fats and ω-3 fatty acids.[28-31]

One diet that appears to be representative of a way of eating that provides an optimal intake of the right types of fat is the traditional Mediterranean diet—a term with a specific meaning. It reflects food patterns typical of some Mediterranean regions in the early 1960s, such as Crete, parts of Greece, and southern Italy. The traditional Mediterranean diet has shown tremendous benefit in fighting heart disease and cancer as well as diabetes.[32] It has the following characteristics:

- Olive oil is the principal source of fat.
- It centers on an abundance of plant food (fruit, vegetables, breads, pasta, potatoes, beans, nuts, and seeds).
- Foods are minimally processed, and there is a focus on seasonally fresh and locally grown foods.
- Fresh fruit is the typical daily dessert; sweets containing concentrated sugars or honey are consumed a few times per week at the most.
- Dairy products (principally cheese and yogurt) are consumed daily in low to moderate amounts.
- Fish is consumed on a regular basis.
- Poultry and eggs are consumed in moderate amounts (1-4 times weekly) or not at all.
- Red meat is consumed in low amounts.
- Wine is consumed in low to moderate amounts, normally with meals.

Olive oil consists not only of the monounsaturated fatty acid oleic acid; it also contains several antioxidant agents that may also account for some of its health benefits. Olive oil is particularly valued for its protection against heart disease. It lowers harmful low-density lipoprotein (LDL) cholesterol and increases the level of protective high-density lipoprotein cholesterol. It also helps circulating LDL cholesterol from becoming damaged by free radicals and has been proven to contribute to a better control of the elevated blood triglycerides that are so common in diabetes.[32]

6. Keep Salt Intake Low, Potassium Intake High

The electrolytes—potassium, sodium, chloride, and magnesium—are mineral salts that can conduct electricity when dissolved in water. For optimal health, it is important to consume these nutrients in the proper balance. Too much sodium in the diet from salt (sodium chloride) can disrupt this balance. Many people know that a high-sodium, low-potassium diet can cause high blood pressure and that doing the opposite can lower blood pressure,[33,34] but not as many are aware that the former diet also raises the risk of cancer.[35]

In modern Western society, only 5% of sodium intake comes from the natural ingredients in food. Prepared foods contribute 45% of our sodium intake; 45% is added in cooking, and another 5% is added as a condiment.

Patients can reduce their salt intake by following these tips:

1. Take the salt shaker off the table.
2. Omit added salt from recipes and food preparation.
3. If you absolutely must have the taste of salt, try the salt substitutes such as NoSalt and Nu-Salt. These products are made with potassium chloride and taste very similar to sodium chloride.
4. Learn to enjoy the flavors of unsalted foods.
5. Try flavoring foods with herbs, spices, and lemon juice.
6. Read food labels carefully to determine the amounts of sodium. Learn to recognize ingredients that contain sodium: salt, soy sauce, salt brine, and any ingredient with "sodium" in its name (such as monosodium glutamate) or "baking soda" (sodium bicarbonate).
7. In reading labels and menus, look for words that signal high sodium content, such as smoked, barbecued, pickled, broth, soy sauce, teriyaki, Creole sauce, marinated, cocktail sauce, tomato base, Parmesan, and mustard sauce.
8. Do not eat canned vegetables or soups, which are often extremely high in sodium.
9. Choose low-salt (reduced-sodium) products when available.

Most Americans have a potassium/sodium (K/Na) ratio of less than 1:2. In other words, they ingest twice as much sodium as potassium. However, experts believe that the optimal dietary potassium/sodium ratio is greater than 5:1—ten times higher than the average intake. However, even this may not be optimal. A natural diet rich in fruits and vegetables can easily produce much higher K/Na ratios, because most fruits and vegetables have a K/Na ratio of at least 50:1. The average K/Na ratios for several common fresh fruits and vegetables are as follows:

- Carrots: 75:1
- Potatoes: 110:1
- Apples: 90:1
- Bananas: 440:1
- Oranges: 260:1

7. Avoid Food Additives

Food additives are used to prevent spoiling or to enhance flavor; they include such substances as preservatives, artificial colors, artificial flavorings, and acidifiers. Although the government has banned many synthetic food additives, it should not be assumed that all the additives currently used in the United States food supply are safe. A great number of synthetic food additives remain in use that are being linked to such diseases as depression, asthma or other allergy, hyperactivity or learning disabilities in children, and migraine headaches.[36-39]

The U.S. Food and Drug Administration has approved the use of more than 2800 different food additives. It is estimated that the per capita daily consumption of these food additives is approximately 13 g to 15 g. This amount is astounding and leads to many questions. Which food additives are safe? Which should be avoided? An extremist might argue that no food additive is safe. However, many food additives fulfill important functions in the modern food supply. Many compounds approved as additives are natural in origin and possess health-promoting properties, whereas others are synthetic compounds with known cancer-causing effects. Obviously, the most sensible approach is to focus on whole, natural foods and avoid foods that are highly processed.

An illustration of the problem with food additives is one of the most widely used synthetic food colors: Food, Drug and Cosmetic Act yellow dye no. 5, or tartrazine. Tartrazine is added to almost every packaged food as well as to many drugs, including some antihistamines, antibiotics, steroids, and sedatives. In the United States, the average daily per capita consumption of certified dyes is 15 mg, of which 85% is tartrazine; among children, consumption is usually much higher.

Although the overall rate of allergic reactions to tartrazine is quite low in the general population, allergic reactions to

tartrazine are extremely common (20% to 50%) in individuals sensitive to aspirin as well as other allergic individuals. Like aspirin, tartrazine is a known inducer of asthma, hives, and other allergic conditions, particularly in children. In addition, tartrazine, as well as benzoate and aspirin, increases the production of a compound that raises the number of mast cells in the body. Mast cells are involved in producing histamine and other allergic compounds. A person with more mast cells in the body is typically more prone to allergies. For example, examination of patients with hives shows that more than 95% have a higher than normal number of mast cells.

In studies using provocation tests to determine sensitivity to tartrazine and other food additives in patients with hives, results have ranged from 5% to 46%. Diets eliminating tartrazine as well as other food additives in sensitive individuals have, in many cases, been shown to be of great benefit in patients with hives and other allergic conditions, such as asthma and eczema.

8. Take Measures to Reduce Foodborne Illness

Foodborne illness is caused by consumption of contaminated foods or beverages. Although the food supply in the United States is one of the safest in the world, the Centers for Disease Control and Prevention estimates that 76 million people get sick, more than 300,000 are hospitalized, and 5000 Americans die each year from foodborne illness.[40] The microbe or toxin enters the body through the gastrointestinal tract and often causes the first symptoms there, so nausea, vomiting, abdominal cramps, and diarrhea are common symptoms in many foodborne diseases. Most cases of foodborne illness are mild, but serious diarrheal disease or other complications may occur.

More than 250 different organisms have been documented as being capable of causing foodborne illness.[41] Most of these cases are infections by a variety of bacteria, viruses, and parasites, but poisonings can also occur as a result of ingestion of harmful toxins or chemicals from organisms that have contaminated the food; for example, botulism occurs when the bacterium *Clostridium botulinum* grows and produces a powerful paralytic toxin in foods. The botulism toxin can produce illness even if the bacteria are no longer present.

Most of the common causes of foodborne infections are microorganisms frequently present in the intestinal tracts of healthy animals. Meat and poultry can become contaminated during slaughter by contact with small amounts of intestinal contents, and fresh fruits and vegetables can be contaminated if they are washed or irrigated with water that is contaminated with animal manure or human sewage.

The most common causes of foodborne infections are the bacteria *Campylobacter*, *Salmonella*, and *Escherichia coli* O157:H7 and a group of viruses called caliciviruses, also known as the Norwalk and Norwalk-like viruses. Undercooked meat and poultry, raw eggs, unpasteurized milk, and raw shellfish are the most common sources of these organisms.

The foremost measure to reduce the risk of foodborne illness is to cook meat, poultry, and eggs thoroughly. Using a thermometer to measure the internal temperature of meat is a good way to be sure that it is cooked sufficiently to kill bacteria. For example, ground beef should be cooked to an internal temperature of 160° F, poultry should reach a temperature of 185° F, and an egg should be cooked until the yolk is firm.

One must also take care to avoid contaminating foods by making sure to wash hands, utensils, and cutting boards after they have been in contact with raw meat or poultry and before they touch another food. Cooked meat should be served on a clean platter, rather than back on one that held the raw meat. To prepare produce, one should wash fresh fruits and vegetables in running tap water. A soft-bristle brush with a little mild soap can be used. Greens can be soaked in cold water as many times as needed to get them clean.

9. Drink Sufficient Amounts of Water Each Day

Water is essential for life. The average amount of water in the human body is about 10 gallons. The recommendation to drink at least 48 oz of water per day to replace the water that is lost through urination, sweat, and breathing is valid. Even mild dehydration impairs physiologic and performance responses.[42] Many nutrients dissolve in water so they can be absorbed more easily in the digestive tract. Similarly, many metabolic processes need to occur in water. Water is a component of blood and thus is important for transporting chemicals and nutrients to cells and tissues. Each cell is constantly bathed in a watery fluid. Water also carries waste materials from cells to the kidneys for filtering and elimination. Water absorbs and transports heat. For example, heat produced by muscle cells during exercise is carried by water in the blood to the surface, helping to maintain the right temperature balance. The skin cells also release water as perspiration, which helps maintain body temperature.

Several factors are thought to increase the likelihood of chronic mild dehydration: a faulty thirst "alarm" in the brain; dissatisfaction with the taste of water; regular exercise that increases the amount of water lost through sweat; living in a hot, dry climate; and consumption of the natural diuretics caffeine and alcohol.

There is currently a great concern over the U.S. water supply. It is becoming increasingly difficult to find pure water. Most of the water supply is full of chemicals, including not only chlorine and fluoride, which are routinely added, but also a wide range of toxic organic compounds and chemicals, such as PCBs, pesticide residues, and nitrates, and heavy metals such as lead, mercury, and cadmium. It is estimated that lead alone may contaminate the water of more than 40 million Americans. Patients should be encouraged to determine the safety of their tap or well water by contacting their local water companies; most cities have quality assurance programs that perform routine analyses. Patients can simply ask for the most recent analysis.

NUTRITIONAL SUPPLEMENTATION

Nutritional supplementation—the use of vitamins, minerals, and other food factors to support good health as well as preventing or treating illness—is an important component of nutritional medicine. The key functions of nutrients like vitamins and minerals in the human body revolve around their role as essential components in enzymes and coenzymes. One of the key concepts in nutritional medicine is to supply the necessary support or nutrients to allow the enzymes of a particular tissue to work at their optimum levels. The concept of "biochemical individuality" was coined by nutritional biochemist Roger Williams in the 1970s to recognize the wide range in enzymatic activity and nutritional needs of humans. These observations also provided the basis for "orthomolecular medicine" as envisioned by two-time Nobel laureate Linus Pauling.

In addition to serving as necessary components in enzymes and coenzymes, many nutrients appear to exert pharmacologic effects. Most of these effects appear to be the result of enzyme induction. In other words, when used at supraphysiologic levels, nutrients

can induce the manufacture of enzymes, induce enzymes to become more active, or even inhibit enzyme action. For example, the B vitamin niacin (nicotinic acid) is well known as a lipid-lowering agent when given at high dosages (2 to 6 g/day in divided doses). Its mechanism of action is quite diverse, but appears to occur via inhibition of enzymes that manufacture very-low-density lipoprotein while stimulating the production or activity of enzymes that take up LDL in the liver. The advantage of using nutrients at pharmacologic dosages is that they are more recognizable and better metabolized by the body, as evidenced by a broader therapeutic index. Even so, the use of nutrients as pharmacologic agents is closely akin to drug therapy. That being the case, it is imperative that they be used and monitored appropriately.



SUMMARY

The dietary guidelines and principles that are detailed in this chapter represent our answer to the hotly debated question, "What is the best diet?" After a review of every popular diet in detail as well as thousands of scientific articles on the role of diet in human health, our offering here is based on the evolutionary understanding of what constitutes the optimal diet. The bottom line for a health-promoting diet is to reduce the intake of potentially harmful substances—foods laden with empty calories, additives, and artificial sweeteners—and replace them with natural foods, preferably organically grown.

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CHAPTER 45

Peat Therapeutics and Balneotherapy

Mark D. Groven, ND

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INTRODUCTION

Nature has provided many gifts of healing. One of the most outstanding and exciting is peat. The use of organic peat and its constituents is ancient, yet people with pain, injury, and dermatologic, rheumatic, and other conditions are benefiting from modern peat therapy today. This pleasant and safe healing discovery has brought relief and cure for many.[1-18]

Balneology is the study of the art and science of bathing. Balneotherapy is the use of natural thermal mineral waters, additive baths, peloids, and other natural substances, as well as various atmospheric or environmental elements singly or in combination for the prevention and treatment of disease. The aim of balneotherapy is to change regulation and reactive functions, leading to improvement of capacity, adaptation, and self-healing.[19]

Peloid refers to the pulp of a substance that is applied to the body. It may be in pack form or bath, either local or whole body. The concentration of peloidal solutions can vary and should be applied to the skin in a specific manner for a specific condition to optimize results. Common peloids are peat pulp, lake or sea muds, and plant substances.

For many conditions, balneotherapy works synergistically with peloid therapy, and the percutaneous absorption of their constituents along with the physiologic and psychological effects provides an excellent therapy for people who can no longer tolerate oral or injectable pharmaceuticals and have chronic degenerative diseases. Life is stressful, and our society is aging. We would be wise to utilize the positive benefits of balneotherapy in the conventional treatment of pain and illness as well as in health maintenance and prevention of disease. The purpose of this chapter is to describe the general concept of balneotherapy with emphasis on the therapeutic application of peat. There certainly is a distinction between the application of peat and the application of other muds, such as lake mud or clay. The characteristics of the specific peat mud constituents being used are vitally important, as well as the manner of their application.*

BALNEOLOGY

History

Therapeutic bathing is an ancient art and probably the oldest of medical procedures. Hippocrates wrote on the application of therapeutic bath in 400 BC and how it soothed pain in the side, improved respiration, soothed the joints and skin, was diuretic, and removed heaviness of the head. It was suited for those who benefited, but could be unsuitable if applied in the wrong way. It enjoyed tremendous popularity until about 75 years ago when, along with other natural techniques, it fell out of favor as conventional medicine produced its modern successes. Since then, the large corpus of empirical wisdom has been expanded on and much scientific evidence has contributed to the advancement of balneology as a science. Many institutions are teaching hydrotherapy and balneologic techniques, and many spas have wonderful programs for people to utilize. It is not hard to imagine that the reason this art survived and improved is because it can better people's health.

*References 7, 10, 11, 13, 16, 18-26.

Balneotherapy's modern day roots lie predominantly in European spas, which have some of the longest continuously running histories of any medical institution. Millions of patients flock to clinics throughout Europe and the world each year for treatment in hydrology departments under the supervision of physicians and their staffs. Such clinics provide a variety of balneotherapeutic techniques. Spa therapy is a term used for the combination of balneotherapy and other techniques usually delivered at a resort setting. The effects of spa therapy are influenced positively by the pleasure of being in a beautiful setting with the stresses of home and work removed. Medical spas are often in an area where earth's elements are present. The pristine air, the ambient temperature, the humidity or amount of light, nourishing food, and exercise can effect a change in the spirit, mind, and body.[19]

Balneotherapy in Combination with Other Therapies

Many therapies work well together, such as phototherapy and mud therapy in the treatment of psoriasis. Mud pack therapy, peloidotherapy, massage, soft and osseous tissue manipulation, iontophoresis, phonophoresis, and exercise work together.[27] The combination of buoyancy and heat in the water make sense, for example, in underwater traction bath and massage, which have been shown to reduce the levels of analgesic consumption in patients.[18] In my own experiences with patients, hydrotherapy, with and without mud in combination with other treatments, such as naturopathic manipulation, can work like nothing else to help people heal and stay healthy. A multitude of conditions can be treated with balneotherapeutic methods—pain, injury, and dermatologic and rheumatic conditions rank high.[2,19,28,29] Under the right conditions and with the right application, balneotherapy stimulates healing and speeds recovery.[30]

Physiologic Effects

Balneotherapeutics induce direct and indirect actions on the body. The direct actions of balneotherapy take into consideration the physical actions of water on the body, such as hydrostatic pressure, buoyancy, viscosity, and frictional resistance, as well as thermal effects and the chemical and pharmacologic effects of the percutaneous absorption of the substance being used.[44] Such substances are found in hot spring waters of various types, such as carbon dioxide, hydrogen sulfide, chloride, sulfate, iron, acid, and radon. Mineral waters contain cations such as sodium, potassium, calcium, and magnesium, and anions SO_4^-, Cl^-, and HCO_3^-. The concentrations of these ions are usually significantly high (1 g/L). In spring water, levels of nitrogen compounds, such as nitrate, nitrogen dioxide,, and nitrogen oxide, are very low and the water is free of or low in bacteria.[17] Peat muds, plant preparations, and mineral-containing muds are also used. In Europe, peat bath and peloids are traditional. These applications are used in combination with exercise, aquatics, steam bath, sauna therapy, climatotherapy, physical therapy, and pharmacotherapy, among others, with important consideration being given during treatment to the chronobiologic and circadian rhythmic phases of the body.[1,14,23,25-28]

The indirect actions of balneotherapy arise from the repeated application of therapeutic stimulation, such as climatic exposure to the elements, training effects of exercises, and social and psychological effects arising from changes in environment. These elements act as a complex stimulation in a nonspecific manner of the physiologic function of the organism's central nervous system, autonomic nervous system, endocrine system, immune system, and so on. The result of these stimulations is a reactive response by the body, leading to activation and improvement of capacity, adaptation, and self-healing potential. In other words, balneotherapy has a normalizing effect on the body's systems and rhythms.*

Circadian Rhythms

Biorhythms are important in the expression of many conditions.[40,41] Sunlight, mealtimes, and seasonal changes are external cues that, together with internal cues such as blood pressure and respiration, affect the hypothalamus or master clock. This part of the brain then signals hormones, enzymes, and other substances to facilitate healing, produce cells, or cause pain and symptoms. It has been shown that different times of day affect the amount of muscle torque potential, body temperature, and clock-gene messenger RNA (mRNA) expression.[42] A cold or hot foot bath can induce a rise in temperature of oral mucosa up to 1°C, but the extent of the oral temperature increase depends on the body's reaction to this stimulus, which is influenced by the body's own internal clock.[1]

Conditions such as arthritis have pain with varying cycles.[43] It is thought that some of these cycles are in synchrony with the moon and the sun. Heart attacks, asthma, and rheumatoid arthritis joint pain are early morning diseases, so medication and treatment can be tailored for different times of day when it is significantly more helpful and less wasteful when not needed. Serum adrenocorticotropic hormone, prolactin, luteinizing hormones, and immune parameters such as plasma levels of soluble p75 tumor necrosis factor and tumor necrosis factor-α (TNF-α) vary in 24-hour rhythms in the body.[30] These may be affected through balneotherapy, as may melatonin production and expression.[44] Melatonin affects the organization and expression of biorhythms and is easily susceptible to oxidative stress. Symptom remission in some conditions coincides with a normalization of circadian rhythms promoted by balneotherapeutic treatment.[45-48] In a European study, the combination of carbon dioxide bath and mud bath was shown to downregulate the systolic pressure in hypertension while having a balancing effect on biological clocks.[49] A study on fibromyalgia patients, in whom altered reactivity of the hypothalamic-pituitary-adrenal axis was observed, supported the theory that mud pack therapy works in synergy with antidepressant treatment to decrease pain and improve depression. Balneotherapy can promote the body's response systems, such as the stress response system, to achieve homeostasis.[46]

PEAT THERAPEUTICS

History

The ancients used peat extract baths, and the antiseptic properties of peat mud were recognized in World War I when it was applied directly to wounds to prevent infection.[50] Natives used mud externally and internally. Peat has been used as a medicinal preparation in baths and peloid packs extensively in Europe for the past 200 years. This unique substance contains many chemical constituents that can interact with organic and inorganic compounds.[20] The scientific basis for the physical, chemical, and pharmacologic effects of peat baths has long been known, and such baths have been used extensively in balneotherapeutic applications in Europe and other parts of the world to treat rheumatic diseases, gynecologic disorders, osteoarthritis, lumbago, sciatica,

*References 2, 4, 7, 10, 11, 15, 31-39.

skin diseases, trauma and its sequelae, and many other ailments and afflictions. The many substances in peat offer a vast possibility of medicinal cure applications.[51-61]

It is important to consider the region and origin of the peat being used for medicinal purposes. Low moor peat has been shown to contain higher concentrations of nitrous substances, which are thought to contain a higher content of biologically active substances than the high moor peats or peats taken from a shallower depth. It is not just high nitrous content that makes a certain peat more medically useful, but the quality, type, and amount of the biologically active substances it contains that are the determining factors in its medicinal effect. In Germany these types of peats are now a national resource.

Skin Response

Skin is a reflex, metabolic, immune, and excretory organ. It affects the autonomic, immune, and circulatory systems and participates in the biosynthesis of not only vitamin D but also acetylcholine, histamine, and serotonin.[2,4,10,15] Significantly higher concentrations of minerals and medicaments can be attained in the epidermis with baths than with systemic flooding via the vascular system. There is percutaneous uptake of many substances by the skin but not in large amounts for most natural substances. Permeation into the dermis does occur especially for humic acids, and uptake beyond the stratum corneum is exemplified by measurable urinary excretion rates.[62,63]

The primary effects of bath components take place within the skin. For instance, hydrogen sulfide acts as a trap for oxygen radicals, functioning to reduce inflammation. It is thought that the action comes from the effect of sulfur on the Langerhans cells, which play a role in immune presentation and inflammation modulation. In this way, skin responses can act as transmitter-activating helper functions. Sulfur-containing peat baths demonstrate a pain-reducing and healing effect on rheumatic and degenerative diseases. One reason may be the reduction in Langerhans cell activity in producing cytokines that results from the combination of the components within peat and thermal radiation.*

Physiologic Effects

Peat has a structure containing micropores, which accounts for its sponge-like, water-carrying capacity and its ability to maintain either hot or cold temperatures. When applied, peat produces a gradient rise or fall in temperature, which is especially desirable in a therapeutic bath. A peat formulation bath influences neuromuscular, endocrine, and pulmonary functions, as well as kidney hemodynamics, depending on the consistency and volume of the partial or full bath.[4,10] Peat has well-documented effects, such as tissue dilatation and increases in stroke volume, metabolism, and immunologic stimulation. Peat bath may be preferable to water bath if one considers the gradient rise and fall of temperature, increased buoyancy, and prevention of heat loss during a bath and the possible positive chemical and pharmacologic effects of the constituents of peat.[60,62-65]

Those who have experienced a therapeutic bath can appreciate the feelings of exhilaration and deep relaxation induced by a bath that contains an additive such as peat. The response is affected by the constituents in the water, the temperature of the bath, and the time of day the stimulus is given.[65]

The patient's genetics and physical capacity are also important. A peat bath enhances circulation significantly longer than a water bath.[21] Microcirculatory vasodilation in the skin has been shown to increase even without hyperthermia. The peripheral and deeper arteries, such as the intrauterine vessels, have shown prolonged increased flow after peat bath. The effects of peat constituents can occur without heat, but heat increases the effect on the body.

The antirheumatic activity of thermal muds has a precise pharmacologic character. Therapy can be prescribed according to the characteristics of the mud for specific conditions.[60,62] For example, specific muds work better with phototherapy for psoriasis and atopic dermatitis. The length of time that the peat mud has undergone humification and maturation lends unique characteristics. Maturation of peat muds increases their thermoinsulating, hydration, and, importantly, biochemical characteristics. The sulfoglycolipid content of mature mud differentiates a natural remedy from a specific application with a precise pharmacologic character. These sulfoglycolipids are absorbed through the skin and stimulate an antirheumatic effect.[66] Several peat substances are able to permeate the skin.[63] Their absorption and action have been documented by the comparisons of placebo, water bath, and peat bath using Doppler ultrasound measurement. One study that measured circulation in the uterine artery after bath therapy showed that only the peat bath achieved the physiologic effect of prolonged vasodilatation and circulation. This effect lasted for several hours after the treatment. It is thought that absorption of peat substances takes place through the hair follicles and apocrine glands via diffusion and partial pinocytosis.[21,38] The fractions of peat components that penetrate the skin include the humic acid fractions, fulvic, ulmic, and volvic. The excitatory effect of humic acid fractions such as fulvic acid impact the reactivity of α2 and D2 receptors of smooth muscle cells.[64]

The functions of peat in medicinal applications are antimicrobial, antiviral, anti-inflammatory, and antineoplastic, to name a few.[65] Many biochemical effects have been demonstrated in humans and animals. The anti-inflammatory effect of peat mud has been attributed to a sulfoglycolipid associated with a decrease in serum interleukin-1 (IL-1) in patients with arthritis.[67] The effects of mud applications include elevation of protein synthesis, reduction of arachidonic acid, and inhibition of inflammatory mediators such as leukotrienes (LTB4), prostaglandins (PGE-2), and thromboxane. Biologic activity is ascribed to peat ingredients, such as sulfur compounds, magnesium, manganese, iron, and humic acids.† Mud pack therapy decreases the proinflammation factors IL-1 and TNF-α and radical-mediated peroxidations, nitric oxide and myeloperoxidase.[68] It also increases serum levels of insulin-like growth factor 1, which is cartilage protective. Humic substances spread widely in nature, and when found mainly in highly degraded peat, have been shown to have a proliferative effect on certain leukocytes. Water-soluble oxihumate, given orally or dermally, increases the proliferative response in mononuclear leukocytes as well as production and expression of IL-2.[2,50,69]

Hyperthermia

The thermal properties of peat mud applications have been shown to be much greater than those of water bath because of the former's dynamic viscosity, decreased convective cooling, and a protective effect on the skin with hot applications.[2] Whole-body, extracorporal, and local infrared applications of hyperthermia

*References 2, 7, 15, 19, 22, 50, 64.

†References 6, 7, 10, 11, 16, 19, 24.

have uses in cancer therapy. Hyperthermic effects include changes in heat shock proteins (HSPs) and upregulation of heart antioxidant defense proteins such as manganese superoxide dismutase.[66] Plasma B-endorphins also rise in response to hot water bathing and may be responsible for the euphoric feeling the bath may bring.[44,70] In a study of patients with cancer, hyperthermia was shown to create the same endorphin rise both after sauna bath and in whole-body infrared hyperthermia.

Whole-body hyperthermia (WBH) stimulates an increase in T cells, such as monocytes and absolute numbers of white blood cells.[70] Heat increases granulocyte mobility, phagocytic and bactericidal properties, and enzymatic activity.[1] There is an increase in homing response to different tissues of lymphocytes, which contributes to antitumor activity. Hyperthermia may increase lymphocyte migration into inflamed tissue or lymphoid tissues such as lymph nodes and Peyer's patches; this effect may help generate the cellular immune response. TNF-α and IL-6 are regulated by the stimulus of hyperthermia.[71-73] HSPs produced by hyperthermia can provide protection against the muscle damage that occurs through a pathologic increase in intracellular calcium or uncoupling of the mitochondrial respiratory chain. Hyperthermia provides protection against typical damage from reperfusion after ischemia or with excessive exercise damage. Calcium homeostasis, energy loss, increased free radical–mediated reactions, and activation of apoptosis pathways are affected. I use a thermal application of the partial or full peat-additive bath for the treatment of back pain, musculoskeletal disorders, skin problems, viral illnesses, and more. The use of heat in the right amount is crucial to treatment efficacy.[66,73,74]

CLINICAL APPLICATIONS

Care must be exercised in the selection of patients for any type of thermal therapy. It is important to allow each patient time to adapt by starting with lower temperature and shorter duration treatments first. Patients with neurodegenerative diseases like multiple sclerosis (MS) and conditions such as diabetes are not good candidates for WBH. In MS, the excitatory effect on nerves from heat leads to muscle cramping and, in diabetes, heat may lead to an ultimate drop in blood sugar and lightheadedness or loss of consciousness. Peat has many beneficial applications, however, as described here.

Discopathy

A series of treatments using first peat bath followed by manual traction and then a peat pack over the affected area of the spine has worked marvelously for many of my patients with discopathy. The first thing that is helped is the pain; then there is an improvement in structural integrity and function over time. It is necessary to perform these combination treatments 3 times a week for 3 to 12 weeks if there is significant discopathy.

Myopathy

Muscle pain is easily treated with a thermal peat bath or peat pack. The increase in circulation is very helpful to muscles and can be valuable in assisting with osseous manipulation once the muscles are more relaxed.

Scoliosis

Peat bath followed by traction of the spine can be very helpful in patients with scoliosis who have back pain. Applying a peat pack over the area of spinal pain can also be useful.

Arthritis

Peat treatments have shown efficacy for both osteoarthritis and rheumatoid arthritis. Matrix metalloproteinases (MMP-1 or stromelysin-1) are significantly reduced in mud bath patients with osteoarthritis.[75] One needs to be careful with acute rheumatoid arthritis because treatment may initially stir up symptoms. Generally, in osteoarthritis, these treatments have been shown in both the literature and my experience to be very beneficial. I have observed significant decreases in swelling and pain with one treatment multiple times in osteoarthritis of the knee and other areas. Generally, a series of either combination bath and pack or single bath or packs is given. Treatments are done every day or two.

Headache

Chronic headaches can respond to peat bath or to peat packs especially on the neck or over the cervical spine. One must be careful not to overheat the medulla with the cervical pack treatment; thus, mud applications are usually applied below the second cervical vertebra.

Hamstring Strain

One of the best applications of bath followed by mud pack is in a hamstring muscle strain. In my experience, athletes even of professional stature have been able to "get back into the game" faster and with more function than they would have with any other type of treatment.

Ankle Sprain

Partial peat bath immersion of the foot and leg for ankle sprain is very effective. One can see in older sprains the immediate reduction of ecchymosis after the treatment. Patients can perform home treatments in a plastic wastepaper basket on a daily basis for three to six treatments. This approach is inexpensive and wonderfully effective.

Hypertension

Ambulatory blood pressure has been shown to be affected positively by balneotherapy. After a series of treatments, blood pressure at rest and during standardized levels of ergonomic exercise tends to decrease, as does nocturnal blood pressure. The effect is sustained sometimes permanently.[49] I do not necessarily recommend this treatment for people with hypertension, because people with hypertension have more cardiovascular problems that must be considered before they undergo thermal therapy. Generally, people with mild hypertension tolerate the bath better than people with mild hypotension.

Dermatologic Problems

Psoriasis and atopic dermatitis are the dermatologic conditions more commonly treated with peat bath. I, however, have had very good success in eczema and dermatitis with both peat bath and cream application. There are multiple possibilities with dermal applications.

Scleroderma

Peat bath weekly for 6 to 12 treatments is often a good method of treating scleroderma. Treatment should start with a tolerable

temperature and increase slowly over the series of baths so that the patient can adapt.

Human Papillomavirus

Antiviral effects of topical peat application have been demonstrated on several viruses, including the human papillomavirus. Remission and prevention of implantation of the virus have been described. This is a measure that prevents cancer. The antiviral and antineoplastic effects are thought to be associated with the ability of peat constituents, such as humate, to bind on lectin-binding junctions, thereby blocking viral entry into cells.[21,52]

Herpes Virus

Topical treatment of herpes virus skin disease with humic and fulvic fractions of peat has been effective. I have had significant success with zoster outbreaks. Most important, the topical application of specific peat formulation creams that include humic acids has been very helpful to some of my patients.

Infertility

A study on infertility due to immature follicle maturation syndrome demonstrated good results with peat therapy in comparison with pharmacotherapy. In the peat therapy group, the rate of pregnancy was very good, along with a practically nonexistent spontaneous abortion rate, whereas in the pharmacotherapy group, the rate of spontaneous abortions was very high.[45]

Ankylosing Spondylitis

In the treatment of ankylosing spondylitis and spondylitis associated with inflammatory bowel disease, mud therapy showed a decrease in the level of C-reactive protein and an elevation of hemoglobin with a series of treatments. This coincided with a significant reduction in pain and an improvement in function.[46,47,76] Peat bath and pack and just the bath are options. If a patient is not a candidate for thermal bath, the packs over the spine can be very useful.

Hematoma

Organic peat with its intense vasodilating, anti-inflammatory effects, interactions of ions and mineral properties, enhances reduction of hematomas. Hematomas treated with thermal peat application have been reported to resolve 50% faster, with no hemosiderin residue, than those treated with only heat applications, which often leaves residues.[77] One can see bruising decrease with pack application immediately after the treatment and an enhancement in the absorption of the hematoma in significantly less time with bath and pack.

Immune Stimulation

Peat bath in combination with hyperthermia demonstrates leukocyte elevation. The immune-stimulating effects of peat bath seen clinically correspond to hematologic changes after baths.[70] Some effects on immune function are due to heat and others are due to the constituents in peat. A favorable effect is seen on peripheral blood lymphocytes in atherosclerotic disease after hydrogen/sulfide bath independent of heat.[74] Oxihumate has shown antiviral activity plus immunostimulatory effect on mononuclear lymphocytes while also having very low or no toxicity, showing promise for treatment of immunocompromised patients.[50] Immune stimulation or regulation may also be due to increases or changes in immunocyte numbers and function and the balancing of chronobiologic rhythms.* Oral oxihumate, a potassium salt of oxihumic acid, may show some activity in blocking human immunodeficiency virus type 1 infection of MT-2 cells and may be helpful in the topical treatment of herpes virus–induced skin diseases.[50]

There are also internal uses for constituents of peat. Interestingly, electrophoresis of peat mud showed benefits in patients with duodenal ulcer, secondary to hormone shifts and normalization of collagen metabolism in the duodenal mucosa.[15] The internal use of peat fractions, such as humic acid, also increased the proliferation of some T cells.[50]

CLINICAL PROCEDURES

The following procedures should be applied with care and forethought as to diagnosis and the skillful administration of the treatment. These procedures are stimulations to the body, and the thermal effects should not be taken lightly. Patients must be thoroughly screened for contraindications to treatment before undergoing full-body immersion hyperthermia. The very young and very old should, in general, have very gentle hot or cold stimulation, if any at all. Generally, up to three thermal baths are given per week if they are hot. Thermal therapy can be depleting for some patients, so consideration to the patient's vitality is primary.

Hyperthermic Medicinal Peat Bath

The indications for and contraindications to hyperthermic medicinal peat bath are given in Box 45-1.

Materials

- Peat bath material—I use a commercially available peat bath formula containing peat extract, sulfur, wintergreen, and pine oil.
- Tub with water thermometer and safety features like handrails and nonslip floor mats.
- Room with table for perspiration time.
- Gown or loose-fitting bathing suit.
- Two sheets.
- Two wool blankets.
- Two large towels (one for patient to dry off after treatment and one for head wrap).
- Basin with iced water and a hand towel for cooling patient's face.
- Digital thermometer or otothermometer for patient monitoring (no glass mercury thermometers). A microcomputer-based data acquisition device that records electrocardiogram (ECG) and body and ambient temperatures during bathing can be used; this is preferred over individual readings of pulse and oral temperature during the bath because the ECG shows heart function and the clinician is freed from the task of doing the monitoring. This device can be a real-time recorder for the bath.[83]
- Exhaust fan or room air filter.
- Footstool for entering and leaving tub.

The design of the bath area should take into consideration getting patients in and out of the tub and then as directly as possible to a treatment table.

*References 45, 50, 71, 73, 74, 78-82.

BOX 45-1 Indications and Contraindications for Hyperthermic Medicinal Peat Bath

Indications
- Acne
- Arthritis pain
- Back pain
- Benign prostatic hypertrophy
- Bursitis
- Carpal tunnel syndrome
- Dermatitis
- Eczema
- Fibromyalgia
- Flu
- Fractures
- Acute gouty toe
- Chronic gout
- Gynecologic disorders
- Headaches
- Hematomas
- Hives
- Insomnia
- Lumbalgia
- Metabolic disorders
- Muscle tension
- Neurologic disorders
- Obesity
- Orthopedic disorders
- Osteoarthritis
- Postoperative rehabilitation
- Premenstrual syndrome
- Prostatitis
- Psoriasis
- Rashes
- Rheumatoid arthritis
- Sciatica
- Scleroderma
- Skin care
- Sprains/strains
- Stress relief
- Trauma
- Viral infections

Contraindications
- Acute hypertension
- Breastfeeding
- Cardiac deficiency
- Diabetes
- Multiple sclerosis
- Neurodegenerative disease
- Open wounds
- Preexisting high fever
- Pregnancy
- Pulmonary deficiency
- Respiratory insufficiency
- Systemic lupus erythematosus

Procedure

1. Before a patient begins treatment, cardiovascular risk and any other conditions that do not respond to or are aggravated by thermal therapy should be ruled out. Once the patient has been classified as to risk factors for thermal therapy, the clinician should ask about previous experience with heat in sauna, steam baths, or other types of infrared heating of the tissues. Much depends on the patient's positive health perspective of the self and of the pain or disease process, and the patient's expectations of the therapeutic bath or application.
2. Make sure the tub is clean without a ring. Check log book on last treatment and cleaning. If any evidence of an unclean tank is seen, it must be cleaned and disinfected before use: wearing rubber gloves, use a soft scouring sponge to scrub the tank with disinfectant soap, followed by a rinse of hot water. Then spray the surface with 10% bleach solution, and wait 10 minutes before rinsing with very hot water. Alternatively, a nonbleach product that is antimicrobial can be used; there are many choices for practitioners to choose from on the market.
3. Fill the tub to 10 inches from the top with water at a temperature of 104°F to 113°F (40°C to 45°C).
4. The starting temperature and possible duration of treatment are determined by the condition.
5. Straight water bath should not exceed 110°F. With peat additive, the temperature should not exceed 113°F.
6. Add peat to the bath.
7. Close monitoring during treatment, by means of periodic recording of the patient's pulse, oral temperature, duration of treatment, and tank temperature, is necessary. A quick spike in pulse above initial pulse within the first minute or minutes is a contraindication to treatment. Any adverse reaction, such as tingling of fingers and toes, nausea, headache, lightheadedness, or vertigo, should be evaluated closely, and treatment terminated. Some patients may be able to tolerate only a low temperature and short duration for the first treatment. For a patient having a series of treatments, the first treatment is of shorter duration and lower temperature to see how the patient responds. The ability to tolerate treatments should improve as patients acclimate through their series of treatments.
8. The patient should enter extremely still water slowly. It will not feel as hot if the water is still.
9. Have the patient remain still as he or she becomes fully immersed, to help decrease the sensation of intense heat.
10. To treat the pelvis, utilize a sitz bath rather than a full bath to concentrate the effects of the treatment. A full bath after the sitz bath may be useful.
11. The water will cool as time passes, although the peat material will help maintain the temperature. If the starting temperature was 105°F, hot water may have to be added.
12. Bath duration is 8 to 20 minutes and should not exceed 20 minutes due to the additive pharmacologic effects and the tendency for hyperthermia to produce increased metabolism and mobilization of chemicals within the body.
13. If the patient becomes fatigued or distressed, he should exit the bath to be wrapped in the waiting sheet and wool blankets; do not wait longer to have the patient leave the bath.
14. The patient must have help exiting the tub, from two people who provide lifting support from under the arms on either side. This is a time to be very careful. The clinician should assist the patient by placing an arm under the patient's arm but having the patient use his or her own ability to walk and get out of the tub. If the clinician tries to lift the patient rather than provide necessary support, the patient's tendency is to put all his or her weight on the clinician, which is not the goal. After thermal therapy, patients are usually fine to walk, but there is a chance of lightheadedness and, in rare cases, vertigo. Patients may need assistance.
15. Encourage the patient to concentrate on walking on his or her own.
16. Have the patient lie down on a fresh sheet and wrap the patient in both sheets and two or three wool blankets. Cover the head with a towel.
17. Continue to monitor pulse and oral temperature for the duration of the 20-minute perspiration time.
18. Rinse a face cloth in cold water and apply for 10 seconds or longer to the patient's face every 1 or 2 minutes during both bath and perspiration times. This is extremely important during the bath.
19. Encourage the patient to relax and help the patient to focus on pleasant matters during the bath. The psychological component of the bath is huge. Having patients think and talk about whatever excites and pleases them about their lives or their future during the difficult part of the bath and the treatment will help them tolerate the heat and reframe their disease processes.
20. After the patient has been wrapped from head to foot in sheet and wool blankets (it is not necessary to have blankets under the patient, because the table is a good insulator that prevents the blankets from getting wet), allow the patient to go through the hydrotherapy reaction of rise and fall in temperature, pulse, and diaphoresis three times. Then remove the patient from the sheets and allow him or her to return to

BOX 45-2 Indications and Contraindications for Medicinal Peat Peloid

Indications
- Acne
- Arthritis pain
- Back pain
- Bursitis
- Carpal tunnel syndrome
- Eczema
- Fibromyalgia
- Fractures
- Acute gouty toe
- Chronic gout
- Headaches
- Hematomas
- Hives
- Lumbalgia
- Molluscum contagiosum
- Muscle tension
- Orthopedic disorders
- Osteoarthritis
- Postoperative rehabilitation
- Premenstrual syndrome
- Prostatitis
- Psoriasis
- Rashes
- Rheumatoid arthritis
- Sciatica
- Skin care
- Sprains
- Strains
- Stress relief
- Trauma

Contraindications
- Open wounds
- Pregnancy
- Very thin, fragile skin
- Heat-insensitive skin
- Allergies to any of the peloid materials

normal activities. This cyclic reaction is seen with peat bath. With water bath, the patient may or may not sweat after the bath. With peat bath, perspiration is helpful, because there is increased absorption or skin effect if perspiration is allowed to continue after the bath.

21. Have the patient rest and replace electrolytes after treatment. The patient should not do a lot of exercise for 12 to 24 hours after a full bath, especially patients with back problems. The patient should promote good posture in the treated area during this time.
22. During the perspiration time, manual traction can be applied to the spine. This is done by grasping the ankles of the supine patient and pulling for 30 to 45 seconds with enough traction that the patient almost slides on the table. Indications for manual traction are disc problems, scoliosis, and impingement; it is a nice addition to any peat bath for any condition because it feels good to the patient.
23. Advise the patient not to shower with soap for up to 12 hours after the peat bath, because absorption rates continue after the bath if peat additives have been used.
24. Patients should dry thoroughly and remain covered, warm, and out of draft for 3 hours after treatment. This precaution can easily be overlooked and cause aggravation if cold stimulation is allowed to happen. More than one reminder to the patient is necessary, since after thermal bath, people naturally are ready to cool down.
25. Clean the tank and room thoroughly after use. Log out times of bath and tank cleaning.

Medicinal Peat Peloid

The indications for and contraindications to this procedure are given in Box 45-2. Care should be taken when performing this application to avoid burns. It is important for the patient to have a strong feeling of warmth without a hot burning sensation. For a typical application, this heat sensation should last for 20 to 30 minutes and may take a few minutes to start once the mud has been applied. Start timing from the point that the patient first feels warmth. The practitioner should use his or her own touch and sense of heat during the application.

Materials

- Peat poultice material—I use Healing Botanical's professional use poultice formula containing peat pulp, peat extract, sulfur, wintergreen, and pine oil. Hot water should be added to this dry material 3 minutes before application, and the solution should be mixed so it becomes very slightly supersaturated. The point at which it just becomes shiny and has the consistency of mixed cake batter is perfect. In 1 to 3 minutes, it will be time to apply it to the area being treated. It will still be warm for application because hot water was used.
- Three large towels.
- Small towel.
- Face cloth.
- Small blanket to cover hydrocollator.
- Two small stainless steel basins.
- One small paper cup.
- Hydrocollator (alternatively, hot water bottle can be used).

Procedure

This is a thermal peat pack meant to be applied for 30 minutes. The procedure is as follows:

1. Make a square layer of peat material about 0.25 inches thick, 2 inches bilaterally over the spine and 6 to 8 inches long over the spine. If the spinal area is not being treated, area to be treated is covered. The area of application should be as flat and level as possible.
2. Cover the peat directly with a single-layer warm, wet facecloth. So as to remember the borders of peloid exactly, ridge the facecloth around the margins of the peat.
3. Border the wet face cloth–covered peloid with a rolled bath towel, making a quarter turn at the corners while folding the towel to match the margin of the peat.
4. Apply one layer of towel over the facecloth and peat material. Depending on the size and mass of the hydrocollator and its temperature, this layer may not be necessary.
5. Put a fresh hydrocollator pack directly over the towel. The hydrocollator should be heated at a gentle boil for 1 hour before use. Do not allow any exposed skin to come in contact with the hydrocollator.
6. Cover the hydrocollator pack with a towel or small blanket to insulate it and prevent heat loss.
7. Have a cup of cold water ready to pour on the wet face cloth–covered peloid if it gets too hot. In a good treatment, the peloid pack should get hot enough to require two to three dousings of water or more.
8. As soon as the patient says that the pack is getting too hot, lift up the hydrocollator pack and towel and pour the water directly over the face cloth–covered peloid until cool. Then replace the hydrocollator and coverings.
9. Never leave the patient unattended with the hydrocollator on the mud!
10. Treatment time is approximately 25 to 30 minutes.
11. To remove the peat from the skin after treatment, slide a small basin along the skin under the peat, scraping the peat into the bowl. Wipe the area with a full facecloth wetted with warm water in a gentle twisting motion back and forth to remove peat residue from the skin.
12. Cover the treated area after treatment to maintain warmth for 3 hours. The patient's clothing is fine but a wool blanket would do a better job.

BOX 45-3 Indications and Contraindications of Partial-Immersion Medicinal Peat Bath

Indications
Arthritis pain
Bursitis
Carpal tunnel syndrome
Eczema
Fibromyalgia
Fractures
Acute gouty toe
Chronic gout
Hematomas
Orthopedic disorders
Osteoarthritis
Plantar fascitis
Postoperative rehabilitation
Psoriasis
Rashes
Rheumatoid arthritis
Skin care
Sprains
Strains
Tendinitis
Tenosynovitis
Trauma

Contraindications
Open wounds
Pregnancy
Heat-insensitive area

Partial-Immersion Medicinal Peat Bath

The indications for and contraindications to this procedure are given in Box 45-3.

Materials

- Deep-well basin; a tall plastic wastebasket size works well for the leg
- Medicinal peat bath
- Water thermometer
- Small towel

Procedure

1. Fill basin to three-quarters full with 108°F to 114°F water.
2. Add peat to the bath.
3. Have the patient immerse the wrist, ankle, or elbow slowly into the water. Try to immerse the forearm and leg if treating the hand or foot.
4. Keep the body part immersed for 25 minutes.
5. After the treatment, cover the area with a wool sock or clothing, and keep covered for 3 hours after treatment.
6. Often peat material is sent home with the patient to do home treatments.
7. Clean up the basin by washing with antimicrobial soap. Then disinfect with 10% bleach solution, and rinse after 10 minutes.

Combination Full Bath and Peat Pack

Materials

The same materials as described for the two preceding applications.

Procedure

This treatment is used for many conditions. I particularly like it for treatment of vertebral disc injury or degenerative joint conditions. This procedure is also very good for injuries such as hamstring strain. It focuses the balneologic effects in the area to which the peloid pack is applied. Performing the peat bath first and then applying the peat pack is the ultimate treatment for those who can tolerate the bath. After the patient steps out of the bath, he or she walks to the table and lies face up for the regular traction sequence. After three tractions, it is appropriate to turn the patient face down and apply the peat pack over the spine or area being treated.



SUMMARY

As a physician using balneotherapy for 15 years, I have achieved excellent results in a large percentage of patients who undergo peat therapy. This therapy often helps other therapies to work better. Balneotherapy can be primary or adjunctive. The potential effect on the body should not be taken lightly.

I have observed excellent results for the following conditions:

- Arthritis
- Tenosynovitis
- Strains and sprains
- Discopathy
- Plantar fascitis
- Low back pain, including sciatica
- Scoliosis
- Fractures
- Gout
- Muscle pain
- Dermatologic conditions such as eczema

The combination of medical sophistication in diagnosis and application of various balneologic methods provides an excellent tool for physicians to treat in a natural way to the great benefit of their patients.

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CHAPTER 46

Rotation Diet: A Diagnostic and Therapeutic Tool

Sally J. Rockwell, CNN, PhD

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INTRODUCTION

Food allergy and/or intolerance is a common component of many chronic diseases (see Chapter 53). However, it is not readily recognized as problematic. Conventional laboratory diagnosis is not geared for testing food allergies, and most allergists dismiss the concept of delayed hypersensitivity reactions to foods (see Chapter 15). A time-honored, effective approach to both diagnosis and treatment of food sensitivities is an elimination–rotation diet. This approach has the advantage of being low cost, and the techniques must be followed assiduously to ensure clinical efficacy. Box 46-1 lists the typical indications for an elimination diet.

THE ELIMINATION DIET

The first step in the elimination diet is to remove from the diet (1) all of the most common allergenic foods—i.e., wheat and other glutinous grains, dairy products, eggs, corn, soy and tofu, peanuts, citrus fruits, yeast, and refined sugars—and (2) other often problematic substances, such as highly processed foods, chemicals, additives, preservatives, artificial colorings, flavorings, caffeine (coffee, tea, cola drinks, chocolate), and alcohol.

The object is to avoid intake of all suspect foods and substances for at least 5 days, or long enough to clear all traces of those foods from the digestive tract. The omitted foods are then reintroduced into the diet one at a time. Keeping an accurate food and symptom diary enables the offending foods to be identified and eliminated; depending on the severity of the initial test response, the foods can be carefully reintroduced into the diet within 3 to 6 months.

Although some authorities recommend eliminating only one food at a time, clinicians in this area have found that multiple allergies are the rule, not the exception. Eliminating only one allergen may not clear symptoms well enough to notice improvement. The advantages of eliminating all major allergens in the beginning are rapid clearing, minimal adverse reactions, and accurate test results. Also, when symptoms clear rapidly, the patient becomes inspired and eager to continue with the testing.

As Dr. Doris Rapp[1] explained:

> *If there are several tacks in the bottom of a shoe, the whole foot hurts; removing only one tack will make little or no difference. But remove all the tacks, let the foot heal, then add back one tack at a time and the source of pain is isolated and easily identified. If only one tack (or food) is removed, no significant difference will be noted.*

Variations of the elimination diet range from the most stringent plan, involving elimination of all the major allergens, refined foods, and toxic substances, to a more lenient approach, which eliminates only wheat, dairy, and refined sugars. Consideration of the patient's lifestyle, age, weight, general health, food preferences, attitude, and family system determines the approach. For children and pregnant or lactating women, the amount of calories or carbohydrates should not be restricted; one should simply omit the major allergens.

Contact the author at PO Box 60266, Shoreline, WA 98160; e-mail: SR@DrSallyRockwell.com; website: www.DrSallyRockwell.com.

BOX 46-1 Indications for the Use of the Elimination Diet

- Documented or suspected food allergies and/or intolerances
- Chronic complaints that have not subsided with treatment
- Patients who have symptoms and whose tests results are all "normal"
- Patients in whom mental health problems are suspected because of lack of significant progress
- Children and teens who are labeled as having attention deficit disorder or as being hyperactive, autistic, or who have behavior problems

TABLE 46-1 **Elimination Diet Variants**

TYPE	PROTOCOL
Water fast	Water-only fast for 5 days; reintroduction of foods
Dilute juice fast	Diluted fruit juice fast for 5 days; reintroduction of omitted foods
Fruit, melon, and vegetable plan	Only fruits, melons, and vegetables for 5 days; reintroduction of omitted foods
Caveman (caveperson) plan	Proteins, nuts, seeds, legumes, fruits, and vegetables for 5 days; reintroduction of omitted foods Only natural, unprocessed foods are eaten

Variations of the Elimination Diet

As can be seen in Table 46-1, all elimination and/or challenge diets are variations of this four "Rs" procedure:

1. Remove suspect foods for at least 5 days.
2. Reintroduce and/or test by challenge ingestion.
3. Record reactions.
4. Rotate foods, avoiding those shown to cause adverse reactions.

Water Fast

Water fast should be implemented only under the close guidance of an experienced health professional. A lifetime of accumulated toxins may be released in a short time, creating unwarranted discomfort and complications that may overwhelm the patient and interfere with testing (see Chapter 37 for a complete description of fasting methodologies).

The Dilute Juice Fast

Less severe than water fasting, and more acceptable to patients, is the dilute juice fast. Diluted juices provide a modest amount of calories, stabilize blood glucose levels, and decrease the adverse detoxification–withdrawal reactions that may occur during elimination of all common allergens. The basic procedure is to use three parts of distilled or mineral water to one part of fresh, sugar-free juice. The diluted juices are sipped throughout the day. Ideally, a different juice is used each day: celery, carrot, papaya, cranberry, berry, apple, pineapple, and other fruits or vegetables that have not been consumed on a daily basis. Citrus fruits should be avoided. Low-allergen protein supplements, such as Ultra Clear, MEDIPRO Protein Powder, pure free-form amino acids, N Foods, and Vivonex, may be added after the third day. In addition, liberal amounts of pure water should be consumed throughout the day to dilute and flush out toxic substances.

Note: This approach works for most patients with *Candida* yeast infections, because the juice is so dilute that it rarely creates a problem. However, commercially prepared juices (especially tomato and citrus juice) often contain molds, which can be problematic.

Fruit and/or Vegetable Plan

In the fruit and/or vegetable plan, the patient consumes unlimited amounts of clean fresh fruit and melons and raw, steamed, or baked vegetables throughout the day. If *Candida* overgrowth is severe, or if weight loss is desired, vegetables should be emphasized and fruits limited.

The Caveman (Caveperson) Plan

The caveperson plan consists of the following basic foods that the caveperson consumed, after the major allergenic foods have been eliminated: vegetables, fruits, berries, honey, nuts, seeds, beans, peas, sprouts, roots, gourds, poultry, fish, seafood, and wild game.

Procedure

Beginning the Elimination Diet

An ideal elimination diet begins as follows:

1. Two days of diluted juices
2. Fruits and vegetables for the next 2 days
3. The caveperson diet for 2 days or until symptoms clear

Any one, or any combination, of the previously described elimination plans will clear the patient of allergenic substances. If after 5 days the patient's symptoms have not diminished (or disappeared), continue the diet for another 5 days. If symptoms are not clear in 10 days, begin to rotate foods, because the patient may be reacting to a food or substance he or she is consuming every day. (Unsuspected environmental allergens may be contributing to the symptoms also; see "Helpful Hints and Suggestions" later in this chapter.)

Testing by Challenge Ingestion

One suspect food is introduced every other day. The object is to give the patient sufficient calories, build a reliable list of safe foods, and delay unpleasant reactions for as long as possible. Challenge should begin with rarely ingested foods that are least likely to cause adverse reactions. Foods that are known to cause severe reactions should not be tested with challenge.

Suggested Testing Sequence. Introduce foods back into the diet in the following order whenever possible: vegetables, fruits, melons, beans, nuts and seeds, yeasts, dairy products, and, finally, grains. When dairy is added, goat products should be tested first: plain yogurt, cheeses, and then milk. Follow the same process with cow's milk. Grains are best tested in the following order: quinoa, amaranth, buckwheat, wild rice, brown rice, millet, *barley*, *spelt*, kamut, teff, oats, *rye*, corn, and, lastly, *wheat* (gluten-containing grains are in italics). Dietary supplements should also be tested one at a time.

Food and Symptom Diary. The patient records, chronologically in a notebook, all foods, liquids, supplements, moods, symptoms, and reactions. The foods eaten throughout the day should be noted in either pencil or blue or black ink. Symptoms are highlighted or circled in colored ink so that those adverse reactions stand out clearly. In 2 to 3 weeks, a repetitive pattern of symptoms will be clearly visible, allowing for identification and elimination of the problematic foods or food combinations that cause symptoms.

In the beginning, a patient may not be able to describe in exact words how he or she feels, so a numbering system may be useful for noting general moods throughout the day. Numbers go from 1

(poor) to 10 (excellent); feeling sort of medium, neither poor nor excellent, would be recorded as a 5. In general, depending on the patient's health and motivation, foods causing a mild reaction should be avoided for 3 months, and those causing a severe reaction are best avoided for at least 6 months before being reintroduced.

Testing Children. Play a game with children to make testing fun. Have them draw a picture of how they feel, or write their names before and after testing a substance. Note all before and after differences in the drawings or writings.



THE DIVERSIFIED ROTATION DIET

The basic concept of the diversified rotation diet is to achieve the following:

- Eliminate all major allergenic substances
- Eat the remaining foods once every 4 days
- Allow 2 to 4 days between food families

Rotation can be simplified by using a template—the "master chart"—with foods correctly arranged according to their botanical family classifications. The spacing of the foods and food families are organized into four columns, one for each day, so the patient simply chooses foods from the appropriate column each day. A color-coding system further simplifies the process of choosing the correct foods.

See Appendix 10 for an easy-to-follow template. The chart provides 4 days between specific foods and 2 days between food families. A second chart (Master Chart II) may be needed for severely sensitive individuals. It provides 4 days between specific foods and 4 days between food families. If necessary, it can be easily adapted to a 7-day rotation.

Using the Master Charts

The clinician uses a pencil to cross out the major allergens, plus any known or suspected problem foods, in each of the four columns. The patient may eat the remaining foods from the appropriate column throughout the day. The foods that are not crossed out are allowed in the diet.

Arrows on the chart (↔) indicate a food that is essentially the only food of a family and that is not cross-reactive with other foods. Therefore, it is not restricted to any one particular day and can be moved to another column if additional food choices are needed.

Patients who will be rotating foods for any length of time will welcome the benefits of using the color-coding system. A color is assigned to each day. Each column represents a day: day 1, green, is column 1; day 2, yellow, column 2; day 3, blue, column 3; and day 4, red, column 4. After day 4, the patient returns to day 1 and repeats the process. Food containers are labeled and color-coded to coordinate with the color of the day; for example, green labels, twist-ties, or rubber bands are placed on all containers of foods for day 1. The color-coding system enables the entire family to see at a glance which foods the patient is permitted to eat on each day.

Modifications for Vegans

The master charts can be used for vegans. Simply cross out all foods of animal origin. Legumes (beans and peas) are generally an important part of the vegan diet, thus all legumes should be tested, one at a time, beginning with the least allergenic, rarely eaten beans and proceeding to soy and tofu, with peanuts tested last. Depending on the allergic response to legumes, the patient may be able to tolerate legumes daily, as long as he or she eats a different legume each day. In other words, although the 4-days-between-foods rule continues to be honored, the 1-day-between-food-families rule may be ignored for less-sensitive patients.

Food Preparation

For testing purposes, fresh, organic foods should be used whenever possible. Otherwise, frozen or dehydrated foods are a better choice than canned goods. Most vegetables are best eaten raw, steamed, or baked. Fish, poultry, and meat are best poached, steamed, sautéed, baked, or simmered in a slow cooker (e.g., crock-pot). Soups and stews are fine. Use only sea salt for seasoning; all spices and flavorings must be avoided unless they are individually tested.

Blood glucose levels may need to be stabilized with small, frequent meals throughout the day. Have the patient prepare four mixtures of "trail mix"—nuts and dried fruits—one for each day (refer to the master chart for specific food choices). A supply of healthy snacks must be maintained everywhere: home, school, office, and automobile.

Helpful Hints and Suggestions

Control of Withdrawal Symptoms and Allergenic Reactions

Vitamin C buffered with calcium, potassium, and/or magnesium is suggested as the daily source of vitamin C for allergenic individuals. These substances help to balance an acidic body pH and are valuable for neutralizing unpleasant allergic reactions. Stabilization of pH eases the symptoms of withdrawal from allergenic foods and the cravings that occur when the patient is breaking an addiction, whether it is to sugar, wheat, coffee, cigarettes, alcohol, or a drug.

For daily supplementation: begin with 1/8 teaspoon of buffered vitamin C powder (or one 500 mg capsule) in 1/2 cup of water three times a day (between meals and at bedtime). Gradually increase the dosage by an additional 1/8 teaspoon (1 capsule) per dose every 2 days until the patient reaches bowel tolerance—loose stool, gas, or diarrhea—at which point the dosage is reduced. As the patient improves, the vitamin C requirement will likely lessen, and the dosage can be reduced again.

Note: Buffered vitamin C should not be taken with meals, since it may neutralize stomach acid, which is commonly deficient in patients with food allergy and/or intolerance (see Chapter 53).

For temporary relief of symptoms or to neutralize an adverse reaction, the patient should mix and drink 1/2 teaspoon of buffered vitamin C in 1/2 cup of water or dilute juice. Available commercial products include Klaire Labs Bi-carbs (see www.klairelabs.com), Cardiovascular Lab's Tri-salts (see www.cardiovascular-labs.com), and Alka Seltzer Gold label (not the blue label, see www.alkaseltzer.com); if none of these products is available, 1/2 teaspoon of baking soda in 1/2 cup of water can be useful.

Environmental Allergies

If the patient does not respond to the diet in a timely fashion, and all other possibilities have been ruled out, the clinician should suspect environmental and/or chemical sensitivities. The first step in this instance is to eliminate use of all scented toiletries, room sprays, and cleaning solutions in the home and workplace.

Ensuring Adequate Protein Intake

The most allergenic foods tend to be those highest in protein, thus, care must be taken to ensure that the patient is consuming adequate amounts of protein. Patients with multiple food allergies

may need to be referred to an experienced nutritionist to develop a balanced diet.

Patience

The clinician must be especially supportive and patient with individuals who have been in only long-term conventional treatment. You may be the first physician to discuss the rewards of listening to their bodies, and explain how symptoms are the body's way of communicating. Learning to pay attention to what they eat and drink and the possible adverse symptoms is a vital part of getting well again.

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CHAPTER 47

Soft Tissue Manipulation: An Overview of Diagnostics and Therapies*

Tim Irving, DC, MS, LMT

CHAPTER CONTENTS

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INTRODUCTION

The term "soft tissue" is a ubiquitous and, at times, vague term. Every profession that deals with the mobility, stability, and dynamic function of the neuromusculoskeletal system must embrace diagnostic and therapeutic soft tissue procedures. Medical and therapeutic systems such as those used by naturopaths, chiropractors, osteopaths, allopaths, physical therapists, massage therapists, and body-centered psychotherapists all have their own procedures for identifying and treating a variety of soft tissue dysfunction. Despite their differences, terms used, or the theories advocated by each profession, they all agree to some degree that soft tissue dysfunction can cause and/or indicate disease, injury, aberrant reflex activity, and aberrant movement patterns, the results of which can have minor or profound effects on the health of the individual. In addition, most professionals that diagnose and treat soft tissue dysfunction seem to refer to a common phenomenon: distinct, palpable, usually sensitive areas of soft tissue aberrations or lesions that are either directly or reflexively related to local or organ dysfunction and/or disease.[1,2]

The thoughts, ideas, and theories that are foundational to physical medicine are evolving; so too are the thoughts, ideas, and theories foundational to soft tissue diagnostics and therapeutics. One clinically relevant and interesting note is that many systems of health care delivery are moving to more encompassing and holistic ideas about the interrelation of many cells, tissues, organs, and systems to obtain and maintain optimal health and wellness. Functional or lifestyle medicine practitioners look at the various systems of the body in hierarchical fashion. Treating systems "upstream" or higher up on a hierarchical list of systems allows the practitioner to optimize the health of the individual without chasing down symptoms.[3] Movement therapists and doctors who help to improve and stabilize movement are looking at movement patterns instead of single or even dual-planar movement. The idea that movement only transmits from muscle origin to insertion is long gone, clinically incomplete, and inferior to the recent, more functional theories.[4-6] Soft tissue diagnostic and therapeutic procedures are currently evolving; this evolution is occurring as a result of clinical treatment and trials and other empirical methods.

Although the working definition of soft tissue has always included muscles, ligaments, tendons, fascia, and more, each individual tissue was looked at and often treated as a separate entity, not as functional units. There has been a recent push to look at functional groups of soft tissues. Ideas like myofascial "chains," "trains," and units are taking the soft tissue world by storm and proving to be clinically superior to some of the incomplete, older, more reductionist ideas.[7-9] Tension relationships are now ideas that permeate soft tissue diagnosis and therapies. Muscle coordination and perception are looked at as functions of these relationships rather than the work of a group of muscles and their respective myoneural units.[7-11]

Soft tissue therapy may be used to accomplish the following:

- Normalize soft tissue dysfunction in preparation for joint manipulation.[12-14]
- Restore postural or functional integrity; this has been one of the primary uses of soft tissue therapies for ages, and now many are thinking about this more in

*This chapter is based on an earlier version by Leon Chaitow, ND, DO.

terms of restoring healthy tension relationships throughout all of the integrated soft tissue structures of the body.[7-9,15]
- Function as part of a comprehensive approach to health care in which tension relationships and subsequent reflex activity, manifested in soft tissues, are used diagnostically and therapeutically.[16]

Of final note, professions that classically have not viewed soft tissue as the primary avenue for their treatment benefits have been evolving their paradigm. Acupuncturists specifically have been viewing soft tissue, more specifically fascia, as part of their diagnostic and treatment foundation. Various authors in the acupuncture world have noted that acupuncture points and connective tissue and soft tissue planes have a very intimate relationship and, at times, are indistinguishable.[17-19]

HEALTH IMPLICATIONS OF SOFT TISSUE MANIPULATION: THE BIG PICTURE

For every therapeutic intervention, we must first determine how best to utilize the technique and/or intervention. For soft tissue manipulation, there are localized responses that will be addressed later in this chapter; this section is devoted to how soft tissue manipulation affects overall health.

Immune System

Clinically, many who practice soft tissue manipulation have noted various immune responses from patients and clients. The evidence for these effects have been elucidated, mostly through studies of massage therapy. Because the immune system receives messages and is controlled by the nervous and endocrine systems, the effects of soft tissue manipulation regarding the immune system are neuroendocrine in nature.[20]

Emotional

Soft tissue manipulation has been shown to help the emotional status of individuals experiencing depression, eating disorders, excessive anger, rage, rejection, and fear. Using soft tissue manipulation as an adjunct therapy when treating individuals with emotional distress can have widespread systemic effects that may prove to be necessary.[21-26]

Endocrine

Inappropriate amounts of hormones will cause a breakdown in this important system of control. Most notable, especially with regard to soft tissue manipulation, is excess cortisol. Soft tissue manipulation has been found to decrease inappropriately elevated levels of cortisol. The effects of chronically high cortisol levels occur at the hypothalamic-pituitary-axis level and can disrupt and create aberrations in neuroendocrine function. In addition, soft tissue manipulation has also been shown to raise low levels of dopamine and serotonin; this effect has implications in treating addictions, eating disorders, depression, and more.[27-31]

What this author is referring to in this subsection is the effect that soft tissue manipulation has on our ability to maintain homeostasis or homeodynamics after the introduction of a stressful stimulus. According to Selye and proponents of the General Adaptation Syndrome line of thought, our physical, biochemical, and emotional being can withstand a certain amount of stress. Everyone has a different threshold, and soft tissue manipulation allows the practitioner the opportunity to remove layers of stress so we can adapt and thrive.

DEFINITION: FUNCTIONAL SOFT TISSUE

As noted in the introduction, thoughts, ideas and theories surrounding soft tissue diagnosis and manipulation are evolving. The phrase "functional soft tissue" has been utilized by this author and others. The idea that muscles, bones, tendons, fascia, and ligaments are separate entities is an idea that, although true in a histologic sense, is not the whole truth in a functional sense. A more clinically useful idea is that all of these structures transmit tension. Some of them contract, others resist tension, others give way to tension; the bottom line is they all respond and transmit tension. What many consider the apex of the soft tissue evolution is that soft tissue pathologies exist when the transmission of this tension is altered. As a result, various authors have developed ideas that link all connective and soft tissues together functionally. Myers developed the "Anatomy Trains" idea, and Stecco developed ideas that link soft tissues together functionally through fascial motor units, centers of coordination, centers of perception, and centers of fusion. Ida Rolf was on the cutting edge of these ideas and looked at the physical body as a transmitter of tension.[7,8,9,32]

Taking the idea of functional soft tissues one step further–the fitness and performance professions are evolving closely with the clinical soft tissue manipulation professions to develop very integrative and useful movement therapies. These movement therapies bridge the gap between more passive soft tissue manipulative techniques and exercise. Many effective soft tissue manipulative techniques include active movement and mobilization on the patient's and/or client's part. These therapeutic procedures, combined with more passive soft tissue interventions, are proving to be more effective than passive techniques alone.[33]

SOFT TISSUE PATHOLOGIES

Many of the focal soft tissue lesions and dysfunctions listed can be classified as myofascial points; some are more descriptive, whereas others are terminology used when describing a diagnosis. This author feels it necessary to note that this is not a comprehensive list of potential soft tissue points and/or lesions, but that most, if not all, soft tissue lesions will fall into these categories:
- Tender points
- Trigger points
- Fascial densifications
- Strains/sprains
- Fibrosis
- Adhesions
- Chapmann's reflex points

Researchers and clinicians have used differing terminology to describe similar phenomena, resulting in confusion of what is essentially an uncomplicated pattern. In the musculature and connective tissues of the body, often in the regions of the origins and insertions of the muscles, soft tissue points are often commonly found at motor points and in the muscle belly. The commonality, despite differing opinions on diagnostic criteria and the manner in which they are assessed, is palpable, sensitive areas of altered structure resulting from injury, anoxia, irritation, stress, aberrant reflex activity, and/or aberrant movement patterns. Another commonality to these points is their size, which ranges from 0.5 to 1.0 cm across, and their feel, which is described either as harder or firmer than surrounding normal tissue, or as having an "edematous," "boggy," "fibrous," or "stringy" feel.[34]

It is often noted that these localized areas of altered structure and function occur in bands of stressed fibers, both fascial and

muscular. In all cases, such localized areas are, to a greater or lesser degree, sensitive or tender out of proportion to the amount of pressure exerted.[35] All these points are potential "trigger points," but only those that, upon pressure, are noted to refer pain or other symptoms to a distant (target) area, and that are recognizable as "familiar" to the individual, are classified as such points.[36, 37]

Methods of Identification

Despite all of the advances in imaging, the most widely used clinical procedure to identify soft tissue pathology is a combination of movement, special (orthopedic) tests, and skilled palpation. The diagnostic use of movement patterns will be discussed in the next section; they too can be used to locate focal soft tissue lesions and points.[16,38-40]

The definitions of the previously mentioned soft tissue pathologies can and are debated. Often, clinicians name a focal soft tissue lesion a "trigger point" when many more of us would call it a tender point. Likewise, fascial densifications can be tender points, trigger point adhesions, and/or fibrosis. Then there are reflex points that can elucidate functional and pathologic problems in and around the viscera; Chapmann's points are examples of such points.

There are a variety of methods by which soft tissue changes may be located through palpation. They include the following:

- Traditional massage methods—mainly palpatory awareness during various massage strokes like effleurage, petrissage, tapotement, and vibration.
- Specific palpation techniques—such as those developed by massage, naturopathic, chiropractic, physical therapy, and osteopathic schools. The common thread is the development of fine motor skills and palpatory awareness, the foundation of which is a solid knowledge of structural and functional anatomy.
- Neuromuscular technique—a method of combined assessment and therapy developed in the 1930s by Stanley Lief, an American-trained naturopathic and chiropractic physician working in Europe.
- Skin distraction, pinching, and gliding techniques.

All of these as well as other methods of palpation may be utilized to identify areas of local soft tissue dysfunction that may be either sources or results of reflex activity or other local adaptive responses. All of these techniques are utilized to assess and notice areas of tone, texture, and temperature abnormalities as well as developmental and structural asymmetry.

The analysis of the available information present in localized areas of the soft tissues requires consideration of a variety of classifications and systems. It is necessary to examine some of the systems that have described the same tissue changes in different ways, to compare the similarities and differences in the descriptions of points (discrete, usually sensitive areas of altered structure and function in the soft tissue) and the diagnostic and therapeutic significance ascribed to them.

Aberrant Movement Patterns

As noted in the introduction, soft tissue diagnostics and therapeutics are evolving into a more functional paradigm; with this evolution comes a journey into the idea that movement patterns will help clinicians elucidate soft tissue dysfunction and focal lesions.[4-9,11,36]

Methods of Identification

The simplest description about detecting and diagnosing movement patterns is that they are performed through observation and patient movements (active and passive). All of the techniques for this type of assessment have this in common; which movements and how should they be performed are debatable.

Simple, single planar movement patterns have been assessed by many.[6,11] These are often easier to assess, but their relevance has been questioned over the last 10 years. Multiplanar movement patterns have been purportedly better, more accurate, and more clinically relevant in the assessment of soft tissue and other neuromusculoskeletal structures.[4-9,36] There is no definitive proof as to which strategy and which motions are the most clinically relevant. Clinicians have begun to use patterns described as "primitive" by Gray Cook and Kyle Kiesel.[4,5] The aforementioned clinicians and authors designed a succinct and concise assessment of seven movements. These movements range from deep squats, to toe touches, to lunges, to push-ups, and to active straight leg raises. The assessment of these motions has been given a 3 point system: 0 means there is pain with the movement pattern; 1 is difficulty performing it even after some compensatory correction; 2 is difficulty performing it without said compensation but having the ability to perform it with said compensation; and 3 is full ability and stability while performing each pattern. The relevance of each pattern is speculative and debatable. Gray[36] designed a complex assessment of movement patterns through triplanar movements. Although the theory behind his assessments is similar to Cook's and others, his procedures are unique. This is not a concise and neatly packaged technique, but many clinicians are seeing great results with their patients using Gray's theories and applications.

Soft Tissue Manipulation Techniques

Therapeutic efforts and techniques may be directed toward the diagnosis and treatment of the mechanical aspects of dysfunction (trauma, strain, aberrant movement patterns, etc.) and toward the use of the available information from such reflex areas in a more wide-ranging, holistic approach to the health of the patient.[37]

General, rhythmic techniques are often employed on the soft tissues to relieve local dysfunction and/or to prepare for subsequent adjustment of osseous structure. There are common threads to each technique; many use rocking and other rhythmic movements, compression and ischemic compression, and a variety of contacts (hands, digital pressure, elbows, and various devices). In all of the available soft tissue techniques, the objectives are improvement of circulation and drainage; release of contracture, fibrosis, and/or adhesion; greater range of movement; decreased pain and improved movement; and stability. Most soft tissue methods can be applied in a stimulatory as well as a relaxing or inhibitory manner, but care should be taken to prevent stimulation from becoming irritation. Table 47-1 represents a survey of various soft tissue techniques and a brief description of each.

The Potential of Soft Tissue Manipulation

The professions that utilize manual medicine are experiencing a resurgence in the tradition of "hands-on" assessment, treatments, and therapies. The musculoskeletal system is both the greatest energy consumer and the largest organ of sensory input in the body. This primary machinery of life has long been unappreciated in therapeutic terms. The development of methods such as strain/counterstrain, muscle energy technique, fascial manipulation, trigger point therapy, and neuromuscular technique and research, as well as other reflex systems, ensures that the diagnostic and therapeutic potential of the soft tissues are increasingly being recognized and utilized.

TABLE 47-1 **General Soft Tissue Manipulative Technique**

TECHNIQUE	DESCRIPTION
Articulation	Repetitive passive movements employing leverage through variable ranges of the arc
Effleurage	Superficial drainage technique derived from massage therapy
Inhibition/ischemic compression	Describes an objective rather than a method; consists of pressure applied for lengthy periods, slowly applied and slowly released, using thumb contact as a rule
Kneading	Deep or superficial rhythmical pressure, usually applied by thenar or hypothenar eminence
Positional release methods	Approaches that, instead of acting directly on restricted or shortened structures, aim to position them in a state of "ease" by moving away from restriction barriers, allowing a spontaneous normalization to occur, involving neural (muscle spindle) resetting and circulatory enhancement These methods include what is known as strain/counterstrain as well as much craniosacral work
Rhythmic traction	Repetitive attempts to separate articulations to stretch interarticular and periarticular structures
Springing	Repetitive, usually slowly applied, pressure of a gradual nature, often used diagnostically
Stretching	Short and long amplitude attempts at separation of muscular attachments and stretching of ligaments, fascia, and membranes
Vibration	Rapid oscillatory pressure or movement

Korr, the premier osteopathic researcher of the second half of the twentieth century, summarized another vital implication of soft tissue dysfunction—interference with axonal transport mechanisms—as thus:

> *"Any factor that causes derangement of transport mechanism in the axon or that chronically alters the quality or quantity of the axonally transported substances could cause the trophic influences to become detrimental. This alteration in turn would produce aberrations of structure, function and metabolism, thereby contributing to dysfunction and disease. Almost certainly to be included among these harmful factors are the deformation of nerves and roots, such as compression, stretching, angulation and torsion that are known to occur all too commonly in the human being and that are likely to disturb the interaxonal transport mechanisms, intraneural microcirculation and the blood-nerve barrier. Neural structures are especially vulnerable in their passage over highly mobile joints, through bony canals, intervertebral foramina, fascial layers and tonically contracted muscles. Many of these biomechanically induced deformations are of course subject to manipulative amelioration and correction."*[41]



SUMMARY

This survey touched on some of the many ways in which soft tissue dysfunction may impinge upon the economy of the body as a whole. Soft tissue manipulation is an important diagnostic and treatment modality and should be considered an integral part of the practice of any physician or practitioner whose intent is to care for the whole person. Although a great variety of assessment, diagnostic, and treatment procedures exist, there are common threads that transcend their differences.

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CHAPTER 48

Spirituality and Healing*

Lara Pizzorno, MDiv, MA, LMT

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INTRODUCTION

Faith and medical science are not mutually exclusive. In fact, faith's efficacy as a powerful healing force has been scientifically validated by hundreds of studies, many of which exhibit all the criteria of the best science.[1] A substantial and growing body of research on the healing power of participation in religious activities such as prayer has demonstrated that faith in a Spiritual Reality, an Almighty Spirit, a Beneficent Presence—whether the label given is God, Allah, Atman, Brahman, the Tao, Qi, the Christ, the Absolute, Universal Mind, or the Ground of Being or Life—produces significant, beneficial effects on health. Some of these effects include:

- Lowering blood pressure
- Protecting against heart disease
- Improving surgical outcomes and lessening recovery time
- Increasing feelings of well-being
- Ameliorating depression
- Improving the ability to cope with stress while lessening its adverse physiologic effects

Well-designed studies provide documentation that:

- Religious commitment can help protect children from drug abuse, alcohol abuse, and suicide.
- Religiosity improves psychological health and satisfaction with life among adolescents.[2]
- Individuals for whom a spiritual dimension of life is integral embrace healthier lifestyle practices.
- Among the elderly, those who live in faith tend to live longer.[3,4]

In contrast, infrequent (never or less than weekly) religious involvement is associated with significantly higher rates of death from circulatory (relative hazard [RH] = 1.21), digestive (RH =1.99) and respiratory (RH = 1.66) causes; associations that are weakened but not eliminated by adjusting for health behaviors and prior health status.[5]

In the current medical model, most physicians are led to believe that any consideration of a patient's spiritual life is beyond the legitimate interest and scope of medical care. The dogma is that faith is not amenable to serious scientific scrutiny, but is merely a relic from earlier, less enlightened ages, a crutch for the scientifically disinclined. Medical students and residents all too often get the subliminal message that to personally pursue an active spiritual life is to court schizophrenia, traveling simultaneously down the right-brain path of faith, prayer and/or meditation, and religion (subtext: irrationality and superstition), and the left-brain road of logic, analytical dialectic, and rational thought (subtext: Science).

In modern medical education, devotions are to be paid only to "Science" with a capital "S," which leaves the whole realm of the numinous outside the Venn diagram locus of serious medicine. So, members of the health care professions tend to disassociate their spirituality from their science, both in their training and later in their clinical practice and academic endeavors. Not only can such an approach desiccate human life, shutting us off from the deepest Source of our

*Dedicated to Larry Dossey, MD, whose pioneering work in spirituality and healing continues to serve as a guide and an inspiration to physicians and patients alike.

strength, insight, and joy, but also recent scientific research has, itself, made such an uncritical stance not only irrational, but medically irresponsible.

THE CONCEPTUAL GROUND FOR THE EFFICACY OF SPIRIT IN HEALING

Significant evidence exists that, to use descriptive terminology coined by Larry Dossey, MD, we live in a nonlocal universe and are, at our deepest level, nonlocal beings ourselves. In the rarefied air of quantum physics as well as in a raft of common experiences that will not neatly fit within the confines of reductionistic rationalism, such as déjà vu, synchronicities, premonitions, and near-death experiences, the evidence clearly suggests that a Creative Intelligent Force is manifest throughout the universe, including us, and that this Force, which I refer to as Mind or Spirit, is not wholly localized to points in space (such as brains or bodies) or even to single moments in time. Recent advances in genomics notwithstanding, we have barely begun to scratch the surface of Who and What We Really Are.

In his books, *Healing Beyond the Body*, and *Reinventing Medicine*, Dr. Dossey provides a conceptual framework that integrates modern medicine's past while providing insight into its future. Dossey divides the history of scientific medicine into three epochs, which he calls Era I, Era II, and Era III.

Era I, the first scientific medical era, which began around 1860, is engendered by the classic laws of matter and energy, the mechanistic model of the universe laid out by Sir Isaac Newton that grounds Newtonian physics. According to this view, the entire universe is a vast clockwork that functions according to deterministic, causal principles. In Era I, reality is composed of energy and matter, and mind is considered an artifact, a delusion produced by chemical reactions occurring in the brain.

Era I—materialistic, mechanistic medicine—continues to function as the conceptual ground of virtually all forms of modern medicine today—drugs (allopathic or "green"), surgery, radiation, cardiopulmonary resuscitation, chiropractic, nutrition, vitamins, gene therapy, DNA manipulation, organ transplants, cloning, etc.—any form of therapy that focuses solely on the effects of things in the body. Obviously, Era I medicine is local in nature—restricted in time and space—and cannot account for a wide range of phenomena, such as the placebo effect, psychosomatic illness (e.g., post-traumatic stress disorder), or the influence of belief (materialism as well as spiritual beliefs) on the body.

Following World War II, Era II, what we now call mind–body medicine (although a more accurate term would be brain–body medicine since this view remains localized and materialistic) began to take shape. Jean-Martin Charcot, the great nineteenth century neurologist, studied hysterical reactions and the effect of suggestion on bodily function. Freud, a student of Charcot, extended these ideas and emphasized the influence of the unconscious on health and behavior.

Although by the mid-twentieth century, most authorities had decided that mind or consciousness was unnecessary, and the terms were simply redundant symbols for the brain, it became obvious via psychosomatic disease that the brain did affect the body. Hans Selye demonstrated that rats and mice confined in close quarters and subjected to environmental stressors they could neither predict nor control (e.g., intermittent loud noises or electrical shocks) developed gastrointestinal ulcerations, hypertension, and heart disease, and often died.[6] It became clear that humans could react similarly when subjected to stress perceived as uncontrollable.

Then, research on the placebo effect demonstrated that through suggestion, expectation, and positive thinking, the mind could have beneficial as well as negative effects on the body. Although considered the bane of researchers who devised the double-blind study to try to eliminate its effects, the placebo not only will not go away, but some researchers estimate the placebo response is responsible for 30% to 50% of the effect of many drugs and up to 100% of certain surgical procedures.[7] The widespread nature and effectiveness of the placebo response has been irrefutably demonstrated in several studies—one published in April 2002 that compared St. John's wort against Zoloft and placebo, and another, a meta-analysis of antidepressant trials between 1979 and 1996, published in May 2002. In the first trial, St. John's wort fully cured 24% of the depressed people who received it, Zoloft fully cured 25%, and the placebo fully cured 32%. The meta-analysis was conducted by Seattle psychiatrist Arif Khan, who studied the placebo effect in 96 trials submitted to the Food and Drug Administration and found that in 52% of them, the effect of the antidepressant, whether botanical or pharmaceutical, could not be distinguished from that of the placebo. Several other reviews recently published in *JAMA* noted that, in the treatment of depression, the placebo effect seems to be growing. Greater percentages of people tended to get better on placebos during trials of antidepressants in 2000 than in 1981.[8-14]

Imaging experiments, during which magnetic resonance imaging scans were performed to assess regional brain activity in response to painful stimuli after subjects were primed to have positive or negative expectations, revealed that different expectations cause different brain networks to be activated after the same stimulus. The analgesic effect accompanying positive expectation was associated with activity in the pregenual anterior cingulate cortex, a key region of the brain for autonomic control and the storage of emotional memories. The negative expectation, which completely reversed the analgesic effect of the pain-killing opioid drug remifentanil, was associated with increased activity in the hippocampus, an area of the brain that plays a central role in memory and anxiety related to pain.[15]

A large single-blind randomized controlled trial conducted with patients experiencing irritable bowel syndrome (IBS) investigated whether placebo effects could be disaggregated into two main components—the placebo ritual alone (sham acupuncture in this trial) and the placebo ritual plus a supportive patient–clinician relationship. The key findings concluded that (1) genuine placebo effects could be statistically and clinically significant over time in a clinical population, and (2) the patient–physician relationship was the most robust component of the placebo effect.[16]

Most recently, a small pilot clinical trial in patients with IBS demonstrated that even placebo pills openly labeled as placebo led to robust clinical improvement. That placebo effects can be elicited without deception has enormous implications for clinical care. One implication of these studies is that the healing context provided by a caring doctor–patient relationship can marshal highly potent forces within the brain, forces at least as powerful as an intravenously delivered opiate drug.[17]

These studies strongly suggest that we have much to learn from mind–body medicine (or Era II medicine in Dossey's heuristic framework). Yet, although Era II medicine has moved beyond the materialistic boundaries of Newtonian physics to include any therapy emphasizing the effects of the individual's consciousness, this medicine, although recognizing the mind as an important factor in healing, restricts the activity of consciousness to within the individual's body. Era II therapies include psychoneuroimmunology, counseling, hypnosis, biofeedback, relaxation therapies, support groups, etc.

Medicine today remains a combination of Eras I and II—for example, cancer patients get psychological counseling along with chemotherapy, surgery, vitamins, and nutritional counseling. In heart disease, stress management is used along with dietary manipulations, β-blockers or statin drugs, and coronary bypass surgery. The key takeaway here is that both Eras I and II are descriptive of a universe in which mind or consciousness is localized and equated with the individual brain. Consciousness is assumed to be a by-product of the brain's chemistry and physiology—despite the fact that no one knows how the brain "makes" the mind, or even if it does. As a number of modern philosophers and physicists have observed, no one has the slightest idea how mind or consciousness can arise from anything material. No one even knows what it would be like to have the slightest idea how anything material could be conscious. To quote physicist Niels Bohr, "We can admittedly find nothing in physics or chemistry that has even a remote bearing on consciousness."[18]

When Descartes spoke his famous dictum "I think, therefore I am," he saw the brain as a signal transducer, a piece of equipment through which the input of Mind was received, specifically in the pineal gland, and thence transmitted to the material plane. Although Descartesian dualism has been used to not only bifurcate reality, but also to dismiss anything not perceivable through the senses, this is the exact opposite of what Descartes actually claimed was the truth about Reality. For Descartes, the material world and our senses are unreliable, whereas Mind (not the brain) on the other hand, is the only bona fide assurance of the fact of our existence.

To sum up, Era I emphasized a completely physical, body-based approach to health and illness, which Era II expanded by recognizing the effects of mind—although the mind is typically (and without scientific foundation) equated with the brain, and mind–body effects remain restricted to within each individual—one's own mind affecting only one's own body. This restriction is the target of the opening and further expansion that is occurring in Era III, where Dossey thinks the evidence in current physics and our own experience is firmly pushing us, albeit kicking and screaming, to paradigm transformation.

Era III, nonlocal medicine, is based on current quantum physics, which describes a world in and through which One Energy, which I will refer to as Mind, God, or Spirit, moves unbounded by time or space. Within the last 50 years, physicists have firmly established that atoms and electrons behave nonlocally, and this suggests that nonlocality is the truth underlying the visible world we inhabit, and thus necessarily our truth as well.

The scientific début of the nonlocal universe occurred in 1935, when Albert Einstein, Boris Podolosky, and Nathen Rosen published the now-famous paper, "Can Quantum Mechanical Description Of Physical Reality Be Considered Complete?" They pointed out that under certain conditions, photons set off in opposite directions at the speed of light might still have a connection with each other, a connection Einstein described as a "ghostly action at a distance," and which bothered him a great deal since it would allow the possibility of messages to be sent faster than the speed of light. Because, according to Relativity Theory, it is impossible for an informational connection to be maintained between two points that are receding from each other at the speed of light, Einstein—mistakenly as we now know—concluded something was fundamentally wrong with quantum theory.

In 1964, physicist John Bell at the European Organization for Nuclear Research (CERN) proved the far-reaching inequality theorem now known as Bell's Theorem and rigorously described the consequences of Einstein's action at a distance hypothesis. Bell's Theorem implied that if an experiment involving protons going off in opposite directions were actually carried out, then, according to another Nobel Prize winning physicist, Brian Josephson, "there must be a mechanism whereby the setting on one measuring device can influence the reading of another instrument, however remote."[19]

The appropriate physics experiments testing this conjecture have been carried out in several laboratories worldwide: by Freeman and Clauser in Berkeley in 1972, by Aspect and his colleagues in Paris in 1982, and by Gisin at the University of Geneva in 1997. What these experiments all showed is that when one measures the polarization of a pair of photons born in the same interaction, but traveling in different directions, the polarization of one photon appears to be altered by the mere act of observing the other, even when the photons are widely separated over distances of several kilometers. In summary, laboratory experiments have confirmed that a nonlocal correlation between photons does exist, a correlation that physicist David Bohm, in his physics textbook, *The Undivided Universe*, calls "quantum interconnectedness."[20]

Although our naïve "realist" picture of our reality is one in which separate individuals occupy their own well-circumscribed points in space–time, modern physics, for the past 30 years, has been asserting that this concept is incorrect. The quantum physicist's view is that we live in a nonlocal reality in which we can be affected by events distant in space and time from our ordinary awareness.

An avalanche of data supports this view. This research includes recently declassified Central Intelligence Agency experiments run during the Cold War involving remote viewing that were conducted at the Stanford Research Institute, as well as literally millions of experiments at the Princeton Engineering Anomalies Research facility (PEAR) that demonstrate that individuals can mentally affect the function of sensitive electronic devices not only regardless of distance, but also in the future or even the past. When applied to the individual, these data clearly suggest that we are fundamentally nonlocal beings for whom the accepted boundaries imposed by space and time are not the ineluctable limitations we have defined them to be. As David Bohm put it, "Each person enfolds something of the spirit of the other in his consciousness. Deep down the consciousness of mankind is one. This is a virtual certainty . . . and if we don't see this it's because we are blinding ourselves to it."[21]

Recent studies have demonstrated that intestinal epithelial cells can induce synchronous behavior in neighboring cells that have been mechanically separated and cannot communicate via chemical or electrical mechanisms. This nonchemical, nonelectrical (nonlocal) communication signaling system may not only play a role in synchronous, stimulus-appropriate cell responses to noxious stimuli, but may also make sense of a number of cellular behaviors impossible to explain based only on conventional cell signaling systems.[22]

The evidence in quantum physics points to One Creative Energy, Intelligence, or Mind as fundamental, as transcending the physical mind or ego, and as present everywhere in both space and time. In a very real sense, the universe physicists now describe is the map upon which a new worldview is emerging. They are the exploratory cartographers of a new view of consciousness, a view that is forcing a significant change in our assumptions about the nature of our mind and its relationship to our physical body.

The truth is that no localized, mechanistic description of what goes on in the brain can shed any light whatsoever on why consciousness exists. According to physicist and astronomer David

Darling, there is a very simple reason for this: "The brain does not *produce* consciousness at all, any more than a television set creates the programs that appear on its screen. On the contrary, the brain *filters* and *restricts* consciousness, just as our senses limit the totality of experience to which we might otherwise have access."[18] This view is seconded by philosopher Michael Grosso who describes the relationship between consciousness or the mind and the brain as somewhat analogous to that between a radio and radio waves. The radio does not produce the radio waves, it simply detects, transmits, and filters them. If your radio breaks down, it does not follow that the sounds you were listening to have ceased to exist. They just cease to be detectable.[23]

In Era III, the mind is recognized to be more than the brain because an overwhelming amount of scientific data demonstrates that the mind can do things the brain cannot, such as acting remotely from the body and outside the present time. Era III medicine recognizes that an aspect of your mind is not restricted to your body, your brain, or this moment in time, but is linked with Mind with a capital "M," the infinite, eternal aspect of Consciousness, which is a natural part of who we essentially are. In addition to the research carried out at Stanford and Princeton, this aspect of our being has been demonstrated in numerous studies that reveal healing can be achieved at a distance by direct, loving, compassionate thoughts, intentions, and prayers for others, even those who are unaware of these efforts for their well-being.

THE HEALING EFFECTS OF PRAYER—EVIDENCE OF THE NONLOCAL ACTIVITY OF CONSCIOUSNESS

A large body of credible scientific evidence shows that mind directed in prayer can function at a distance to change physical processes in a variety of organisms. In addition to humans, study subjects have included water, enzymes, bacteria, fungi, yeast, red blood cells, cancer cells, pacemaker cells, seeds, plants, algae, moth larvae, mice, and chicks—a wide range of entities whose response is highly unlikely to be due to placebo effect.

Processes influenced include the activity of enzymes, the growth rates of leukemic white blood cells, mutation rates of bacteria, germination and growth rates of various seeds, the firing rate of pacemaker cells, healing rates of wounds, decreasing the size of goiters and tumors, decreasing the time required to awaken from anesthesia, autonomic effects such as electrodermal activity of the skin, rates of hemolysis of red blood cells, and hemoglobin levels.[24]

As noted by Dossey in an article published in *Explore* in 2008, entitled, "Healing Research: What We Know and Don't Know," approximately eight systematic or meta-analyses of studies involving healing intentions and prayer have been published in peer-reviewed journals; all but one arrived at positive conclusions. The most thorough analysis to date is a 2003 review by Jonas and Crawford in which they analyzed data from 2200 published reports, including 122 laboratory studies, 80 randomized controlled trials, 128 summaries or reviews, 95 reports of observational studies and nonrandomized trials, and 271 descriptive studies, case reports, and surveys.[25] Their conservative conclusion: "There is evidence to suggest that mind and matter interact in a way that is consistent with the assumptions of distant healing. Mental intention has effects on nonliving random systems (such as random number generators) and may have effects on living systems."[26]

Dossey zeroes in on the key significance of this conclusion: if mental intention can affect nonliving random systems, this suggests that consciousness is nonlocal in nature, a finding that has implications far beyond being simply "a new tool in the physician's black bag."[25]

As Dossey notes, "If we examine the array of categories analyzed by Jonas and Crawford, we find intentionality effects at the macroscopic level, as in healing studies involving whole persons; at the tissue level, as in studies involving populations of various types of cells; at the microbial level, as in studies involving growth rates of bacteria, yeasts, and fungi; at the molecular level, as in studies involving enzyme kinetics and biochemical reactions; and at the subatomic level, as in random event generators where people attempt to influence the distribution of ones and zeroes. The fact that intentionality effects are demonstrated across this enormous spectrum of nature, from the macroworld to the mesoworld to the microworld, suggests that we have discovered a general, pervasive principle in nature—the ability of intentionality to change the world." Its application in health care is obvious.[25]

SPECIFIC AREAS IN WHICH PRAYER AND RELIGIOUS ACTIVITY HAVE BEEN SHOWN EFFECTIVE IN HUMANS

Cardiovascular Disease

Social epidemiologist, Jeff Levin, PhD, a Senior Research Fellow of the National Institutes of Health, is recognized as one of the leading researchers in the field of spirituality and health. In his book, *God, Faith and Health*, Levin provides an overview of the published studies that offer compelling evidence for the connection between health and a wide spectrum of spiritual beliefs and practices, including prayer, attending religious services, meditation, and faith in a Spiritual Reality (i.e., God by whatever name).[4]

As a first year graduate student in the School of Public Health at the University of North Carolina in Chapel Hill, Levin became intrigued by two articles that found a surprisingly significant connection between spirituality and heart disease, a connection that remains one of the best researched areas of the positive effects of religious behavior on health.

In *God, Faith and Health*, Levin noted that in 2001, the medical literature contained more than 50 studies in which religious practices were found to be protective of a wide range of heart disease related conditions: death due to circulatory system diseases; atherosclerotic heart disease incidence and death; myocardial infarction incidence and death; coronary heart disease incidence, prevalence, and death; rheumatic, nonrheumatic, and hypertensive heart disease death; angina pectoris incidence; aortic calcification prevalence; death due to chronic endocarditis; and incidence of numerous risk factors, including cholesterol, lipids, caloric and fat intake, and triglycerides.

The protective effects offered by religious belief and/or practice Levin cites from a number of studies are far from insignificant:

- Scientists at the Missouri Center for Health Statistics found that the death rate due to ischemic heart disease in members of the Reorganized Church of Jesus Christ of Latter Day Saints was 20% lower than that of other Missourians.
- Investigators at the University of Colorado, Case Western Reserve University, and Johns Hopkins University studied death rate patterns in the Old Order Amish people of Indiana, Ohio, and Pennsylvania. Males aged 41 to 69 years had a 35% lower death rate due to circulatory system diseases than non-Amish males of the same age.
- A team from the University of Utah found that among Mormons, the death rate due to ischemic heart disease was 35% lower than non-Mormons, and Mormons also had a lower risk of death from hypertensive and rheumatic heart disease.

- Researchers from the Institute for Social Medicine in Utrecht found that Seventh Day Adventists had a 57% lower risk of death due to ischemic heart disease than non-Adventists.

In addition to these studies focusing on communities with well-known health promoting lifestyle practices, a study not limited to a specific religious group also found an inverse association between frequency of religious attendance and rates of atherosclerotic disease in both men and women.[27] Even after allowing for the effects of smoking, socioeconomic status, and water hardness, the risk for atherosclerosis among men who were frequent church attendees was 40% less than that of men who attended church infrequently. The risk of dying from heart disease among women was approximately twice as high among infrequent church attendees compared with those who attended church weekly or more.

Coronary Heart Disease

Perhaps the research that most decisively forced the issue of acknowledging and incorporating our nonlocal nature into the practice of medicine occurred in 1988 in the Coronary Care Unit at San Francisco General Hospital, when cardiologist Randolph Byrd conducted a study on the effects of distant prayer on healing.[28] Byrd and his research assistant, Janet Greene, asked each patient in the coronary care unit whose condition was stable if he or she would agree to help study the effect of prayer on treatment. Over a 10-month period, a computer assigned the 393 patients who agreed to participate to either a group that was prayed for by home prayer groups (192 patients) or a control group that did not receive this prayer support (201 patients).

The study was randomized and double-blind, so neither patients, nurses, nor doctors knew which patients were in which group. Byrd recruited members of several Protestant and Roman Catholic groups from around the country to pray. The persons praying were given their patients' first names and a brief description of their diagnosis and condition and were asked to pray each day, but given no instructions as to how to do so. Each person prayed for many different patients, so each patient had between five and seven people praying for him or her.

Ten months later, when the results were evaluated, Byrd presented a significant challenge to the medical status quo. The patients receiving prayer support were five times less likely to require antibiotics (3 vs 16 patients); three times less likely to develop pulmonary edema (6 vs 18 patients); none of the prayed-for group required endotracheal intubation versus 12 in the group not prayed for; and fewer patients in the prayed for group died (13 vs 17 patients), a difference that was not considered statistically significant. Overall, the prayed-for patients achieved a 5% to 7% advantage over the controls, a very respectable level of improvement compared with other areas of medicine, as Dossey makes clear in his comparison in *Reinventing Medicine* of the Byrd study results with those found in a meta-analysis of whether aspirin helped prevent heart attacks published in *Science* in 1990. Although aspirin has long been touted as effective in the prevention of heart attack, this meta-analysis found that only 5 of 25 studies showed aspirin to be of any value, whereas 80% found it provided no clinical advantage whatsoever.

A 2001 study was designed to investigate whether the scores from a questionnaire measuring spiritual well-being correlated with progression or regression of coronary heart disease as measured with computerized cardiac catheterization data. Participants in Dr. Dean Ornish's Lifestyle Heart Trial were given the "Spiritual Orientation Inventory." A significant difference was found in the spirituality scores between a control group and a research group that practiced daily meditation. The spirituality scores highly correlated with the degree of an individual's progression or regression of coronary artery obstruction over a 4-year period. Those with the lowest scores of spiritual well-being experienced the most progression of coronary obstruction, whereas those with the highest scores showed the most regression. The authors concluded that lack of spiritual well-being might be an important factor in the development of coronary artery disease.[29]

Other recent studies have had less positive results, notably the highly publicized Harvard Medical School Study of the Therapeutic Effects of Prayer (STEP) published in 2006.[30] STEP involved 1802 patients who underwent coronary artery bypass surgery in six different U.S. hospitals. Subjects were assigned to three groups: 604 patients who were told they might—or might not—be prayed for, but were (Group 1); 597 patients also told they might—or might not—be prayed for, and were not (Group 2); and 601 patients were told they would definitely be prayed for, and were (Group 3).

Two Catholic groups and one Protestant group were chosen to pray. They were given the first name and the initial of the last name of those for whom they were praying, and were directed to pray for them using a prescribed prayer, after which they were allowed to pray as they wished. Prayers began on the evening or day of surgery and ran for 2 weeks.

Results were dismal. In Group 1 (those told they might be prayed for and were), 52% had postoperative complications. In Group 2 (those told they might be prayed for but were not), 51% had postoperative complications, and Group 3 (those told they would definitely be prayed for and were) had the worst outcome—59% had postoperative complications.

Dossey's 2008 review of the state of healing research, "Healing Research: What We Know and Don't Know," provides a detailed exploration of the possible explanations for this outcome.[25]

Key issues Dossey raises are:

1. The effect of extraneous prayer both by the patient and his/her friends and family could have made it impossible to separate out the effects of study prayer.
2. Group 3, compared with Groups 1 and 2, was at higher risk of postoperative complications because this group had higher incidence of smoking history, higher incidence of emphysema and chronic bronchitis, a higher rate of three-vessel coronary bypass surgery, and a lower rate of β-blocker use (which some experts believe is protective during coronary bypass surgery) prior to surgery.
3. Telling Groups 1 and 2 they might not be prayed for could have caused these patients to have prayed more for themselves and to have more aggressively solicited prayer from friends and family, so they could have ended up receiving more, rather than less prayer, than Group 3.
4. Telling patients in Group 3 they would be prayed for could have caused "performance anxiety" in this group, mitigating prayer's beneficial effects.
5. The beliefs and intentions of the experimenters, who are known to be proponents of intrapersonal mind–body effects but not of nonlocal interpersonal effects, could have negatively impacted outcomes.
6. STEP got a great deal of media attention for years before it was published, with several scholars predicting that it would decisively show whether prayer was effective, and critics smugly predicting it would fail. Given other evidence, such as studies in nonhumans in which experimenters' negative thoughts and intentions correlated with negative biological effects in a variety of living systems,[31] it is not unreasonable to raise the possibility that skeptics' intentions impacted the outcome of STEP.

A further, and possibly the most important, critique is that the methodology used in the STEP (and to date all the clinical trials of distant healing intention) does not resemble "real life." We pray for our loved ones, whom we know intimately, care for deeply, and for whom we feel unconditional empathy and compassion. We pray from the heart, not a scripted "standardized prayer" recited for persons we do not know. Plus, we do not limit our prayers for those we care for to a mere 2 weeks; in comparison, in the Byrd study, subjects were prayed for over a 10-month period. As Dossey so aptly put it, "'Prayer in the wild' in 'free-range humans' does not resemble STEP prayer."[25]

Research looking at the results of "prayer in the wild," such as the Achterberg study utilizing Native Hawaiian healers, produced strong positive results.[32] After two years gaining the trust of this community of healers, Achterberg recruited 11, who on average had pursued their tradition of healing for 23 years. Each was asked to select a person with whom they felt a deep connection. Recipients were placed in a functional magnetic resonance imaging scanner and isolated from all forms of sensory contact with the healers, who then sent their distant healing intentions at 2-minute random intervals that could not be anticipated by the recipients.

Significant differences between the experimental (send) and control (no send) conditions were found ($P = 0.000127$); that is, there was less than approximately one chance in 10,000 that chance could explain the results. Areas of the brain activated during send intervals included the anterior and middle cingulate area, precuneus, and frontal area. This study not only demonstrates that remote, compassionate, healing intentions can exert measurable effects on the brain of a sensory isolated recipient, but suggests that an empathic connection between the healer and recipient is vital.

Hypertension

So many studies have been conducted in this area that Levin et al felt the need to summarize them and did so in a detailed review that was published in the British journal, *Social Science and Medicine*.[33] Their review noted a significant inverse correlation between strong religious commitment and blood pressure that was evident no matter what religion an individual chose to practice, their geographical location, or ancestry.

Some of the studies discussed in this review included:

- A California study of adults of Chinese, Filipino, and Japanese ancestry that found those with religious affiliation had a 15% rate of hypertension, approximately half that of a 29.3% rate in those with no religious affiliation.
- A Harvard School of Public Health examination of the incidence of hypertension in South African Zulus, which found that among urban women, membership in a Christian church was associated with normal blood pressure, whereas nonmembership was linked to hypertension, particularly among women who reported being "bewitched," who were twice as likely to have high blood pressure as their church-going peers.
- A study of Jewish families in Jerusalem, which found that the advantage of religious affiliation extended even to the families of those involved, regardless of their own religious activity. Female children whose father had attended yeshiva for at least 5 years had a mean diastolic blood pressure of 65.2 mm Hg compared with 74.5 mm Hg for those whose fathers had less than 5 years religious training, and 71.5 mm Hg for those whose fathers had no formal Jewish education. Levin's comment about these statistics was, "A little religion may be worse than none." I suggest that the disparity between the daughters of those with no formal religious education and those with less than 5 years religious education may be explained by the fact that merely having no formal religious training does not mean one has no spiritual life, whereas choosing to discontinue religious education may indicate a disaffection with all things spiritual due to an unsatisfactory encounter with religion. How many of us have not only thrown away a form of organized religion we found intolerable, but mistakenly limited God to the concept of It taught in the religion we disavowed?
- A Duke University matched study, which found that people who attended religious services at least weekly and prayed or studied the Bible at least daily had consistently lower blood pressure than those who did so less frequently or not at all.
- A study conducted by the National Cancer Institute and Georgetown University that compared death rates in clergymen with those in the general Caucasian population and found American Baptist ministers were almost 40% less likely to die of hypertension complicated by heart disease, Presbyterian ministers 29% less likely, and Episcopalian and Lutheran ministers 41% less likely to die from hypertensive-related causes.
- A Japanese study in which researchers found Zen Buddhist priests were half as likely to die from hypertension as other Japanese men.

More recently, a meta-analysis of the research on Transcendental Meditation in the PubMed and Cochrane databases through December 2006, which identified nine randomized controlled trials, found that the regular practice of Transcendental Meditation reduced systolic and diastolic blood pressure by clinically meaningful amounts: approximately 4.7 and 3.2 mm Hg, respectively.[34]

Another recent study Levin did not discuss in this meta-analysis focused on women and examined the association between blood pressure, selected health behaviors, and religious activity. Data were obtained on 112 women who were at least 35 years of age and of Judeo-Christian faith. Resting blood pressure measures were taken with an automated sphygmomanometer; height and weight were measured to determine body mass index (BMI), and intermediate health variables (e.g., physical activity, smoking, diet, and alcohol consumption) were measured by questionnaire. A multifactorial questionnaire was used to assess various dimensions of religious activity. Multiple regression analysis found a direct inverse effect between both systolic and diastolic blood pressure and the level of religious activity, not mediated by changes in health behaviors.[35]

Two other studies that were included in Levin's meta-analysis contradict the thesis that religion is clinically beneficial only because it helps people avoid risk-producing behaviors. In one of these studies, people who were both frequent church attendees and rated their religion as very important were found to have lower diastolic blood pressures, and this association held true even for smokers. Smokers who rated religion as very important were 7.1 times less likely to have to have an abnormal diastolic pressure than those smokers who gave a low rating for the personal importance of religion. The second study found that smokers who attended church weekly or more were four times less likely to have abnormal diastolic pressure than low attendees or nonattendees. Even when the analysis was adjusted for other blood pressure risk factors, such as age, socioeconomic status, and weight, those who rated religion as highly important to them and attended church weekly or more had mean diastolic pressures almost 5 mm Hg lower than those who rated religion as unimportant and infrequently or never attended church.[33]

One recent study found religiosity had a deleterious effect on blood pressure. This study looked at the effect of religiosity on systolic blood pressure, diastolic blood pressure, and hypertension

using data taken from the Chicago Community Adult Health Study, a probability sample of adults (n=3105) aged 18 and over living in Chicago, Illinois. Prayer was associated with an increased likelihood of hypertension, and spirituality was associated with increased diastolic blood pressure. However, variables for meaning and forgiveness were associated with lower diastolic blood pressure and decreased likelihood of hypertension—findings that emphasized the importance of analyzing religiosity as a multidimensional phenomenon.[36]

Cancer

Dozens of epidemiologic studies report that some religious groups have a significantly lower risk of cancer, both overall and for many specific types. This research, summarized by Levin in *God, Faith and Health*, includes the following[4]:

- Studies at UCLA, the University of Utah, and the University of Alberta which found a lower overall death rate in Mormons of both sexes from the 1950s to 1970s, in Utah, California, and Canada. Mormons were shown to be protected not just from dying of cancer, but from developing cancer.
- Studies at Loma Linda University School of Public Health that identified lower cancer incidence and death rates for Seventh-Day Adventists overall and for several cancer sites, including the colon, rectum, lung, and mouth.
- A study from the Danish Cancer Registry that showed Adventist men had significantly lower risk for cancers of the colon, respiratory system, and bladder.
- An Indiana University study that summarized 30 years of data from California and found Adventist women had higher 1-, 3-, and 5-year survival rates after a diagnosis of breast cancer.

Levin cites data from studies dating back to the first half of the twentieth century that document that some religious groups have a much lower incidence of reproductive cancers. Levin reviews data from more than 50 studies published into the 1990s, all of which consistently show that Mormons, Seventh Day Adventists, Hutterites, Amish, Muslims, Parsis, and Jews, especially Jewish women, have lower incidence (new cases), prevalence (total cases), and mortality from reproductive cancers.

Among Jews, the lower rates of uterine and cervical cancer and virtual nonexistence of penile cancer have been ascribed to the hygienic benefit of circumcision, yet a number of other studies have found Jews to have considerably lower rates of other unrelated cancer sites, including[4]:

- A Dutch study from over 50 years ago that found fewer than expected deaths among Jews from cancers of the stomach and bile passages.
- A University of Texas Medical Branch study conducted over a 15-year period that found an average annual death rate due to lung cancer in gentile men of 148.6/100,000 compared with 95.5/100,000 in Jewish men—more than 60% lower.
- A National Cancer Institute review of data from studies conducted in New York City that found lower rates of death in Jews relative to non-Jews for cancers of the buccal cavity, pharynx, prostate, and bladder.

At least 10.8 million living Americans have been diagnosed with cancer, and about 1.5 million new cancer cases were diagnosed in 2008. A study examining prayer for health and self-reported health among 2262 men and women with a history of cancer found 68.5% reported having prayed for their own health, and of these, 72% reported good or better health status.[37]

In patients with advanced cancer, spiritual well-being has been found to dramatically improve quality of life and patients' ability to cope, and to significantly lessen distress, depression, and anxiety.[38-40]

AIDS

Acknowledgement of a spiritual dimension in an individual's life and intercessory prayer have both been found to benefit patients with acquired immunodeficiency syndrome (AIDS):

- A study of 100 patients with AIDS found a significant positive correlation between a sense of spiritual well-being and hardiness.[41]
- A longitudinal study examined the relationship between changes in spirituality/religiousness from before to after diagnosis of human immunodeficiency virus (HIV) and disease progression (CD4 and viral load every 6 months) over 4 years in 100 people with HIV. Forty-five percent of subjects showed an increase in religiousness/spirituality after HIV diagnosis; 42% remained the same; and 13% decreased. Those reporting an increase in spirituality/religiousness had significantly greater preservation of CD4 cells over the 4-year period, as well as significantly better control of viral load. Results held even after controlling for church attendance and initial disease status (CD4/viral load), medication at every time point, age, gender, race, education, health behaviors (adherence, risky sex, alcohol, cocaine), depression, hopelessness, optimism, coping (avoidant, proactive), and social support.[42]
- A double-blind, randomized, controlled trial published in the *Western Journal of Medicine* by researchers at the California Pacific Medical Center examined the effects of distant healing and prayer on 40 patients with advanced AIDS and found that those who were prayed for did significantly better than controls. In this study, patients were randomly assigned to treatment and control groups; treatment was 1 hour a day, 6 days a week for 10 weeks. Investigators recruited 40 distant healers from eight traditions, including Christians, Jews, Buddhists, Native Americans, students of shamanism, and graduates of training programs in bioenergetic and meditative healing. The healers, who were scattered across North America and averaged 17 years' experience, were assigned on a rotating basis, with each patient receiving treatment from a different healer each week. The healers were given only the first name and a photograph of their patients, whom they never met. At the conclusion of this 6-month study, a medical chart review—also conducted in blinded fashion—found that those prayed for had fewer new AIDS-defining illnesses (0.1 vs 0.6 average per patient), less severe illness (severity scale score of 0.8 vs 2.65), required fewer doctor visits (9.2 vs 13.0), fewer hospitalizations (0.15 vs 0.6), fewer days of hospitalization (0.4 vs 3.4), and experienced improved mood according to scores on the Profile of Mood States scale (–26 vs 14).[43]

Alcohol and Drug Abuse

A PubMed review found 688 studies that noted a relationship between spirituality and prevention of substance abuse with 95 new studies published in this area since 1998. Studies consistently found that drug abuse was correlated with the absence of religious commitment in a person's life, and that religious commitment was protective against alcohol and drug abuse, was of significant benefit in recovery from addiction and substance abuse, and made a crucial difference in the prevention of drug and alcohol use among youth. A *Journal of Psychology and Theology* review of the empirical data in the field published in 1991 summarized findings that have been corroborated in well over a hundred studies since then, "Whenever religion is used in an analysis, it predicts those who have not used an illicit drug, regardless of whether the religious variable is defined in terms of membership, active participation,

religious upbringing, or the meaningfulness of religion as viewed by the person himself."[44-62]

Depression, Anxiety, Suicide

In a randomized, crossover clinical trial, direct person-to-person prayer was shown to significantly lessen depression and anxiety, and to increase optimism, despite having little effect on salivary cortisol levels.[63]

A number of studies indicate that an individual's spiritual convictions significantly impact the likelihood of his or her choosing to commit suicide, including the following:

- One community study found that persons who did not attend church were four times more likely to commit suicide than were frequent church attendees.
- A review of studies on suicide found 12 out of 12 studies showed that persons with a strong religious commitment were substantially less likely to commit suicide. The religiously committed had fewer suicidal thoughts and more negative attitudes towards taking their life.[64]
- A study that evaluated a possible link between religious activity and suicidal ideation in a sample of adult Latin American immigrants (145 women, 56 men) found that self-perception of religiosity, influence of religion, and church attendance were significantly negatively associated with suicidal ideation. No relationship was found between religious affiliation and suicidal ideation; all religiosity was protective against suicide.[65]
- Findings from the Baltimore epidemiologic catchment area study (n = 1091) revealed attending religious services and seeking spiritual comfort at baseline were associated with greatly decreased odds of suicidal ideation (adjusted odds ratio [OR] = 0.55).[66]

Surgical Outcome

Both an individual's spiritual beliefs and intercessory prayer have been shown to improve surgical outcome in a number of studies, including the following:

- A study of elderly women recovering from hip surgery found that those who regarded God as a source of strength and comfort and who attended religious services frequently were less depressed and could walk a greater distance at discharge. The authors suggested that the ability to walk farther was possibly explained by the fact that the more religious patients were less depressed and thus responded better to physical therapy.[67]
- In a study of patients with end-stage liver disease who underwent liver transplantation, those actively searching for God had an almost three-fold (2.95) increased likelihood of survival, whereas those who were passive or fatalistic had a three-fold increased risk of dying.[68]
- Results of a study that assessed the effects of prayer on postoperative psychological recovery in a group of 151 older patients after coronary bypass surgery showed that 1 year after coronary artery bypass grafting, those patients who prayed about their postoperative problems experienced significantly less depression and general distress than those who did not.[69]
- As noted previously, cardiologist Randolph Byrd ran a double-blind intervention study that measured the effect of prayer on cardiac surgery outcome. In a coronary care unit in a large general hospital, 393 patients who consented to participate were randomly assigned, half to receive and half not to receive regular intercessory prayers by an interdenominational group of committed Christians unknown to them. The patients themselves, staff, and doctors were unaware which patients were assigned to which group. Each intercessor was asked to pray on a daily basis for each of the following clinical issues: rapid recovery, prevention of complications and death, and any other areas the intercessor believed would be beneficial to the patient. Patients who received daily intercessory prayer were found to have a 5% to 7% advantage over those who did not, including fewer life-threatening events and complications (congestive heart failure, cardiopulmonary arrests, intubations, and pneumonia) during their stay in the hospital coronary care unit than the control group, who were five times more likely to need antibiotics and three times more likely to develop complications.[28]
- In contrast, several recent studies showed no benefit from religious participation (although religious subjects in one study were more likely to be obese, which likely impacted cardiovascular risk[70]) or even adverse effect, e.g., the STEP (discussed under "Coronary Heart Disease") in which higher incidence of complications after coronary artery bypass graft surgery were seen in subjects receiving intercessory prayer. Possible reasons for the negative outcome in the STEP also apply to the following two negative studies:
 - A 2007 Cochrane review (10 studies involving 7646 patients) on the effects of intercessory prayer versus standard care found that the majority of studies showed no positive effect.[71]
 - A study of the effect of intercessory prayer on outcomes in 748 patients who underwent percutaneous coronary intervention also showed no benefit.[72]

Length and Quality of Life

Numerous studies involving large numbers of older individuals show that living with an awareness of Spirit translates to living longer and more joyfully. The mechanisms by which religious involvement appear to influence mortality include aspects of social integration, social regulation, and psychological resources.[73]

- Five community-based studies showed that the religiously committed person, particularly the church attendee, had a greater likelihood of living longer than did persons lacking a religious commitment.[74,75] Not only did the religiously committed have a greater chance of living longer, but they were more satisfied with their life, as the data suggested in these five studies and another study, which also showed that those who frequently pray and who have a close relationship with God have high levels of life satisfaction, existential well-being, and overall happiness.[76]
- One of the largest of the community-based studies, which was conducted by scientists at Harvard and Yale and funded by the National Institutes of Health, investigated the protective effects of spirituality on death rates in a population of nearly 400 older adults living in Connecticut. Among those healthy at the onset of the study, the death rate was so low it was thought unlikely that any additional factors would lower it further. Among those ill at the study's outset, however, very different findings emerged. Over the course of the study, the death rate in sick men who did not have a spiritual life was 42% compared with 19% in sick men whose lives included a spiritual dimension. Similar results were found for women; those with no spiritual practice had a death rate of 20% compared with 11% for women whose lives included spiritual awareness and activity. Actual attendance at religious institutions had the smallest effect, which led the researchers to conclude that it was "unlikely that the benefits of religiousness are predominantly due to the social contacts associated with church attendance."[77]

- A clinical study at Dartmouth that involved more than 200 postsurgical cardiac patients found similar results. During a 6-month follow-up after open-heart surgery, the mortality rate was 11% in patients who considered themselves "not at all," "slightly," or "fairly" religious. In those who saw themselves as "deeply" religious, the death rate was zero.[78]
- A systematic quantitative review of 69 studies investigating the association between religiosity/spirituality and mortality in initially healthy populations found that religiosity/spirituality was associated with reduced mortality (combined hazard ratio [HR] = 0.82). Notably, the protective effect was independent of behavioral factors (smoking, drinking, exercising, and socioeconomic status), negative affect, and social support.[79]
- A quantitative review of prospective observational studies of the association between positive psychological well-being and mortality that included 35 studies in initially healthy populations and 35 studies in disease populations showed psychological well-being was associated with reduced mortality in both the healthy (combined HR = 0.82) and the disease population (HR = 0.98).[80]
- A U.S. nationally representative cohort study of 8450 American men and women aged 40 years and older followed an average of 8.5 years, after adjusting for confounding by baseline sociodemographics and health status, reported the following HRs (95% confidence limits): never, 1.00 (reference); less than weekly, 0.89; weekly, 0.82; and more than weekly attendance, 0.70.[81]

Delinquency

Studies indicate that Spirituality protects not only the elderly but also the young.

In two reviews that summarized 13 studies, 12 found that religious commitment—particularly church attendance—played a protective role against delinquency.[64] An additional study found that the black males who were able to leave the ghetto and avoid falling prey to delinquency or drug abuse were those who attended church on a regular basis.[82]

The protective effects of religion against delinquency were also corroborated in a review published in 2001 in the *International Journal of Psychiatry and Medicine,* which evaluated 630 separate data-based reports on the protective effects of religion not only on delinquency, but also on depression, suicide, anxiety, psychosis, alcohol and drug abuse, cigarette smoking, and extra-marital sexual behaviors, as well as its beneficial effects on well-being, hope and optimism, meaning and purpose, and marital stability.[83]

SPIRITUALITY—THE PROVINCE OF PHYSICIANS?

In an excellent editorial on spirituality and clinical care in the *British Medical Journal* (December 2002), psychiatrist Larry Culliford appeals to physicians to "recall, reinterpret, and reclaim our profession's sacred dimension."[84] Culliford cites research indicating that the benefits of recognizing the spiritual dimension of your patient's life are threefold: aiding prevention, speeding recovery, and fostering equanimity in the face of ill health.

One particularly impressive reference Culliford discusses in support of the need for physicians to treat the whole person is a critical, systematic, and comprehensive analysis of empirical research on the relationship between spirituality and many health conditions that cover more than 1200 studies and 400 reviews.[85] In this work, a 60% to 80% relationship between better health and spirituality was found in both correlational and longitudinal studies of heart disease, hypertension, cerebrovascular disease, immunologic dysfunction, cancer, mortality, pain and disability, psychoses, depression, anxiety, suicide, and personality problems. The high correlation between health and spirituality was also evidenced in health behaviors such as exercising, smoking, substance abuse, burnout, family relationships, and marital breakdown.

In his review of medicine's evolution over the last century, entitled, "Weaving Medicine Back Together: Mind-Body Medicine in the Twenty-First Century," Mark Gilbert, MD, remarks that although the medical profession has taken pride in the rapid and often effective advancement of diagnostic technology, surgical interventions, and pharmaceutical remedies, it has also witnessed the unraveling of the woven connection among mind, body, and the human soul. Yet a substantial body of laboratory and clinical research evidence built over the last three decades has made the scientific connection between mind, body, and belief systems indisputable. Numerous clinical studies have shown that emotional, cognitive, and spiritual beliefs directly affect physical well-being.[86]

These include clinical studies finding:

- Women in a mind–body support group for women with metastatic breast cancer lived, on average, 18 months longer than a control group at 10-year follow-up.[87]
- After only 6 weeks, men in a mind–body support group for men with malignant melanoma did better than controls 6 years later.[88]
- Women in mind–body support groups for infertility conceived 44% of the time (as opposed to the expected 8% to 10% rate).[89]
- Eighty percent of men with essential hypertension in mind–body groups were able to decrease their medication; 16% were able to stop their antihypertensive medication entirely.[90]
- Data evaluating more than 1000 post-myocardial infarction patients showed that introducing behavioral counseling altered type A behavior and reduced cardiac morbidity and mortality significantly.[91]
- Hostility is significantly related to cardiac disease, and patients at cardiac risk who were not married or without a confidante were three times more likely to die.[92]
- Psychological stress was associated in a dose–response manner with an increased risk of acute infectious respiratory illness.[93]
- Wound healing was slower in the stressed spouses of patients with Alzheimer's disease.[94]
- Immunity was suppressed in medical students before examinations,[95] as well as in marital partners in conflict.[96] Spiritual belief could increase longevity and protect against illness.[97, 97a]
- "Religious struggle"—feeling punished or deserted by God, or believing that one's illness was caused by the Devil—were predictors of increased mortality among medical patients after hospital discharge.[98]

Patients have clearly indicated that they want greater attention to spirituality when they are in hospital. A 2003 survey of 1,732,562 patients, involving 33% of all U.S. hospitals, revealed that patient satisfaction with the emotional and spiritual aspects of care had one of the lowest ratings among all clinical care indicators, and was an area in greatest need of improvement.[99]

The Joint Commission on Accreditation now requires all hospitals to have a vehicle in place to assess the "spiritual health" of all incoming patients. This is usually done through taking some sort of "spiritual history."[100,101]

Two popular methods for taking a spiritual history are:

SPIRIT,[102] an acronym for:

S—Spiritual belief system
P—Personal spirituality
I—Integration with a spiritual community
R—Ritualized practice and restrictions
I—Implications for medical care
T—Terminal event planning

and FICA,[103] an acronym for:

F—Faith: A broad, open-ended question is usually asked, e.g., "What do you believe in that gives meaning to your life?"

I—Importance and Influence: "How important is your faith (or religion or spirituality) to you?"

C—Community: "Are you a part of a religious or spiritual community?"

A—Address or Application: "How would you like me to address these issues in your health care?" "How might these things apply to your current situation?" "How can we assist you in your spiritual care?"

In summary, mind–body medicine is one of the most researched and evidence-based branches of complementary medicine. Although we may disagree as to what factors actually create the health-promoting, healing changes that occur when the individual's spiritual dimension is engaged—or even what this "spiritual aspect" of our being is, the fact that these highly beneficial effects occur cannot be denied.

Physicians who ignore spirituality—even in their patients who do not believe in God as described by organized religions—are dismissing a central human core that strives for meaning, purpose, and healing, and that is universally a source of reverence and awe in the recognition of the simple, miraculous fact that Life is, and is manifest in and as each one of us.

It is a fact that prayer is a common practice in the United States, and much of that prayer is for health concerns. Results of a national survey (n = 2055, 60% weighted response rate) published in the *Archives of Internal Medicine* (2004) on the use of prayer for health concerns revealed that 35% of respondents used prayer for health concerns; 75% of these prayed for wellness, and 22% prayed for specific medical conditions. Of those praying for specific medical conditions, 69% found prayer very helpful. Factors independently associated with increased use of prayer included age 33 to 53 years (OR, 1.6); age more than or equal to 54 years (OR, 1.5); female sex (OR, 1.4); and education beyond high school (OR, 1.5). Depression, chronic headaches, back and/or neck pain, digestive problems, and allergies were also associated with more frequent prayer. Only 11% of respondents using prayer discussed it with their physicians.

The growing recognition that spirituality powerfully affects human health is also reflected in recent polls, according to which the majority of patients want physicians to include faith as part of a comprehensive doctor–patient interview:

- In a poll conducted in 1996 of 1000 U.S. adults, 79% of the respondents believed that spiritual faith could help people recover from disease, and 63% believed that physicians should talk to patients about spiritual faith.[104]
- A telephone survey conducted in 2002 found that 80% of respondents believed God acts through physicians to cure illness, 40% believed God's will was the most important factor in recovery, and 69% said they would want to speak to someone about spiritual concerns if seriously ill, although only 3% would initiate a conversation about spiritual factors with a physician. Perhaps this is because their physicians have seen merely the disease rather than the spiritual truth of the person who has come to them for care.[105]



IMPROVING HEALTH CARE PROFESSIONALS' ABILITY TO INCLUDE SPIRITUALITY IN HEALTH CARE

Although evidence of the importance of spirituality to both physical and emotional health continues to accrue, and the need for spiritual concerns to be addressed by all disciplines, not just those of a religious orientation, has been recognized, particularly in palliative and end-of-life care,[106,107] health care professionals typically do not broach the topic of spirituality. Reasons for this failure include a lack of confidence in discussing spiritual topics, the wide variety of ideologies, philosophies and creeds, and a lack of shared spirituality outside the confines of traditional religious terminologies.

Recently, in response to a perceived need to include spirituality in palliative care, a multidisciplinary team of health and religious professionals at the University of Queensland, Australia, in consultation with people with life-limiting illness, their family members, and those employed in the clinical field, decided to develop a set of training resources to increase the knowledge and confidence of staff in knowing how to address issues of existential and spiritual care with patients.

The resources they have created were designed to appeal equally to health professionals and pastoral caregivers with religious and nonreligious orientations, and to be used as either a self-paced independent learning package or a workshop that could be delivered by a member of any profession.

Four pilot workshops involving 120 palliative care staff were conducted using this Spirituality in Palliative Care training resource. Follow-up analysis revealed significant increases in Spirituality, Spiritual Care, Personalized Care, and Confidence in this field immediately following the workshops. Improvements in Spiritual Care and Confidence were maintained 3 months later, with Confidence continuing to grow. This Spirituality in Palliative Care training resource is available, free of charge, from Palliative Care Australia on their national website at www.pallcare.org.au.[108]



THE PRACTICAL APPLICATION: INTEGRATING SPIRITUALITY INTO MEDICAL PRACTICE

Given the cumulative scientific evidence of prayer's potential beneficial effects, not praying or meditating with the intention of gaining the best insight or understanding of how to treat your patients for their best possible outcome is equivalent to deliberately withholding an effective therapeutic intervention.

Yet, given the time constraints of the typical practice, along with the reticence to approach the subject of spirituality bred into Western medicine along with the "scientific method," availing oneself of the power of prayer or meditative insight is indeed a formidable challenge. Potential rewards, both personally and professionally, however, make a trial run of the following simple practices the rational choice:

- Before going in to see your first patient, take just a few seconds to get in touch with your Self: the vital, creative, exuberantly loving, effortlessly and deeply insightful being who is you on your best day and, in truth, is always who you are. Open your heart and mind and tune in to your strength, your compassion, your benevolence, and healing intention.
- Invite dialogue on the subject of spirituality. Ask about your patient's innermost Self as part of the medical history. "Do you feel supported by the Life Force within you?" "Are your beliefs a source of strength?" "Can you see any goodness, anything of value, any life lessons that you are gaining from this experience?" "What has become clear to you since last we met?"
- Be compassionate and validating. Support your patients' belief in their essential Spirit as a healing force that reveals meaning and value in their lives—in sickness as well as in health.
- Empower patients with information about research on the positive effects of spirituality on health. Provide a handout of possible resources such as those listed in the Further Reading section. Add some of these books to your waiting room reading materials.

- Draw strength and solace from your own faith in the drive to express health that is an essential part of the nature of all life. When concern for a patient overwhelms you, get quiet and listen to your heart for guidance. When you have given your best, know you are not alone in your healing efforts. Recognize that the Life Force in the form of the vis medicatrix naturae is at work in your patient. Let go and trust in Life.

EFFECTIVE PRAYER

After spending more than a decade performing simple laboratory experiments that demonstrated that prayer works, the Spindrift organization in Salem, Oregon, investigated which type of prayer strategy works best. Distinguishing essentially two types of prayer, directed prayer in which prayers have a specific goal, image, or outcome in mind, and undirected prayer, in which no specific outcome is requested, researchers found that while both types of prayer produced results, the undirected approach was quantitatively more effective, frequently yielding results twice as great, or more, compared with the directed approach.[109]

A trusting openness and acceptance of Life's essential benevolence confers its own immediate blessing, regardless of physiologic outcome. Such undirected prayer, a letting go and affirmation of trust in the Absolute, is at once a source of release, peace, and hope.

SIDE EFFECTS AND CONTRAINDICATIONS

As with any intervention, misuse or inappropriate use of our nonlocal nature can cause problems. As the previously mentioned research collectively and conclusively demonstrates, our thoughts, intentions, and prayers do exert effects, and negative intention or negative prayer can be harmful. In *Be Careful What You Pray For…You Just Might Get It*, Dossey reviews a surprising amount of research on negative prayer and makes a cogent case for the need for each of us to assume responsibility for our negative thoughts and wishes. His insightful discussion of the unfortunate effects of *nocebo* underscores the physician's difficult responsibility—to convey truth with compassion and without eradicating hope.[31]

Additionally, although the explicit inclusion of faith and prayer in health care can have a significant positive impact on clinical outcomes, this does not mean these approaches can take the place of effective treatment. Unfortunately, some religious beliefs can be interpreted to prohibit many types of conventional medical interventions. One disconcerting study evaluated the deaths of children from families whose beliefs prohibited certain types of medical interventions. The researchers evaluated the records of 172 of these children who died in the United States between 1975 and 1995 and for whom sufficient documentation existed to determine the cause of death. Of these, medical intervention would have resulted in a typical survival rate of 90% in 140, more than 50% in 18, and all but 3 of the remainder would likely have had some benefit.[110] Although the research was flawed by the design bias, i.e., researchers did not look for positive results—only negative results—the study is cause for concern.

Although it is easy for the clinician and social worker to condemn the belief systems of these children's families, how much does the well-documented unwillingness of most practitioners to consider faith and religious practice as factors in the therapeutic process contribute to these families' extreme position? It is clearly time for physicians to acknowledge and utilize both science and spirituality as effective factors in health and healing.

ILLNESS, THE GIFT OF SPIRITUAL HEALING

We assume illness is the enemy, when, in fact, it is our teacher. Illness always offers a door to spiritual awakening, to an expansion of understanding that is healing. In the words of Paramahansa Yogananda,

> *"Your trials did not come to punish you, but to awaken you—to make you realize that you are a part of Spirit and that just behind the spark of your life is the Flame of Infinity."*

As Germany's great poet, Ranier Maria Rilke, explained, illness can teach us to be patient and can help us learn to trust in the vis medicatrix naturae, the healing power that naturopathic philosophy recognizes is life's fundamental impulse towards health,

> *"So you must not be frightened…You must think that…life has not forgotten you, that it holds you in its hand; it will not let you fall. Why do you want to shut out of your life any agitation, any pain, any melancholy, since you really do not know what these states are working upon you? Why do you want to persecute yourself with the question when all this may be coming and whither it is bound?…just remember that sickness is the means by which an organism frees itself of foreign matter; so one must just help it to be sick, to have its whole sickness and break out with it, for that is its progress…you must be patient as a sick man…there are in every illness many days when the doctor can do nothing but wait. And this it is that you, insofar as you are your own doctor, must now above all do."*[111]

Although physicians are taught to banish pain at all costs, and allopathic doctors are trained to eliminate symptoms as quickly as possible with drugs and surgery, failure to effect an immediate physiologic cure does not necessarily mean failure to assist in a patient's healing process. Particularly during times of serious illness, we are forced to be quiet, to tune in to our true center. When our stillness is grounded in faith, what we recognize when we search within is our Source, the life-giving, benevolent, creative energy that is called God. Prayer at this intersection of quiet and acceptance, where we become truly aware that we are not our disease, but essentially something inviolate, is the type of prayer most frequently associated with miracle cures, radical spontaneous remissions, and healings. On a spiritual level, simply to recognize this dimension of ourselves, to know the numinous, is to be healed. As Jung put it, "The approach to the numinous is the real therapy and inasmuch as you attain to the numinous experiences, you are released from the curse of pathology. Even the very disease takes on a numinous character."[112]

THE EXPERIENCE OF SPIRIT

The practice of Era III medicine involves a personal choice, a commitment to openness, to an awareness of and an alignment with Spirit that is both the most intimate and the most universal aspect of our being. How do we tune in to and draw from this inner Source of our Life in which we are all joined as One, this Source that manifests as the drive to an ever fuller unfolding of Life, this Source that is the Pervasive Loving Intelligence, which is the vis medicatrix naturae and the Dynamic Pattern that encompasses both the widest spans of rational thought and the intuitive nonrational aspects of our being?

How do we open up our awareness to and align with this Power, which has been called Spirit, Mother/Father God or Abba, Atman, Brahman, Qi, the Tao, the Christ—so many names for One Reality, of which the Life Force is one demonstration, this reality which is the Core of Healing, of Health? How do we tune in?

Many traditions have tried to codify and develop the Way, and essentially, all share the common concept: "Be still, and know that I AM." In silence, you, who have been chosen by Life as Its healers, who have through long and diligent study learned to discriminate the facts of Science, will be given the gift of another knowing, that of the perfection of Life that is within you and within each of your patients. You need only be quiet and open your heart and mind and listen to the heartbeat of the ground of your being, for It will speak, and you will know. Simply set the intention to hear, and the recognition that the Power driving the Universe is Love expressed as Intelligence in an infinity of ways will flow through you.

This Reality is always available to us; It is always expressing through us, It breathes us; we are immersed in It, but we must choose to recognize this, we must choose to be quiet and receptive and to listen, deeply within ourselves where this Truth is undeniable. In the Bible, Jesus tells us that God stands at the door and knocks. God does not arrive in a bulldozer and force entry (although if ignored, I have found the knocking can become quite insistent); our spiritual realizations wait upon us. We only have ears to hear the Self's most fundamental wisdom when we choose to listen.

Tools for becoming aware of the guiding voice within each of us take many different forms. For we are each unique and may need to try and to use different methods of access, not only among ourselves, but at different times within our individual lives. Try all that call to you. Seek out those that work for you now and gain an acquaintance with others that may prove useful later.

Reverend Kathianne Lewis, Senior Minister at the Center for Spiritual Living in Seattle, Washington, suggests three ways in which we can develop our spiritual practice: prayer, meditation, and availing ourselves of the thoughts and words given to us in the sacred works of the many spiritual traditions of our world.

Prayer is active, directive, generative. In our prayers, we talk of and to our Source, manifesting our realization of the nature of Spirit and therefore of Life and ourselves. Remembering, recognizing Who God is and that we are Its beloved creations enables us to find the faith, the knowing that Good that is present in every situation.

Meditation is passive, open, receptive. In meditation, focusing on our breath, we can experience the understanding that we are literally inspired by the Creative Intelligence that is the Source of Life. We can rest in knowing that we are cradled, held and supported, our very being renewed in every second by Life Itself, a gift given freely and the understanding of which is only limited by our ability to receive it.

The record written by Spirit upon human history offers insights recorded in every culture and in every age. The selection is voluminous and includes the Bible; the Koran; the Tao Te Ching; the writings of Native American healers, of Buddhism, of the Sufi mystics Hafiz and Rumi; the Transcendentalists such as Wordsworth, Shelly, Thoreau, and Emerson, and their descendants; the founders of New Thought, Emma Curtis Hopkins, Thomas Troward, and Ernest Holmes, *A Course in Miracles;* or recent works like Neale Donald Walsh's *Conversations with God*, Ram Dass' *Journey of Awakening*, and Naomi Remen, MD's *Kitchen Table Wisdom*. Seek out what nourishes you and spend the last moments before falling asleep or the first minutes of your day replenishing your spiritual stores. Consider it an investment in yourself and your practice that will pay immense untold dividends.

Take the time to tune in to the recognition that your life, your awareness is a gift, the most incredible, outrageous, wonderful gift! That you are Spirit using a body, not simply a physical being, but a unique manifestation of the joyful creativity of Life. And that you and your patients are alike, are One in this most essential fact of your being. This is where the true doctor–patient interaction takes place, the level that generates placebo effects—the deepest level where we experience that the essence of Life itself is Good, is driving towards an ever fuller expression of Itself, ever more complete Health, and that It lives within each of us as our very core.

Your patients come to you not merely for analysis of dysfunction to be corrected by the dosing of some supplement or green drug—they come to you to be recognized as Who They Really Are. They come to you for your faith in their true Health. They come to you for the recognition that Health is their natural state, their God-given inheritance. And when you see, when you really see them, you will be seeing yourself.

Really seeing the Truth, the Essence of Health, the Goodness in another human being is the core of all healing interactions. When you greet your patient, take a moment and see the unique, beautiful manifestation of Spirit that he or she is. Bask in the recognition of the Life Force that informs this person's life, your life, the Life that you share.

When you walk into the examination room and see your patient, see yourself. See a unique expression of the abundant and perfect realization of Life and Health that is God. See Love expressing through Wisdom as Joy.

Open yourself to intuition, to guidance, insight, support, and peace. Be bold in your confidence, in your trust, in your delight—for your path is truly grounded in Spirit, and is blessed and is a blessing to all you will serve.

In the path of the healer, it is so easy to become aware that you are in the service of Life, that all that you do is for your patient's fullest, most joyful expression of Spirit. Do your healing work for the joy of it, for the love of one another, and you will never lose heart or hope or strength.

Everything we do is sacred service; it is just a question of becoming aware of this and taking this awareness with us as the ground upon which we live and walk and breathe, into every situation, every exchange. May all your exchanges be healing.

SUMMARY

Religious faith, as primarily measured by regular attendance at religious services and a personal belief in a benevolent Life Force, is remarkably effective in the promotion of health. A substantial body of research published in diverse journals documents the efficacy of faith and prayer, both for the those praying and those prayed for, in longevity, recovery from surgery, prevention of disease, and improvement in lifestyle and behaviors. Every practitioner committed to providing the best possible care needs to be aware of, and use, this powerful healing factor—not only for our patients but ourselves.

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CHAPTER 49

Unani Medicine

Yaser Abdelhamid, ND, LAc, MS, BS, BA

INTRODUCTION

Unani Medicine: Greco-Arabic Healing and the Islamic Genius

The Arabic term unānī derives from the word "Ionian," which is a general adjective signifying "things-Greek." The linguistic translations and transliterations of this word took place between the Greek, Arab, and Persian civilizations. The particular usage of this term, however, has more often been an allusion describing the composite system of medicine born of the Arab world's inheritance—within the larger framework of the Islamic spiritual universe—of the medical tradition of ancient Greece.

The literary sources of Unani medicine (al-tibb al-yunānī, or sometimes referred to simply as "Tibb," or "Hikmat" in Pakistan and Afghanistan) were Arabic translations of ancient Greek, Roman, Egyptian, Arabic, Persian, Indian, and Chinese medical texts. However, there is no question that the initial, primary, and most honored textual sources were of Greek origin. The Arabs immersed themselves in the medical knowledge and wisdom contained in the writings of Hippocrates (Buqarāt) and Galen (Jālinūs),* as well as Plato (Aflātūn), Aristotle (Aristatīl), Dioscorides, and Empedocles (Abrāqlīdis).

It is well recognized by contemporary historians that the ancient Greek—and to some extent Roman—intellectual heritage of the West would have been almost totally lost were it not for the integrating and synthesizing Arab genius within the Islamic world.[1] In this regard, one must marvel at the Arabs' level of care and precision in "first collecting, then translating, then augmenting, and finally codifying the classical Greco-Roman heritage that Europe had lost."[2] However, "so many people in the West wrongly believe that Islam acted simply as a bridge over which ideas of Antiquity passed to mediaeval Europe. Nothing could be further from the truth, for no idea, theory, or doctrine entered the citadel of Islamic thought unless it became first Muslimized and integrated into the total world-view of Islam."[3]

Unani Medicine: Comparisons and Contrasts with Other Health Care Systems

Apart from Unani medicine's introduction onto the stage of world history as a legitimate synthesis—in time and space—of primarily Greek and Islamic civilizational influences, there is yet another dimension to Unani medicine that is often overlooked and yet of great significance. Along with the great medical traditions of other civilizations of the past, like the Ayurveda of Hindu India or Traditional Chinese Medicine, Unani medicine continues to be preserved and persevere, especially in the face of modern cultural trends in many nations that have moved towards changing the old guards of ancient medicine for the shiny hopes and promises of a new system of powerful drugs, "healing steel," and high-tech diagnostic tools and machinery. Unani medicine is still practiced today as an organic, living, breathing, whole system of health care helping millions of people around the world (especially in the Indian subcontinent, Pakistan, Afghanistan, Persia [Iran], China, Indonesia,

*For an introduction to the significance of Galen from a thoroughly contemporary Western historical and clinical paradigm, see the *Journal of the American Herbalists Guild* 2002;3(1).

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Malaysia, Bangladesh, Sri Lanka, South Africa, and certain sectors of the Middle East [such as Saudi Arabia, Kuwait, and Dubai]).

Furthermore, Unani medicine historically had the opportunity, capacity, and satisfaction of embracing the numerous folk medicines that existed within the borderlands of the Islamic world, from the traditional use of herbal remedies in ancient Palestine to the folkloric ore-based therapeutics of the people living on the high plateaus of the Himalayan Hindu-Kush mountains.

Unani medicine also shares medical theories, philosophies, cultural identity, and spiritual insights regarding human health and disease with ancient systems of medicine, such as Hindu India's Ayurveda and Traditional Chinese Medicine, because its knowledge and wisdom hail from the traditional Eastern "Orient," while contrasting tremendously with the single system of contemporary medicine that one could say belongs to the world of the modern Western "Occident."* This is what led Hakim Chishti (an American researcher and practitioner of the science and art of Unani medicine) to present a very thoughtfully indexed comparison between all of these healing systems (as found on http:/www.unani.com whose general points are in Table 49-1).

HISTORY

Contributions and Influences from Antiquity

There were a variety of strands of medicine that came together at the crossroads of Islamic history that proved to be of tremendous significance for the birth of Islamic medicine and for Unani medicine in particular.[4]

First, there was the synthesis of the ancient sciences (including medicine), of Egyptian and Mesopotamian civilizations in Greek life and thought, centered in Alexandria. Only in the light of recent archeological and anthropological discoveries have we discovered the high level of scientific sophistication that was present in these two kingdoms. The medical knowledge attributed to these earlier civilizations became forged in the fire of the Greek intellect into an even more systematic model of diagnostics and therapeutics.

Secondly, the main centers of Greco-Hellenistic learning were pushed further East as a result of a decline of intellectual energies due to shifting political and economic realities constantly confronting and fracturing Western Christendom. This encouraged two other civilizations to take up the reins of transmission of essential elements of Greek knowledge: Persian and Harrānian (i.e., Sabaean). The Sabaeans were independent heirs to the Babylonian and Greek scientific estates through their reliance upon the wisdom contained in Hermeticism and Neo-Pythagoreanism. Also, it was in the city of Jundishapur that the Persians vivified the sciences coming out of India and China.

In summary, the "scientific knowledge that originated in India, China, and the Hellenistic world was sought out by Arab and Muslim scholars and then translated, refined, synthesized, and augmented at different centers of learning, starting at Jundishapur in Persia around the sixth century—even before the coming of Islam—and then moving to Baghdad,* Cairo, and finally Toledo and Cordoba, from whence this knowledge spread to Western Europe."[2]

The Torchbearers of Islamic Medicine

With the advent of the Islamic spiritual tradition, one must mention the intellectual power and genius found in the physicians of Islam. For if history did not give birth to these giants in the field of medicine, one cannot really speak in the present tense at all of contemporary Unani medicine, let alone its subtle historical influences upon the character of modern conventional medicine.

Ibn Ishāq (Johannitus Onan), 809-873 AD

Hunayn ibn Ishāq al-ʿIbādi was "the greatest of all translators of this period … [and] an outstanding physician of his day. [He] often translated texts from Greek into Syriac. At other times he would translate directly from Greek into Arabic."[4] He was "reputed to have been paid for his manuscripts by an equal weight of gold. He and his team of translators rendered the entire body of Greek medical texts, including all the works of Galen, Oribasius, Paul of Aegin, Hippocrates, and the *Materia Medica* of Dioscorides, into Arabic by the end of the ninth century. These translations established the foundations of a uniquely Arab medicine."[2]

Al-Tabari, 810-855 AD

Ali ibn Rabbān al-Tabari was the teacher of the great Rhazes. He was the "author of the first major work of Islamic medicine … entitled Kitāb Firdaws al-Hikma ('The Book of the Paradise of Wisdom'). In 360 chapters, he summarized the various branches of medicine, devoting the last discourse, which consisted of 36 chapters alone, to a study of Indian medicine (Ayurveda). The work, the first large compendium of its kind in Islam, is of particular value in the fields of pathology, pharmacology, and diet, and clearly displays the synthetic nature of this new school of medicine, now coming into being."[4]

Al-Rāzi (Rhazes), 841-926 AD

Abu Bakr Muhammad ibn Zakariyya al-Rāzi was born in the town of Rayy in Persia, near what is present day Tehran. He was reputed to be Islamic medicine's greatest clinician. His works include *al-Kitāb al-Mansūri* (*The Book of Mansūr* or the Latin *Liber Almansoris*, in which Rhazes delineated principles of medical theory, diet, pharmacology, dermatology, oral hygiene, epidemiology, toxicology, and even climatology and its effects on the human body), *al-Judari wa al-Hasbah* (*Smallpox and Measles*, which was the first treatise ever written on the subject), and his magnum opus *al-Kitāb al-Hāwī* (*The Comprehensive Work* or the *Liber Continens* of later Latin translators; this monumental collection of 25 volumes contained all the medical knowledge of the age, including the master's own observation and experience).[2]

*Please see Professor Edward Said's thoroughly engaging study on this topic in his popular book, *Orientalism* (Vintage Books, New York, 1979). Furthermore, it should go without saying that Orient and Occident are terms that transcend time (although one can generalize and say that the world of antiquity was primarily governed by the laws of Tradition and the dictates of Heaven) and space (although one can summarize the fact that most of what is called the Western world is governed by the laws of Secularism dominated by the will of Man). As to a logical, brilliant, and intellectually sound study of an understanding of this dichotomy and all that it means, please read S.H. Nasr's *Knowledge and the Sacred* and Professor Harry Oldmeadow's *Traditionalism: Religion in the Light of the Perennial Philosophy.*

*It was in Baghdad, Iraq that Caliph Ma'mun founded the very famous "Bayt al-Hikma [literally 'House of Wisdom'], a sort of academy, in which translators found a convenient working place equipped with the necessary working facilities" to conduct the highest quality and quantity of manuscript translations, which was demanded of them by the Caliph.[5]

TABLE 49-1 **Comparing the Three Great Traditional Healing Systems with Modern Western Medicine***

	UNANI	AYURVEDA	CHINESE	MODERN WESTERN
Origins	Persia; circa 980 AD	India; circa 2000 BC	China; circa 2700 BC	Europe; United States; late 19th century
Primary dynamic elements	Rūh (spirit force)	Prana (life breath)	Chi (life energy)	Brain and heart
Disease correlates	Humors	Tridoshas	Yin-Yang; Chi	Named pathology
Disease causes	Imbalance of humoral temperament	Ama is the "harbinger of misery"; the cause of disease	Systemic imbalances; no overriding emphasis on one	Bacteria; virus; fungus; parasite; metabolic disturbances; trauma
Basis of diagnosis	Humors: blood, phlegm, yellow bile, black bile	Tridosha: Vata, Pitta, Kapha	Four diagnoses of Traditional Chinese Medicine	Based on patient's history, physical examination, laboratory testing
Diagnostic models	Restore balance to humors and organ systems	Concept of Shiva-Shakti; balance in the tridosha or three humors system	Achieve balance of yin (passive) and yang (active) physiologic functions	Specifically named pathology
Chief diagnostic modality	Differential; mizāj or temperament assessed for each of four humors	Differential; states of consciousness aligned with each of the three humors	Differential, questioning, observation, palpation, and listening; Zang Fu organ syndromes	Differential; named disease
Diagnostic tests	Observation, lifestyle, pulse, urine, stool, and palpation	Tongue, pulse, urine, and palpation	Tongue, pulse, and palpation	Urinalysis, x-rays, and standard blood tests; sampling organ tissues; diagnostic x-rays; angiography (Note: in the U.S., as a whole, about 8.5 billion laboratory diagnostic tests were done in 1996)
Pulse diagnosis	Reveals humoral imbalance in organ system. Taken with three fingers at radial pulse of wrist; more than 1,000 potential factors evaluated in seconds	Correlates pulse to the tridosha or three humors. Taken by the index finger of the physician; qualities of pulse are described in terms of several animals	Direct manifestation of the circulatory energy of the body; classical five phase pulse correspondences. Taken on the wrist; about 40% reliable as a sole diagnostic method by most TCM practitioners	Speed: fast pulse to slow pulse
Elements of nature	Four: fire, air, water, and earth	Five: fire, earth, water, air, and ether	Five: fire, earth, metal, water, and wood	22 basic elements of chemistry
Main dietary influences	Nonalcoholic; regular fasting; nonporcine	Vegetarian	Rice and Vegetables	High refined sugars; alcohol; fats; drugs
Patient participation and will	Empower patient to make changes in diet and lifestyle	High objectivity	Personal determination	Not significant
Deity of system	Abrahamic monotheism; primarily God (Allah) of Islam	Polytheistic; Panentheistic; Nondualistic Advaita Vedanta (Brahma Siguna, Brahma Nirguna); God of Hinduism	Nontheistic; Confucianism; Taoism (Tao); Buddhism (Amida Buddha, Avalokiteshvara)	Secular atheism; agnosticism; modern evolutionary nihilism
Primary treatment modalities	Diet; herbs; fasting; cupping; purgation; baths; attars (essential oils or medicinal scented perfumes)	Pancha Karma (detoxification)†; herbs; diet; emetic therapies	Acupuncture, herbs; cupping; moxibustion; diet	Chemotherapy; radiation therapy; pharmaceutical drugs; surgery; rehabilitative physical therapy
Primary treatment objective	Mizān: restore to balance; provoke "The Healing Crisis"	Clear the entire GI tract; regulate the bowels; improve digestion	Tonification of energy	Symptom suppression; kill germs and bacteria; palliative end-of-life management

Continued

TABLE 49-1 **Comparing the Three Great Traditional Healing Systems with Modern Western Medicine*—cont'd**

	UNANI	AYURVEDA	CHINESE	MODERN WESTERN
Some instruments used	Glass cups	Glass cups	Glass cups; acupuncture needles	Ophthalmoscope, laryngoscope, and x-ray; sphygmomanometer; electrocardiogram; chemical tests of body fluids and tissues
Side effects	Overdose of herbal substances; very rare	Overdose of herbal substances; very rare	Potential for acute symptoms from improper needle techniques; overdose of herbal substances; all very rare	106,000 die annually from improper medications; severe and frequent drug reactions;‡ very common
Cancer rates (WHO rates out of 93 countries)	6th lowest	6th lowest	30th lowest	93rd lowest (worst of all)
Annual per capita health care expenses	$9.45 Source: World Bank	$9.45 Source: World Bank	$3.96 Source: World Bank	$1,301.00 Source: World Bank
Common medicines used	Senna pods, black seed, cumin, ginger	Amla; guggul; Bibhitaki; triphala	Ginseng, codonopsis, dang quai, astragalus	Antibiotics, antidepressants, corticosteroids, analgesics
Chief complaints	Nonregulation of practitioners; lack of clinics	Nonregulation of practitioners; lack of clinics	Obtuse language	Adverse reactions; patient dissatisfaction; skyrocketing medical costs
Direction of development	Training practitioners in powers of observation; building schools; sources for formulations	Training practitioners; building schools; develop formulations	Integration with Western hospital medicine	Higher costs; more complex diagnostics; genetic medicine; shaped by new health care reform laws
Typical U.S. $ cost of treatment	$15-$200	$150-$200	$45-$300	$200-$4,000

GI, gastrointestinal; TCM, Traditional Chinese Medicine; WHO, World Health Organization.

*Modified from the American Institute of Unani, Comparison of healing systems. http://www.unani.com/comparison.htm. Accessed April 23, 2012.

†"An Introduction to Panchakarma" by Vasant Lad at http://www.ayurveda.com/pdf/pk_intro.pdf

‡"A 1998 report estimated that 106,000 Americans die each year as a result of adverse reactions to prescription medications. This figure represents three times the number of people killed by automobiles and is the fourth leading cause of death in the United States. Only heart disease, cancer, and stroke kill more Americans than adverse reactions to drugs. This staggering figure does not include drugs administered in error nor those taken as a suicide gesture. If medication errors were included in this statistic, the death toll would probably be as high as 140,000 deaths per year. As a result of 39 separate studies nationwide, it was found that 3.2 out of every 1,000 hospitalized patients die each year as the result of adverse reactions to prescription drugs in each and every hospital in this country. Of the 106,000 people killed each year by an adverse reaction to a prescription drug, 43,000, or 41%, were initially admitted to the hospital because of the adverse drug reaction. The other 59%, or 63,000 patients, were hospitalized for some other cause but developed a fatal reaction to a prescription drug received while hospitalized." (Montague P, National Writers Union, UAW Local 1981/AFL-CIO. Another kind of drug problem. Rachel's Environment & Health Weekly 1999;632 and at http://www.drsuzy.com/summaryInterest.html.)

Ibn Sīna (Avicenna), 980-1037 AD

Abu 'Ali al-Husayn ibn 'abd Allāh ibn Sīna was born in the city of Bukhāra in what is today Uzbekistan. He was the preeminent physician of his time, earning the epithet of "Prince of Physicians." He began studying medicine at the precocious age of 13, became a physician at 16 years of age, attended to kings and princes at 18 years of age, and was appointed as court physician to the ruler of a Persian province at 20 years of age. His literary corpus includes *Kitāb as-Shifā'* (*The Book of Healing*, which was primarily a text of encyclopedic proportions on medicine and philosophy) and *al-Qanūn fi 'l-Tibb* (*The Canon of Medicine*, a one-million-word text summarizing the entire Hippocratic and Galenic traditions and describing the Syro-Arab and Indo-Persian medical practices of his time). *The Canon* quickly was, for several hundreds of years, the standard medical textbook of the Islamic, medieval Christian, and later Indo-Pakistani worlds. Avicenna's *Canon of Medicine* was "a five-volume compendium of Greek and Islamic healing that became one of the principal textbooks in European universities centuries later."[6]

It is from this remarkable polymath that Unani medicine draws its breath of life. Avicenna is perceived by some to be the "Father of Unani Medicine," and his *Canon* its gospel.[2]

Post-Avicennan Medicine

Egypt and Syria: Ibn Nafīs

Ibn Nafīs was born in Damascus and died in Cairo in the twelfth century AD. Ibn Nafīs has only recently gained fame as the rightful discoverer of pulmonary circulation, which was mistakenly thought to have been identified in the 16th century by Michael Servetus. There have been several studies in recent years that incontestably demonstrated that Ibn Nafīs discovered the lesser circulation of the blood before Servetus. See A.O. Soubani's "The Discovery of the Pulmonary Circulation Revisited," in

which this medical doctor and researcher pooled together and summarized a host of earlier literature regarding this hallmark of medical subjects.[4,7]

Spain and Morocco: Al-Zahrāwī (Albucasis) and Ibn Rushd (Averroes)

Abu al-Qāsim al-Zahrāwī (976-1013 AD) is considered to be the greatest surgical figure in Islamic medicine. He was also original in this medical arena in inventing and manufacturing the requisite surgical instrumentation that did not exist, or existed previously in very crude form only, to conduct operations as painlessly and effectively as possible. Some of these instruments of surgery have not changed significantly in design for over 1,000 years. A more comprehensive sketch of the significance of Albucasis in the field of surgery can be found in Kasule.[8]

Abu al-Walīd Muhammad ibn Ahmad ibn Muhammad ibn Rushd[9] (1126-1198 AD) was born in Cordoba, where he trained in law and philosophy, although he made his living as a physician. He wrote his *Kitāb al-Kulliyyāt* (the Latin translator's Colliget, *The Book of General Principles*) in which he covered the whole field of medicine in abridged form.

The Eastern Lands of Islam, Persia, and India: Al-Jurjāni, Nurbakhski, and Dara Shukūh

Isma'īl Sharaf al-Dīn al-Jurjāni followed Avicenna by one generation, producing the most important medical encyclopedia in the Persian language, the *Zakhira-i Khwarizmshahi (Treasury Dedicated to the King of Khwarazm).* The size, as well as the style of the work, places it between Avicenna's *Canon* and Rhazes' *Continens*.

Muhammad Husayni Nurbakhski was a physician of fifth-teenth century Safavid, Persia, who wrote a large medical work entitled *The Quintessence of Experience*. He was the first person to identify and treat several common diseases, including whooping cough.

The sixteenth and seventeenth centuries were the major centuries in which Islamic medicine spread into India and came to be known as al-Tibb al-Yunānī (Unani medicine). One of the major patrons of the medical arts in India during this time was Dara Shukūh, a Mogul prince who was also a Sufi and a student of the Vedanta. ʿAyn al-Mulk al-Shirāzī was responsible, at least in large part, in composing *The Medicine of Dara Shukūh*, which is the last great medical encyclopedia written in the world of Islam.



METAPHYSICAL AND PHILOSOPHICAL FOUNDATIONS

Unani medicine's philosophical underpinnings are tied to the Islamic spiritual tradition. The true and original meaning of the word "philosophy" as "philo-sophia" (love of wisdom) has only accidental affinities to what is termed philosophy in the modern lexicon today. Traditional philosophy as philo-sophia was, and still is, tied to a spiritual vision of humanity and the cosmos.

Epistemology and Ontology

Epistemology and ontology deal directly with the nature of knowledge—what something "is," how it is obtained, and its methods of utilization—and the study of existence or "being." Because Unani medicine is rooted in the Islamic tradition, it is from this spiritual source where one must search for the answers to the questions regarding its theories on knowledge and existence.

Within the Islamic, as well other traditional religious worlds, knowledge has a definite hierarchical structure.* This hierarchy maintains the essential links that exist between Heaven and Earth, between God and humans. First, there exists an acknowledgement of a presiding Divine Knowledge (i.e., God as Wise and All-Knowing). Following this is the knowledge found in Revelation (i.e., a perfect dispensation from Heaven that enlightens the human intellect).† As this revelatory knowledge sparks the heart's depths, it necessarily begins to involve the mind–intellect in its quest for knowledge of this earthly domain ('ilm al-dunya), this physical world.

Ontologically, the "being-ness" of humanity is intimately connected with the Being of God. God is seen as the Supreme Being Alone, without whom nothing can rightfully claim existence for itself. Thus, God's Being is termed Wājib al-Wujūd ("Necessary Being"). In this light, humanity—and everything else in the world of forms—is seen as "borrowing" its existence from the indispensable nature of Divine Being.

Cosmology and the Human Microcosm

The basic cosmologic premise in Islam, as well as in other traditions such as Hinduism, Christianity, and Judaism, is that the Absolute Truth of Divinity (al-Haqq) manifests Itself in the world of forms and within the human heart in a process called the "arc of descent."‡ There is in response to this arc of descent of the Divine a reciprocal "arc of ascent" of the human spirit.[10] These adwār ("arcs" or "cycles") of descent and ascent relate directly to the interdependence of all things on all levels of existence. Everything in creation is perceived as acknowledging, in one form or another, the all-pervading Divine Presence. From the traditional view, the human being is seen as the most concentrated theophany (i.e., a locus of Divine Presence in the world of forms), especially as it concerns the qualities of an active intellect and free will. According to the Hermetic dictum, "As Above, so too below," the human being acts as a mirror to the Divine. Furthermore, the Sufis (the mystics of Islam) have a popular saying that addresses this reality on the cosmic scale: al-insān qawn saghīr wa 'l-qawn insān kabīr ("Man is a small universe and the universe is a large man").

The guiding principle of the dynamic interplay between the Divine Order and the rest of creation is called Tawhīd ("the principle of Divine Unity"). All traditional sciences agree that there exists a dependence of creation on the Divine, an interdependence between all forms in the cosmos, and an intradependence of all

*Professor Osman Bakar has compiled two wonderful studies on the topic of philosophy (including its epistemologic and ontologic dimensions) and its relationship to the traditional Islamic sciences in his books, entitled *The History and Philosophy of Islamic Science* and *Classification of Knowledge in Islam*.[9a,9b]

†The word intellect here is used in its original sense, not as a "fallen word" cut off from its true etymologic source as perceived by many of us in the modern world, but as a word signifying that knowing faculty within the human being that knows immediately and without recourse to analytic or discursive thought, a faculty that is constantly in touch with God. It is precisely this faculty of intellectual intuition that the profound mystic of the German Rhine, Meister Eckhart, described as being the "divine spark" within the human heart that is the seat of all true knowledge and wisdom.

‡There is a famous Qur'ānic verse (41:53) that addresses this claim, wherein the "signs" of God's authorship of creation are known most evidently as *fi 'l-āfāq wa fi anfusihim* ("upon the horizon [of creation] and within their [human] souls").

elements within each specific form. There is an obvious analogy to the profound knowledge found in that sacred oriental symbol of the Tao's Tai Chi ("Supreme Principle of Unity") with the complimenting and harmonizing forces of Yin and Yang. This is also known in Islamic cosmologic language as al-wahdah fi 'l-kathrah wa 'l-kathrah fi 'l-wahdah ("the one in the many and the many in the one").

Unani medicine bases its medical theories of diagnosis and treatment upon this specific understanding of the intradependent relationships that exist between the four humors as it concerns the subtle (latīf) aspects of human physiology and spiritual psychology.*

Teleology and Spiritual Correspondences

The teleologic component of Unani medicine's philosophy entails extracting "meaning" and "purpose" as it relates to the realities of creation and the human experience. To what end is human life? What is the goal of all of creation? Is there a plan of purpose that governs the created order and all of its particular elements?

The Qur'ān explicitly states that inna li 'Llāhi wa inna ilayhi rāji'ūn ("Verily we belong to God, and to Him is our return"). The human race hurls itself forward, in time and space, toward an inevitable reunion with its Creator. It is this understanding of the nature of things that permits traditional Hakīms (the "doctors" of the Unani medical tradition) to find solace in the fact that every patient is ultimately a patient at the doorsteps of the Divine Doctor.

The notion of forcing "heroic" measures upon the sacred human frame is problematic to the philosophical principles upon which Unani medicine is based. This is not to say that surgery and trauma care are perceived in a negative light in Unani medicine. Rather, the question is really one of proportions. The traditional Tabīb ("man of medicine," or physician) always has an eye to the Divine within the human temple. This is really a cultivated virtue that the hakīms practice as part of their art to remain true to the doctrine that "God is everywhere present"; that in keeping with the wisdom of Plato, it is the "eye of the soul" that witnesses "tō Agathōn" ("the Supreme Good"). Therefore, any decision made by a hakīm must include an analysis of risks-to-benefits within the larger ethical framework of the Divine's presence in human life. As a prayerful supplication of عAli, the son-in-law of the Prophet Muhammad and the spiritual pole of Shiite Islam, says: Yā man Ismuka dawā', wa dhikruka shifā' ("Oh Ye whose Name is a sacred medicine, and in whom remembrance of Thee [dhikruka] is a healing balm …").

UNANI MEDICAL THEORY IN PRINCIPLE

Vis Medicatrix Naturae

It is only with the "eye of the heart" ('ayn al-qalb') that the doctors of Unani medicine are able to gain proper intuition of vision concerning the state of the jism al-latīf (the "subtle body") of the patient in whom is found the flowing, dynamic streams of the humors. It is at the level of the subtle body that the hakīm desires to enliven the self-healing power, the vital force, or the vis medicatrix naturae to affect a change in the patient's being in the direction of health and wellness. It is this particular "organizing principle" (al-quwwa al-mudabbirah), as a component of the hidden physiology of the subtle body, that affects a harmonizing reaction in the face of "disease" or illness. One may perceive the Vis as being the thread that holds the fabric of the human body, mind, and soul together in close conjunction with the spirit. This is the general medical theory of the "healing power of nature" that Unani medicine posits as a guiding principle upon which is built more complex specific understandings of human health and disease.

A Personal Thought on the Invisible Vis or Quwwa

I believe that we encounter many opportunities in life that allow us to witness obvious demonstrations of the vis medicatrix naturae. An everyday example of the obvious workings of the Vis is seen when someone gets a paper cut. Many of us have had this experience and have considered it a very irritating situation. However, if we look carefully at what is actually happening, we cannot but assume that the "natural healing instinct" in the human body, when undergoing injury or trauma, is to mobilize mechanisms that will allow for self-preservation and homeostasis, and not disorder. Why should the body even mobilize these mechanisms to begin with? We know to a great degree the science behind these mechanisms, but what we do not know is why these mechanisms should initiate such a nonentropic response. This is still a mystery.

As simple as a paper cut is, it is usually followed by a natural biochemical and physiological inclination towards wound healing (homeostatic repair). We usually never see a paper cut to a finger progressively develop into an open wound, fester with pus and infection, turn gangrenous or necrotic, die, and then have the finger be amputated; this is simply not the natural instinctual response of the human body. In actuality, what we do see happen is the influence of this organizing principle—call it what you may: qi, prana, vis, quwwa, ki, etc.—leading the organism's biochemistry towards a prolife, healing homeostasis, and not a death-inducing "diseased" chaos or disturbance.

There is yet another common example that relies heavily on the signaling of this "power" or "quwwa" for healing, and that is surgery. How many times have we heard what surgeons say after surgery? It usually goes something like "Well, it's now up to the patient to heal" or "I've done all I can, the rest is up to the patient" or "I look forward to seeing you in 1 week in order to see how your hand is healing." What do statements like this really mean? I believe that what is actually being invoked is a subconscious acknowledgement of and reliance upon the Vis. However, because the language of modern conventional medicine does not give this ever-present healing power a name, it is vicariously mentioned under ambiguous terms, phrases, and allusions. All other traditional systems of medicine in the world have a name for this "elephant in the room," as a distinct reality.

The Doctrine of the Seven Naturals

There are hosts of medical systems around the world with their own understanding of what constitutes the primary and basic functional components that cause health to reign or disease to take root, progress, and finally show itself in constellations of signs and symptoms of illness. In Chinese medicine, we have physiologic concepts such as Qi, Blood, Yin, and Yang. In conventional medicine, physiology is dominated with the key concepts of organic issues relating to organ tissue morphology (anatomy) and fluid dynamics (medical biochemistry).

*For a scholarly treatment of this subject, see Seyyed Hossein Nasr's *An Introduction to Islamic Cosmological Doctrines,* Albany, NY: State University of New York Press, 1993.

In Unani medicine, these concepts fall under the strict heading of umūr al-tabīʿiyyah ("principles of natural physiology"), comprised of the "Seven Naturals" that are the pillars and determinants of health. These are as follows:

Elements (arkān)
Temperaments (mizāj)
Humors (akhlāt)
Organs (aʿdāʾ)
Forces, drives, faculties, or powers (quwwāt)
Actions or functions (afʿāl)
Pneuma or spirit substance (rūh)

Elements, Qualities, Properties, and States

The elements are the simple building blocks of matter in nature, including the human body. They are nondivisible, but do have qualities that are both active and passive that determine the states of matter. They are:

Fire (nār), which is hot and dry (hār and yābis): determines energy state.
Air (hawāʾ), which is hot and wet (hār and ratab): determines the gaseous state.
Water (māʾ), which is cold and wet (bārid and ratab): determines the liquid state.
Earth (ardh), which is cold and dry (bārid and yābis): determines the solid state.

These elements do not mean literally clods of dirt, buckets of water, and so forth. "Likewise, the burning fire that we see is not the element fire, which is really the potentiality of fire within the substance."[11]

Temperaments

The interplay between the qualities of the elements leads ultimately to a uniform configuration of a temperament. "Each [Temperament] is named after a certain Humor, and is characterized by the predominance of that Humor and its associated basic qualities."[12] The classical temperaments correlate well to today's psychological constitutional types: choleric, melancholic, phlegmatic, and sanguine. Imbalances of temperaments cause disharmony, especially on the mental and emotional fronts. The following is a concise, but thorough medical depiction of the temperaments (Table 49-2).

Humors

There is no doubt that the principle of the humors (Akhlāt) originated with the "father of medicine," Hippocrates, describing it in his book entitled *Tabīʿat al-Insān*.[13] He observed upon examination of blood that the red portion of fresh blood is the blood humor (Dam) (corresponding to the sanguinous temperament), the white material mixed with blood is the phlegm humor (Balgham) (related to the phlegmatic temperament), the yellow-colored froth on top is the yellow bile humor (Safra) (corresponding to the choleric temperament), and the heavy part that sediments down is the black bile humor (Sauda) (related to the melancholic temperament).[11]

It is important to realize that the humor associated with the blood and called "sanguine" is not identical with the blood drawn by phlebotomy. Nor is the phlegm the same physical phlegm produced by the lungs. Cameron Gruner, MD, called them "quasi-material," or what some have termed "semi-gaseous vapors."[11]

Similarly, Qi is beyond physical or corporeal form. Qi and the Seven Naturals are really and truly best understood as "formless substance," often referred to in the language of philosophy as a Platonic "form" or "idea."* Ultimately, it is understood that true "health is a harmony of [these] humors."[11]

Organs

This component in the doctrine of the Seven Naturals is actually very straightforward. There are four primary organs that the rest of the organs support and whose work they may enlist. These are as follows:

Heart: the seat of vital power and heat
Brain: the seat of sensations and movements
Liver: the seat of all vegetative, nutritive, and eliminative powers
Gonads: the seat of generative capacity for reproduction of the species

The medical traditions of antiquity all agree that when considering an approach that is focused on health, wellness, and prevention, the two most important organs to care for are the liver and the colon. Modern medicine focuses on the heart and the brain, for good reason. "Miracles" occur everyday in emergency rooms, operating rooms, trauma care facilities, burn units, first-line responder ambulance services, life flight transportation services, etc. "In fact, emergency medicine is one of the most legitimate and impressive achievements of [modern] orthodox medicine."[11]

Forces, Energies, Faculties, Drives, or Powers

The ground work energies that animate the Seven Naturals are termed forces or faculties (quwwāt). These forces are the legitimate activating principles for the functioning of the humors. Without the quwwāt there would be no accomplishment of organ function or of anything else. There are primarily three faculties that give rise to a variety of functions. These faculties are:

Natural (as in "from the world of nature") or vegetative faculty (quwwah tabīʿiyyah): governs the nutritive power of the liver and reproductive powers of the generative organs.
Vital or animal faculty (quwwah haywāniyyah): responsible for preserving the integrity of the vital force.
Psychic or soul faculty (quwwah nafsāniyyah): controls the brain and the rational faculty. "It is of significance to note that in Arabic as in many other languages the words for breath (nafas) and soul (nafs) are related. Therein lies a profound cosmological principle which is also related to the invocation of the Name of God (dhikr) as the central technique of Sufism for spiritual realization."[3]

Actions or Functions

Functions or actions (afʿāl) are the manifesting activities of the previously mentioned humoral and organ powers. The functions ultimately are the by-products of the will or power of the humors and organs. For example, the heart's function is to beat; the stomach's function is to receive food and drink and prepare it for further digestive processing; the brain's function is to allow for reception of stimuli with higher functioning allowing for the expression of reason and thought.

Pneumata or Spirits

The spirit (Rūh) is the other-worldly vehicle for the transmission of that divine spark of life force, a heavenly command "which descends upon this mixture of the humors and which is the subtle

*An excellent discussion concerning the notions of "physical," or "corporeal," Platonic "forms" or "ideas," and "energy" or "quantum" entities within the context of many traditional cultural and spiritual knowledge frameworks, can be found in *The Quantum Enigma* and other works by Wolfgang Smith, physicist and Christian scholastic philosopher.

TABLE 49-2 **The Four Different Temperaments**

Sanguine Temperament	
HUMOR	**BLOOD**
Basic qualities	Hot and wet
Face	Oval or acorn-shaped face and head. Delicate, well-formed mouth and lips. Beautiful almond-shaped eyes, often brown. An elegant, swanlike neck.
Physique	In youth, balanced, neither too fat nor too thin. Moderate frame and build. Elegant, statuesque form, with ample, luxuriant flesh. Joints well-formed; bones, tendons, veins not prominent. Can put on weight past 40 years, mostly around hips, thighs, buttocks.
Hair	Thick, luxuriant, wavy. Abundant facial and body hair in men.
Skin	Pink, rosy, blushing complexion. Soft, creamy smooth, luxurious feel. Pleasantly warm to the touch.
Appetite	Quite hearty, often greater than digestive capacity. A predilection for rich gourmet foods.
Digestion	Good to moderate; balanced. Can be overwhelmed by excessive food.
Metabolism	Moderate, balanced. Bowel tone can be a bit lax.
Predispositions	Metabolic excesses of the blood. Uremia, gout, diabetes, high cholesterol. Intestinal sluggishness, putrefaction. Congested, sluggish liver and pancreas. Congested blood, bleeding disorders. Respiratory catarrh, congestion, asthma. Urinary conditions, genitourinary disorders. Excessive menstruation in women. Skin conditions, hypersensitivity, capillary congestion.
Urine	Tends to be rich or bright yellow and thick.
Stool	Well-formed, neither too hard nor too soft.
Sweat	Balanced, moderate.
Sleep	Moderate, balanced, sound. Can be some snoring.
Dreams	Usually pleasant, of a charming, amusing, romantic nature. Travel, enjoyment, games, distractions.
Mind	Faculty of judgment well-developed. A synthetic intellect that likes to see the whole picture. An optimistic, positive mental outlook. Rather conventional and conformist; good social skills.
Personality	Exuberant, enthusiastic, outgoing. Optimistic, confident, poised, graceful. Expansive, generous. Romantically inclined; loves beauty, aesthetics, arts. Sensual, indulgent nature. Sociable, gregarious, light-hearted, cheerful.
Choleric Temperament	
HUMOR	**YELLOW BILE**
Basic qualities	Hot and dry
Face	Broad jaw. Sharp nose, high cheekbones. Sharp, angular facial features. Reddish face common. Sharp, fiery, brilliant, penetrating eyes and head.
Physique	Compact, lean, wiry. Good muscle tone and definition. Prominent veins and tendons. Broad chest common. An active, sportive type. Weight gain usually in chest, arms, belly, upper body.
Hair	Often curly. Can also be thin, fine. Balding common in men. Blonde or reddish hair common.
Skin	Ruddy or reddish color if heat predominates; sallow or bright yellow if bile predominates. Rough and dry, quite warm.
Appetite	Sharp and quick. Soon overcome by ravenous hunger. Fond of meat, fried foods, salty or spicy foods, alcohol, intense or stimulating taste sensations.
Digestion	Sharp and quick. Tendency towards gastritis, hyperacidity, acid reflux. When balanced and healthy, can have a “cast iron stomach,” able to digest anything.
Metabolism	Strong, fast, active; catabolic dominant. Strong innate heat of metabolism. Liver and bile metabolism can be problematic. Digestive secretions strong, bowel transit time short. Adrenals, sympathetic nervous system dominant. Strong inflammatory reactions.
Predispositions	Fevers, infections, inflammation. Hives, rashes, urticaria. Fatty liver, bilious conditions. Hyperacidity, acid reflux, inflammatory and ulcerative conditions of middle GI tract. Headaches, migraines, irritability. Eyestrain, red sore eyes. Purulent conditions. High cholesterol, cardiovascular disorders. Gingivitis. Bleeding disorders from excess heat, choler in the blood. Hypertension, stress.
Urine	Tends to be scanty, dark, thin. Can be hot or burning.
Stool	Tends towards diarrhea, loose stools. Can have a yellowish color, foul odor.
Sweat	Profuse, especially in summer, or with vigorous physical activity. Strong body odor. Sensitive to hot weather, suffers greatly in summer.
Sleep	Often fitful, restless, disturbed, especially with stress, indigestion. Often tends to wake up early or in the middle of the night.
Dreams	Often of a military or violent nature. Dreams of fire, red things common. Fight or flight, confrontation.

TABLE 49-2 **The Four Different Temperaments—cont'd**

Choleric Temperament	
HUMOR	**YELLOW BILE**
Mind	Bold, daring, original, imaginative, visionary. Ideation faculty well-developed. Brilliant intellect, sharp penetrating insight. The idea man who prefers to leave the details to others.
Personality	Prone to anger, impatience, irritability; short temper. Bold, courageous, audacious, confrontational, contentious. Dramatic, bombastic manner; high powered personality. The rugged individualist and pioneer; thrives on challenge. The fearless leader. Seeks exhilaration, intense experiences. Driven, "Type A" personality. Prone to extremism, fanaticism.
Melancholic Temperament	
HUMOR	**BLACK BILE**
Basic qualities	Cold and dry
Face	Square or rectangular head and face. Prominent cheekbones, sunken hollow cheeks common. Small, beady eyes. Teeth can be prominent, crooked or loose. Thin lips.
Physique	Tends to be thin, lean. Knobby, prominent bones and joints common. Prominent veins, sinews, tendons. Muscle tone good, but tends to be stiff, tight. Rib cage long and narrow, with ribs often prominent. Can gain weight in later years, mainly around midriff.
Hair	Color dark, brunette. Thick and straight. Facial and body hair in men tends to be sparse.
Skin	A dull yellow or darkish, swarthy complexion. Feels coarse, dry, leathery, cool. Calluses common.
Appetite	Variable to poor. Varies, fluctuates according to mental or emotional state.
Digestion	Variable to poor; irregular. Digestion also varies according to mental or emotional state. Colic, gas, distension, bloating common.
Metabolism	Often slow. Can also be variable, erratic. Prone to dehydration. Nervous system consumes many nutrients, minerals. GI function variable, erratic; digestive secretions tend to be deficient. Blood tends to be thick. Nutritional deficiencies can cause a craving for sweets, starches. Thyroid tends to be challenged, stressed.
Predispositions	Anorexia, poor appetite. Nervous, colicky digestive disorders. Constipation. Spleen disorders. Nutritional and mineral deficiencies, anemia. Blood sugar problems, hypoglycemia. Wasting, emaciation, dehydration. Poor circulation and immunity. Arthritis, rheumatism, neuromuscular disorders. Nervous and spasmodic afflictions. Dizziness, vertigo, ringing in ears. Nervousness, depression, anxiety, mood swings.
Urine	Tends to be clear and thin.
Stool	Can either be hard, dry, compact; or irregular, porous, club-shaped. Constipation, irritable bowel common.
Sweat	Generally scanty. Can be subtle, thin, furtive, indicating poor immunity. Nervous stress can increase sweating.
Sleep	Difficulty falling asleep, insomnia. Stress, overwork, staying up late aggravates insomnia. Generally a light sleeper.
Dreams	Generally dark, moody, somber, disturbing. Themes of grief or loss common.
Mind	An analytical intellect; detail oriented. Efficient, realistic, pragmatic. Reflective, studious, philosophical. Retentive faculty of memory well-developed. Thinking can be too rigid, dogmatic. A prudent, cautious, pessimistic mental outlook.
Personality	Practical, pragmatic, realistic. Efficient, reliable, dependable. A reflective, stoic, philosophical bent. Can be nervous, high strung. Frugal, austere; can be too attached to material possessions. Serious, averse to gambling and risk taking. Can be moody, depressed, withdrawn. Can easily get stuck in a rut. Excessive attachment to status quo.
Phlegmatic Temperament	
HUMOR	**PHLEGM**
Basic qualities	Cold and wet
Face	Round face; full cheeks, often dimpled. Soft, rounded features. Double chin, pug nose common. Large, moist eyes. Thick eyelids and eyelashes.
Physique	Heavy frame, stout, with flesh ample and well-developed. Often pudgy, plump, or overweight; obesity common. Joints dimpled, not prominent. Veins not prominent, but can be bluish and visible. Lax muscle tone common. Feet and ankles often puffy, swollen. Women tend to have large breasts. Weight gain especially in lower body.
Hair	Light colored, blondish hair common. Light facial and body hair in men.
Skin	Pale, pallid complexion; very fair. Soft, delicate, cool moist skin. Cool, clammy perspiration common, especially in hands and feet.
Appetite	Slow but steady. Craves sweets, dairy products, starchy glutinous foods.
Digestion	Slow but steady to sluggish. Gastric or digestive atony common. Sleepiness, drowsiness after meals common.
Metabolism	Cold, wet, and slow. Conserves energy, favors anabolic metabolism. Congestion, poor circulation, especially in veins and lymphatics. Kidneys slow, hypofunctioning, inefficient. Adrenals and thyroid tend towards hypofunction; basal metabolism low. Metabolic water drowning out metabolic fire.

Continued

TABLE 49-2 **The Four Different Temperaments—cont'd**

Phlegmatic Temperament	
HUMOR	**PHLEGM**
Predispositions	Phlegm congestion. Water retention, edema. Lymphatic congestion, obstruction. Poor venous circulation. Gastric atony, slow digestion. Hypothyroid, myxedema. Adrenal hypofunction. Weight gain, obesity. Frequent colds and flu. Chronic respiratory conditions, congestion. Swollen legs, ankles, feet. Cellulite. Poor tone of skin, muscles, and fascia.
Urine	Tends to be clear or pale and thick. Tends to be scanty in volume, with excess fluid accumulation in the body.
Stool	Well-formed, but tends to be slightly loose, soft. Bowels tend to be sluggish.
Sweat	Cool, clammy sweat common, especially on hands and feet. Sweating can be easy and profuse, especially with kidney hypofunction. Sensitive to cold weather; suffers greatly in winter.
Sleep	Very deep and sound. Tends towards excessive sleep, somnolence. Snoring common; can be loud or excessive.
Dreams	Generally very languid, placid. Water and aquatic themes common.
Mind	Tends to be dull, foggy, slow. Slow to learn, but once learned, excellent and long retention. Patient, devoted, faithful. Faculty of empathy well-developed. Sentimental, subjective thinking. A calm, good-natured, benevolent mental outlook.
Personality	Good natured, benevolent, kind. Nurturing, compassionate, sympathetic, charitable. Great faith, patience, devotion; tends to be religious, spiritual. Sensitive, sentimental, emotional, empathetic. Passive, slow, sluggish; averse to exertion or exercise. Calm, relaxed, takes life easy. Excessive sluggishness can lead to depression.

From Osborn D. The four temperaments. http://www.greekmedicine.net/. Accessed April 23, 2012. Used with permission.
GI, gastrointestinal.

body standing intermediate between the physical body comprised of the humors and the force of life which comes from the world above. It is worth drawing attention to the similarity between the words rūh (spirit) and rīh (the wind or air) in Arabic."[3]

The spirit or rūh in its medical sense is, according to Muslim physiologists, and following Galen, of three kinds:

Vital Spirit: hot and dry, has its centre in the left ventricle of the heart, preserves life, causes the body to grow, move and reproduce, and travels within the arteries.

Psychic Spirit: cold and wet, has its centre in the brain, causes sensation and movement, and moves within the nerves.

Natural Spirit: hot and wet, has its centre in the liver, is concerned with the reception of food, growth and reproduction, and travels within the veins.[3]

Thus, there is an association between physical health and spirituality. "According to some of Avicenna's writings, and in keeping with the Hermetic Tradition, Avicenna sees these natural laws as embodying a component of Divine creative perfection, which to him explains the tendency inherent in natural systems to direct themselves towards a point of … equilibrium."[14]

Another aim towards understanding the physiology and pathology of the doctrine of the Seven Naturals involves answering the question "to what end?" The answer to this has to do with achieving a healthy constitution for every patient by meeting the goals of the six essential causes (of health) (al-asbāb al-sittah al-dharūriyyah)[13]:

- Air
- Food and drink
- Body movement and repose
- Mental movement and repose
- Sleeping habits
- Retention and evacuation

It is these basic causal pillars that ultimately guide the hakīm towards satisfying the criteria for health as set forth by Avicenna himself in his *Canon of Medicine*, which are as follows:[15]

- The complexion of an individual is pleasing with shades and color that are normal to their respective biological environment
- Body build is medium, neither too lean nor too heavy
- Hair is not too profuse nor scanty
- Feel of the body is balanced in respect of heat, cold, moisture, and dryness
- Sleep and wakefulness are moderate
- Movements are free and easy
- Intellectual functions and memory are good
- Habits and behavior are balanced between timidity and assertiveness, anger and calm, leniency, humor, pride, and humility
- Growth and repair is rapid, whereas deterioration is slow
- Dreams are interesting and pleasing
- Enjoys food
- Digests and assimilates normally
- Excretory functions are regular

Techniques of Inquiry and Assessment

Pulse

Unani medicine pulse diagnosis as a science takes tremendous practice and sensitivity to the characteristics of ten physical criteria of the radial pulse[11]:
Quality of expansion (length, width, depth)
Quality of impact (strong, weak, moderate)
Duration of cycle (fast, slow, moderate)
Duration of pause (successive, different, moderate)
Between-beats (full, empty, moderate)
Compressibility (hard, soft, moderate)
Pulse perspiration (full, empty, moderate)
Regularity
Order and disorder (ordered, irregular, irregularly disordered)
Rhythm (similar, different, out of rhythm)

Avicenna's pulse diagnosis was so profound that he even "recognized 'physiological psychology' in treating illnesses involving emotions. From the clinical perspective Ibn Sina developed a system for associating changes in the pulse rate with inner feelings which has been viewed as predating the word association test of Jung. He is said to have treated a seriously ill patient by feeling the patient's pulse and reciting aloud to him the names of provinces, districts, towns, streets, and people. By noticing how the

patient's pulse quickened when names were mentioned, Ibn Sina deduced that the patient was in love with a girl whose home Ibn Sina was able to locate by the digital [pulse] examination. The man took Ibn Sina's advice, married the girl, and recovered from his illness."[16]

Uroscopy, the "Urine Wheel," and the "Alvine Discharge"

Unani medicine demonstrates sophistication in realizing that there is much legitimate insight and wisdom to be gained through the macroscopic study of urine (often termed "uroscopy") and stool. These tissues of the body reveal indexes of the body's internal metabolic terrain and activity. For example, "urine wheels" were used by hakims to forward assumptions about diagnosis or prognosis, treating urine essentially as a "liquid window through which physicians felt they could view the body's inner workings."[17]

"Laboratory medicine began 6000 years ago with the analysis of human urine, which was called uroscopy until the 17th century and today is termed urinalysis. From ancient times until the Victorian era, urine was used as the primary diagnostic tool. Physicians spoke of urine as a 'divine fluid', or a window into the body. Babylonian and Egyptian physicians began the art of uroscopy. Uroscopy, from the word 'uroscopia,' means 'scientific examination of urine.' The word is derived from the Greek 'ouron' meaning 'urine' and 'skopeo', meaning to 'behold, contemplate, examine, inspect'."[17]

Building on the uroscopy and medicine of Galen, "Theophilus Protospatharius, a seventh century physician, wrote De Urinis. This manuscript from Byzantium was the first publication exclusively on the subject of urine."[17] It was later used in the system of Unani medicine and translated for use down through the European Middle Ages.

In Avicenna's system of urine inspection, "important points to be considered in using urine in diagnosis are color, density, turbidity, sediment, quantity, froth, and odor."[15] Of course, one can quickly see allusions in these criteria to even modern macroscopic urinalysis. However, even collection techniques were considered. "Ismail of Jurjani, an 11th century physician, recommended collecting the full amount (of urine) over 24 hours in a large clean vessel and keeping it out of the sun or heat, which could alter color. Ismail also recognized that food and aging altered urine, and required a good night's sleep and empty stomach before collection. He wrote about this in what became the most comprehensive instructional book on urine collection and examination"[17] of his time.

Stool analysis and the patient's history of bowel movements were also tools used by hakīms that allowed for the responsible investigation into the possible causes of illness. Stool has "certain characteristics vis-à-vis color, odor, volume, and consistency," [13] whereas bowel movement history includes "time, duration, and frequency of defecation."[13]

Just to give a brief example, differing stool colors approximate differing illness and imbalances of humors. Hakim Moinuddin Chishti (Robert Thomson, ND) summarized this category of investigation by what stool color signifies from a Unani medicine point of view in his book's section called "The Alvine Discharge"[11]:

- White stool: an obstruction of the passages carrying bile; is seen with jaundice.
- Red stool: reveals the crisis point of a disease.
- Black stool: means high oxidation; maturing of a disease caused by imbalance of the black bile humor; bad sign; presence of blood in small or great quantities, which is a sign of diseases of the liver, intestinal ulcer, or rupture of internal vessels.
- Green stool: indicates diminished internal heat.
- Yellow stool: sign of the imbalance of the yellow bile humor (at the onset of illness); is a sign that the body is eliminating harmful substances (at the resolution of an illness).
- Multi-colored, pus-filled, sticky stool: very grave sign of the degeneration of internal organs.[11]

UNANI MEDICAL THEORY IN PRACTICE

The Practice Framework

Because of the obvious difficulties that confronted personalized physician-to-patient travel and care, Avicenna drew up plans on the centralizing and standardizing of medical operations for the masses in hospitals. "These hospitals kept records of all their patients and their medical care, something done for the first time in medical history."[16]

"From the tremendous impetus of advancement of medicine supplied by Avicenna, the Arabs took the huddled masses of sick and established them in sleek and elegant hospitals. Their hospitals were immense structures with courtyards and had features such as lecture halls, libraries,* mosques and chapels (they treated people of all religious beliefs), charity wards, kitchens, and dispensaries. All patients were attended by qualified male and female nurses. The mood at the magnificent Mansūr Hospital of Cairo is reflected in the following account of the amenities arranged for the benefit of all patients:

'Day and night, fifty reciters intoned the Qur'ān aloud. At nightfall, musicians played soft melodies to induce drowsiness in the patients. Professional storytellers entertained the sick with their tales. When the patients left the hospital, they were given enough money so that they would not have to resume work immediately'."[11]

Furthermore, even before Avicenna's lifetime and progressive influence, "there was a separate hospital in Damascus for lepers, while, in Europe, even six centuries later, lepers were condemned and burned to death by royal decree."[16] The Bimaristans (hospital systems) and smaller "mobile hospitals," which could possibly be regarded as the first ambulances in the world, dedicated to serving under times of civil or community distress, urgency, or emergency,[16] were complex in structure and function.

Therapeutic Modalities

The bridge of therapies, in time and space, between Unani medicine and North American holistic and naturopathic medicine had much to do with the cross-pollinating of research, scholarship, practice, and politics of Europe's (especially old Germany's) "back to nature" movements, which made the trans-Atlantic shift, and became rooted in the medical movements known as Eclectic Medicine,[18] Thomsonian Medicine, the American Medical Vitalism school (which was philosophically opposed to scientific materialism[19]), and the Nature Cure,[20] wherein, like Unani medicine, "the patient is kept close to nature during illness."[13]

*"The library of the Tulum Hospital which was founded in Cairo in 872 AD (1100 years ago) had 100,000 books. Physicians had their own extensive personal book collections, at a time when printing was unknown and book editing was done by skilled and specialized scribes putting in long hours of manual labor. Mustansiriyya University in Baghdad contained 80,000 volumes; the library of Cordova 600,000 volumes; that of Cairo 2 million, and that of Tripoli 3 million books" (see Athar[16]).

Examples of this North American connection with Unani medicine were found in the lives of personalities such as Nicholas Culpeper,* Benedict Lust, Henry Lindlahr, or William Kellog, and their applied therapies. "By the time of the early eighteenth century, the Tibb system was the basis of virtually all medicine in the civilized world, having been translated and formed as the basis of the work of such men as Father Sebastian Kneipp (1821-1897) and Samuel Hahnemann (1755-1843), the founder of homeopathy, who is reputed to have known Arabic and read Avicenna's works."[11] In this regard, it is important to remember that historically:

> *The practical approaches of the Greeks and Romans were the antecedents of the 19th century nature cure pioneers. They were the only forms of medicine available, and, to this extent, naturopathic and orthodox medicine had what Saks describes as "a relatively undifferentiated past." Indeed, both schools of medicine claim Hippocrates as their progenitor. There is no doubt that Hippocrates set many of the principles we hold dear as naturopathic physicians; in particular, the concept of the healing power of nature* (… vis medicatrix naturae)… *Hippocrates advocated dietary adjustments, fasting, physical therapy, rest, and herbal medicines, but even he and his followers were not above using chemical drugs.*[21]

For those who perceive that there is no doubt of Hippocrates' influence on setting the practical and theoretical standards for contemporary naturopathic medicine, then it must hold true that by direct historical relevance—and all that has been stated previously in this chapter regarding this—naturopathic medicine is without question an offspring of the life and thought of the "prince of physicians," Avicenna. It was Avicenna, with his singular intellect, who synthesized and expanded upon all who came before him in his *Canon* and other works, and who handed down humoral medicine, along with its practical therapeutics, to generations of physicians after him.

> *In the late 1950's, a small group of BCNO (British College of Naturopathy, now formally recognized as the British College of Osteopathic Medicine) graduates, medical herbalists, and homeopaths formed the Research Society for Naturopathy to explore a wider range of treatment modalities. They ran seminars on such topics as humoral therapy…*[21]

Food-Based or Dietary Therapies

The objective of dietary therapy (علاج bil ghida) is to properly regulate a patient's appetite, in terms of quality or quantity, to maintain the balance of the humors and strengthen the vital force. This is accomplished by prescribing patients food-based protocols, such as restriction, fasting† (which is an effective, natural process of detoxification and healing[15]), liquid diet, excess eating, semi-solid diet, bland diets, and so on.[13] Attention should be paid to the seasons and the requirements of the body in relationship to the environment as to what foods to recommend, depending on the "degree of effectiveness of types of cereals, of leguminous plants, vegetables, root crops, fruits, types of meat, types of milk, of honey and sweet-meats, of water, of drinks, and [edible] aromatic herbs."[5]

Ultimately, "food is one of the most potent and yet safe instruments of establishing balance in a disturbed organism."[15] This is in line with the Hippocratic proclamation of: "Let food be your medicine and medicine be your food," as well as conforming to the first principle of therapy which stipulates "first do no harm." "It is not accidental that the Andalusian physician Abū Marwān ibn Zuhr in the 12th century wrote the first scientific work on diet ever composed, the Kitāb al-Aghdiyah ("The Book of Diet")."[3]

Pharmacy, Materia Medica, and the Black Seed

Historically, and as far as pharmacology and the materia medica is concerned, among the Arab inheritors of Greek knowledge and wisdom, "it is sufficient to say that Dioscorides was indisputably the greatest authority, that his work was many times translated and elaborated"[5] by scholars such as al-Biruni, Ibn-Bajjah (Avempace), and al-Idrisi (the famous geographer whose maps purportedly influenced the maritime travels and adventures of Christopher Columbus).[22]

The predominant therapeutic modality in Unani medicine is without doubt علاج bil dawā' (pharmacotherapy). Raw material medica resources for this therapy came from the plant (90%), mineral (5%), or animal (5%) kingdoms. As Khan noted, "in treatment the principle that each human being is a reflection of all creation is followed by using a whole range of substances."[15]

Some examples of Unani medicine phytotherapy include the following conditions and their respective remedies (Table 49-3).

The Spiritual Lore and Medicine of the Black Seed. There is no doubt that the most well-known herb used in Unani medicine, and revered by the cultures of the Middle East and Asia, is the black seed (al-habba al-sauda, or al-habba al-barakah ["seed of grace" or "blessed seed"]). It also goes by the scientific name *Nigella sativa*.[23]

The Prophet of Islam specifically mentioned the black seed as he exhorted members of his community to "Use the black seed, which is a healing for all diseases except al-Sām, and al-Sām is Death."[24] With such a pronouncement, one may infer that the Prophet was the prototypic hakīm. This observation is important to note because over 1.2 billion people in the world follow, as closely as possible, the life and thought of the Prophet of Islam.

Thus, the Prophet's statement regarding the black seed elevates and ennobles this plant beyond its investigated scientific benefits.

However, it was posited that "advancements in the methods of analytical chemistry, physiology, pharmacology, and microbiology, etc. have led to the discovery of many active principles of the *N. sativa* [seed] such as nigellicine, nigellidine, nigellimine-N-oxide, thymoquinone, dithymoquinone, thymohydroquinone, nigellone, thymol, arvacrol, oxy-coumarin, 6-methoxycoumarin, and 7-hydroxy-coumarin, alpha-hedrin, steryl-glucoside as well as rich amounts of flavonoids, tannins, essential fatty acids, essential amino acids, ascorbic acid, iron, and calcium.

"The black seed also has a number of pharmacological effects of profound therapeutic value such as analgesic, anti-inflammatory, anti-histaminic, anti-allergic, anti-oxidant, anti-cancer, immune

*"Culpeper was an herbalist who followed the classical medical precepts of Hippocrates and Galen. A medical populist, Culpeper's mission was to put medicine and natural healing back into the hands of the people… Culpeper's best known and loved work is called *A Complete Herbal* [which has been studied and used by many contemporary naturopathic physicians for academic and clinical practice purposes], which has never really gone out of print since it was first published… *A Complete Herbal* is Culpeper's treatise and alphabetical catalog of the medicinal plants of his native England, including their astrological correspondences and indications." See http://www.greekmedicine.net/whos_who/Nicholas_Culpeper.html.

†"Biologically, fasting is an effective, natural process of detoxification and healing" (see Khan[15]).

TABLE 49-3 **Examples of Unani Medicine Phytotherapy**

CONDITION	REMEDY
Fever	Lemon juice with pinch of salt
Constipation	Rose petals with milk
Diarrhea	Amla (*Emblica officinalis*)
Conjunctivitis	Aloe and opium paste
Toothache	Basil leaves paste
Baldness	*Tamarix articulata* in mustard oil
Eczema	Ghee (clarified butter)
Influenza	Long pepper (*Piper longum*)
Asthma	Turmeric powder in milk
Insomnia	Fried cumin seed powder with ripe banana pulp
Menstrual absence	Carrot and black sesame seed cold decoction
Diabetes	Coccinia, Evolvulus, Eugenia, and poppy seeds
Obesity	Guggul gum resin (*Commiphora mukul*) powder

Data from Jamal A, and Qadeer HA. Unani: The science of Graeco-Arabic medicine. New Delhi, India: Lustre, 1998:25.

stimulation, anti-asthmatic, anti-hypertensive, hypoglycemic, anti-bacterial, anti-fungal, anti-viral, and anti-parasitic effects."*

Environmental Regimens

There are primarily three regimental therapies[13] to take advantage of as part of the Unani medical approach:

- Activity (riyādhāt), which usually means some form of voluntary movement or exercise with the purpose of achieving:
 - Organs that perform their functions efficiently
 - Better absorption and assimilation of food and nutrition
 - Clearing of pores in the skin
 - Removal of waste products through the lungs
 - Strengthening the physique
- Massage (tadlīk), which is physical pressure and movement given by another through gentle or aggressive touching, moving, or rubbing of muscles and soft tissues for the purpose of achieving:
 - Bracing the body
 - Relaxation response
 - Decreased body fat
 - Enhanced circulation
 - Good organ function
- Thermarium baths (hammāmāt), which are found around the world. These baths sometimes contain mineral constituents (e.g., sulfur) that leech out of the terrestrial basin holding these waters; the benefits of these hot baths include:
 - Releasing waste products and impurities through the skin
 - Reducing the viscosity of the humors
 - Reducing obesity

Of these regimental therapies, it is without a doubt the hydrotherapeutic hammām (the thermarium) that many people may have either heard of or maybe even experienced firsthand. The hammām is probably more familiar to Western ears as the "Turkish Bath." (There are many medical and recreational resort facilities around the world today that incorporate traditional steam baths in cavernous, underground, or open-air communal systems.)

What follows is an average description of a hammām experience[25]:

> *Traditionally the hammām is made up of a number of chambers with domed white roofs. The 'istirāha' is the 'rest salon,' where visitors are received and un-robed. The inner sanctum of the hammām is usually set down from the istirāha, with further descents into the various steam rooms. The walls of the steam rooms are customarily made from hajar habash (a black stone) which holds heat for a long time. Once you have achieved a good sweat [taʿrīk], you then proceed on to another warm room where the hammāmi greets you.*
>
> *The hammāmi is the person who cleans or exfoliates your body and gives you a [vigorous] massage. One person commented, 'I was pummeled, stretched, twisted like a pretzel, and scrubbed with a floor-like brush for about an hour.' However, you do emerge glowing and gleaming with your metabolism raring and your fat cells pummeled and detoxified. Finally, you are returned to one of the outer chambers, wrapped up in a robe, and led to a cubicle to rest and relax and enjoy a mint tea or juice.*[25]

History records that knowledge of the "medical benefits of the hammām dates back to 200 BC when Hippocrates stated, 'Give me the power to create a fever and I shall cure any disease.' Essentially, the steam bath induces a hyperthermia, which raises the body temperature above normal. Hyperthermia stimulates the immune system by increasing production of antibodies and interferon (an anti viral protein with cancer fighting capabilities). A good healthy sweat can help relieve pain and stiffness of joints and muscles, treat respiratory problems like sinusitis, and ward off symptoms of colds or flu. It is also excellent for detoxification, and especially in conjunction with massage it can reduce cellulite by releasing toxins from fat cells. Also, increased blood flow stimulates metabolism and rejuvenates the skin."[25]

In the West, "hydrotherapy enjoyed a great resurgence in 18th and 19th century Austria and Germany, and was a key part of Father Sebastian Kneipp's system of natural therapeutics, which went on to become the basis for Naturopathy. For example, in many European countries that have hot springs or spa resorts, [hydrotherapy] treatments are a recognized subspecialty of medicine."[26]

Surgery, Cauterization, and Blood Letting

In Manfred Ullmann's *Islamic Surveys II* and Seyyed Hossein Nasr's *Islamic Science*, there are illustrated plates demonstrating a caesarean section[5] from an ancient Arabic manuscript; a plate[5] illustrating the diagrams for surgical instrumentation ("Numerous surgical instruments especially various types of scalpels were developed, some quite elaborate and combining as elsewhere utility and beauty, and most have survived relatively unchanged over the ages with only small local variations."[3]) developed and used by Abu al-Qāsim al-Zahrāwī (known to the West as Albucasis), who was one of the greatest surgeons of antiquity that "took surgery [jarh] out of the hands of barbers and put it into the realm of scientific medicine"[5]; and images of surgical interventions involving hemorrhoidal correction, bone-setting, reductions of dislocations of joints, dental procedures ("Muslim physicians would even make false teeth from the bones of animals[3]), etc.[3] "Surgery was also used by the Arabs to correct cataracts."[27]

Many hakīms accept the fact that today it is probably best to triage the surgical option for patients to modern medical

*The scientific references for all of the most recent scientific literature for the black seed's pharmacologic profile can be found on the second page at http://www.ayubmed.edu.pk/JAMC/PAST/20-2/Editorial.pdf or the article by Dr. Mohammad Akram Randhawa.[24]

school-educated and trained surgeons. The same would hold true for cauterization (kay) (healing through heating or burning of tissue), which today is accomplished with the help of lasers, bloodletting (fasād) (releasing of venous blood to purge toxic or disturbed humoral physiology), and leeching (taʿlīk) (the use of leeches to evacuate "corrupt" blood).[28]

Other therapies such as cupping (hajamāt) and cathartic colonic purgatives (ishāl) are often used hand-in-hand as supportive or adjunct therapies to surgery as well.

Pneumatology, Wellness, and the "Infallible Remedy"

Hakīms were often part of guilds, craft orders, or philosophical schools of thought that were supported by influential political or religious leaders of their time. Also, these guilds were mostly attached to one of the many mystical brotherhoods of Islam, known as Sufi Tarīqahs (which were spiritually or esoterically-oriented "Paths" or "Initiatic Orders" leading to God, realization, and enlightenment for the aspirant).*

A hakīm (male doctor) or hakīma (female doctor) was usually invested in practicing more than just his or her medical science, but also turning their mind, soul, heart, and spirit towards Heaven in pursuit of the perfection of the virtues. The very word hakīm has as its etymological basis words denoting a physician or doctor, as well as an individual who has attained a certain level of spiritual hikmah (wisdom, sagacity, or saintliness) through the practice of the virtues. These virtues are such things as beauty of character, wisdom, respect, and compassion for all of creation, charity through self-sacrifice and altruism, and most important of all, constant "remembrance" (dhikr) of God as Divine All-Possibility.

In this light, there is a natural concern and goal on the part of the hakīm for improving the lot of patients in regard to their mental and emotional well-being, not just caring and tending to the health of the physical body.

Unani doctors have always known that wellness is a state of wholeness, a wholeness that cannot be learned through an academic investigation of health and disease. True wellness is a state of total satisfaction and contentment, a state of understanding that everything is as it should be (otherwise, metaphysically speaking, God would not be God and we would not be we).

Hakīms teach that wellness can be approached through various life lessons, experiential methods, and psychospiritual disciplines. Lao Tzu explained that "at the center of your being you have the answer; you know who you are, and you know what you want."[28] The hakīm will often prescribe a variety of treatments when tending to the soul of a person with guidance ("huda") by precipitating in the patient a profound desire to be a more "balanced, emotionally stable, and successful individual who is able to make better decisions and realize better achievements in life."[16] This is accomplished through the practice of pneumatology (traditional psychospiritual counseling or healing), which includes some of the following subjects:

Prayers (personal, supplicatory, or intercessory).[30]
Meditation (fikr), with breath and sacred sound.[31]
Contemplation or intellection (tasawwur bil ʿaql).[32]
Dhikr (remembrance through repetition of a sacred formula or divine name): This would be very similar to the "Jesus Prayer" or the "Ave Maria" within Orthodox and Western Christianity, as well as the tradition of Japa Yoga within Hinduism.
Recitation of holy scripture: "The Qur'an in its totality, and certain sections and verses in particular, is curative of serious conditions not amenable to other forms of treatment. The methods of using the Qur'an are many: Taʿwīdh ("seeking refuge from harm or evil" with God), Daʿwah ["supplication for help from God"], and Ruqya [reciting sacred verse to a sick person]."[15]
Solitude in nature: We should remember the contemporary resurgence of the direct healing power of nature in the movement of ecopsychology and all that it has to offer.
Visualization.[33]
Music therapy: "In addition to baths, drugs, kind and benevolent treatment given to the mentally ill, musico-therapy and occupational therapy were also employed. These therapies were highly developed. Special choirs and live music bands played daily to entertain the patients by singing, music, and other light-hearted performances."[16]
Forgiveness for self and others.*
Elimination of unhealthy and disturbed attitudes, thoughts, and behaviors such as "arrogance, pride, self-deception, lack of concentration, giddiness, frivolousness, irreverence, degrading others, forgetfulness, fear of failure, hypocrisy, excessive emotionality, severe anger, and being inconsiderate."†
Philosophical counseling.‡
Making pilgrimages to local and international holy sites or cities such as Jerusalem, the Kaʿba, Benares, Angkor Wat, the shrine of our Lady of Guadalupe, Lourdes, Mt. Shasta, Mt. Fuji, etc.[34]

The "Infallible Remedy"

The "Infallible Remedy" is the recitation, in the original sacred Arabic language, of the first chapter of the Noble Qur'ān 41 times for 40 days during the interval between the obligatory canonical dawn prayer and the optional prayer immediately after it. "The Prophet said: 'In Sūrat al-Fātihah there is a balm for all ailments.' He went on to provide the specific instructions for utilizing this most treasured remedy… The accumulated experience of the Sufis confirms that the reading and reciting of Sūrat al-Fātihah with true faith and sincere conviction, cures all maladies, whether spiritual or worldly, external or internal… The Companions [of the

*For more information on the topic of traditional Sufism, please see works by Martin Lings, such as *What is Sufism?*, Seyyed Hossein Nasr's *Sufi Essays*, Titus Burckhardt" *An Introduction to Sufism*, William Stoddart's *Sufism*, and one of the most profound esoteric expositions on Sufism available to the general public, which is Frithjof Schuon's *Sufism: Veil and Quintessence*.

*For an incredible assessment of the various humoral personality types in regard to personality traits, please visit the following website for further information: http://www.intraspec.ca.

†Sometimes physiologic fever is coincident with such disturbances, but according to the Prophet Muhammad (peace be upon him) this type of fever "constitutes a deep spiritual cleansing causing 'the sins to fall off like leaves being shed from a tree.' These fevers burn off impurities on the soul level."[31]

‡"In ancient and pre-modern times, people saw the practical value of philosophy as a guide for living… But then, in the early 1980's, German philosopher Gerd Achenbach decided to revive the old and time-honored practice and offered his services as a philosophical counselor for those seeking to solve their problems philosophically. In 1982, Achenbach founded the Society for Philosophical Praxis to establish philosophical counseling as a profession. Praxis is a Greek word meaning the practical application of a branch of learning — in this case philosophy — to solve life's problems. In classical Greek astrology and counseling, Praxis *also refers to one's career, life path, or calling. Helping clients find their career or life path is a specialty of philosophical counseling.* For further information about this technique of counseling, see Osborn.[29]

BOX 49-1 The "Opening Chapter" of the Holy Qur'an Written in Arabic

1:1 بِسْمِ اللّهِ الرَّحْمَـنِ الرَّحِيمِ

Bismillāhi r-raḥmāni r-raḥīm
In The Name Of Allah, The Most Merciful, The Most Compassionate
1:2 الْعَالَمِين رَبِّ للهِ الْحَمْدُ
Al ḥamdu lillāhi rabbi l-'ālamīn
Praise Be To Allah, Lord Of All Worlds
1:3 الرَّحْمـن الرَّحِيم
Ar raḥmāni r-raḥīm
The Most Merciful, The Most Compassionate
1:4 مَـالِكِ يَوْمِ الدِّين
Māliki yawmi d-dīn
King Of The Day Of Judgment
1:5 إِيَّاكَ نَعْبُدُ وإِيَّاكَ نَسْتَعِين
Iyyāka na'budu wa iyyāka nasta'īn
Thee Alone Do We Worship, And In Thee Alone Do We Trust
1:6 اهدِنَـــا الصِّرَاطَ المُستَقِيمَ
Ihdinā ṣ-ṣirāṭ al-mustaqīm
Guide us to the straight path;
1:7 أَنعَمتَ عَلَيهِمْ غَيرِ المَغضُوبِ عَلَيهِمْ وَلاَ الضَّالِّين صِرَاطَ الَّذِينَ
Ṣirāṭ al-laḏīna an'amta 'alayhim ġayril maġḍūbi 'alayhim walāḍ ḍāllīn
The path of those upon whom you have bestowed your favor, not of those who have earned your anger, nor of those who go astray.

Bismi 'Llāh Al-Rahmān Al-Rahīm
Translation: "In the Name of God, the Most Merciful, the Most Compassionate." This statement, recognizing the sacred and all-embracing nature of the Divine, traditionally begins any and all literature in the Islamic world. It is an affirmation of the long-held spiritual doctrine that the Divine is everywhere and always present. This author chooses to follow the worthwhile literary tradition of respecting the Sacred as the Divine Origin of all truth born into human thought and deed.

Prophet] used to read it for treatment of diseases, both physical and mental."[31] If, for whatever reason, one cannot accomplish this level of intensity or precision in the recitation of the Opening Chapter of the Holy Qur'ān as methodically instituted and practiced by the Prophet of Islam himself, then "simply recite 11 times: Bismi Llāh ir-Rahmān ir-Rahīm ["In the Name of God, the Most Merciful, the Most Compassionate."]."[31]

The Opening Chapter of The Qur'an is in Arabic, translated and transliterated. This allows those who do not read Arabic to simply pronounce the words and phrases, and thus benefit from the sacred sonorous quality of the recitation as it surrounds and penetrates the human body and its immediate environment with theurgic energy and influence from Above.

Clinical Quick Notes

The function of this section discusses a few condition-specific protocols that are true examples of the diagnostic and therapeutic paradigms of Unani medicine. These cases and the pursuant tables will illustrate the clinical mind-set and logic of a hakīm or hakīma in their traditional mode of prescriptive authority.[11,31]

Lethargy (Chronic Fatigue)

"Its cause is the prevalence of moisture in the brain, brought on either by phlegm or by blood. Use an enema. Make the person smell vinegar and feed him only light, easily digested foods."[11]

Melancholy (Sadness, Low Mood, or Depression)

"It is caused by an imbalance of the phlegm humor. Use an enema at waking and at bedtime. Eat only soft foods. Sexual intercourse has a remarkable effect in removing melancholy."[11]

Tinnitus (Ringing in the Ears)

"Detoxification of the system should be accomplished first, along with relaxation techniques. However, it has been determined that those who suffer from a constant ringing in the ears continue to 'hear' the sound even if the auditory nerve is severed…"[11]

Nosebleed

"A nosebleed can be controlled by cupping the back of the head. If blood is coming out of the right nostril only, also apply cupping to the area of the liver. Apply cupping over the spleen if there is blood coming out of the left nostril only."[11]

Asthma

"If the cause is phlegm, then the remedy is to first eliminate all foods that produce mucus, such as milk, eggs, cheese, fruits, and all sugars of any kind. Syrup of hyssop with warm water three times a day is recommended after a bout with asthma. Rub the chest with linseed oil and beeswax… If the cause of the asthma is too much internal heat affecting the lungs, then the remedy pursued should be with cold drinks and a cucumber pomade on the chest… Gargling with milk and cinnamon with honey added is also recommended."[11]

Coughing

Black Bile. A blackish or dark greenish substance comes out when coughing. Give boiled wheat bran with sugar or honey.

Cough Powder. "This remedy relieves general irritation of the throat and lungs. Use 1/8th teaspoon (in all) of each of the following; skunk cabbage, horehound, African cayenne, bayberry bark, valerian root, and gentian; mix with three ounces molasses, and take 1 teaspoon with hot tea."[11]

Unani Medicinal Herbs Used to Treat Diabetes

Plant species and preparations of Unani medicinal herbs used to treat diabetes, as well as additional uses, are listed in Table 49-4.

Unani Medicinal Herbs Used to Treat Skin Diseases

Plant species and preparations of Unani medicinal herbs used to treat skin diseases, as well as additional uses, are listed in Table 49-5.

SUMMARY

The hakīms of ancient times were persons of tremendous insight and wisdom, both in theory and in practice, inheritors of ancient Greek knowledge, and players on the stage of world history that ultimately allowed for the birth of many aspects of modern medicine. A very brief and pointed summary follows as an example of what is meant, in the best sense of the phrase, by the statement that "knowledge is power."

- Avicenna was the first to describe meningitis so accurately and in such detail that the description has scarcely been added to after 1,000 years.
- Avicenna was first to describe intubation (a surgical procedure to facilitate breathing that Western physicians began using only at the end of the eighteenth century).
- The use of plaster of Paris for fractures by the Arabs was standard practice; it was "rediscovered" in the West in 1852.
- Surgery was used by the Arabs to correct cataracts.
- Ibn Al Nafis discovered pulmonary circulation.

TABLE 49-4 **Unani Medicinal Herbs Used to Treat Diabetes**

PLANT SPECIES	PREPARATION	ADDITIONAL USES
Astragalus macrocarpus DC	Leaf decoction	Heart disease
Ceratonia siliqua L.	Leaf decoction	Herpes and lip sores
Cichorium pumilum Jacq.	Foliage decoction	Bacterial infection, poisoning, and rheumatism
Cupressus sempervirens L.	Fruit decoction	Antiseptic and nervous system
Eryngium creticum Lam.	Foliage decoction	Liver diseases, poisoning, anemia, and infertility problems
Juglans regia L.	Leaf and flower decoction	Asthma and sexual weakness
Lupinus varius Gaertn	Soaked seeds	Kidney stones
Mercurialis annua L.	Leaf decoction	Cancer and skin diseases
Morus nigra L.	Leaf, stem, and fruit decoction	Teeth or gum inflammation and cholesterol
Paronychia argentea Lam.	Leaf and flower decoction	Stones in kidney and heart diseases
Pinus halepensis Mill.	Leaf and seed dedoction	Sexual weakness
Prosopis farcta Sol. Ex Russell	Foliage decoction	Menstrual cramps and kidney stones
Quercus calliprinos Decne	Fruit and bark decoction	Cancer, bed wetting, and ulcer
Salvia fruticosa Mill.	Foliage infusion	Stomachache, intestinal gas, and inflammation
Sarcopoterium spinosum L.	Leaf, seed, and root decoction	Intestinal pain, kidney diseases, and ulcer
Smilax aspera L.	Fruit and root decoction	Poisoning
Teucrium polium L.	Foliage decoction	Kidney stones, liver diseases, and stomach and intestinal inflammation
Trigonella foenum-graecum L.	Seed decoction	Sexual weakness and stomach and intestinal pain

Data from Azaizeh H, Saad B, Khalil K, Said O. The state of the art of traditional Arab herbal medicine in the eastern region of the Mediterranean: a review. Evid Based Complement Alternat Med 2006;3:229-235.

TABLE 49-5 **Unani Medicinal Herbs Used to Treat Skin Diseases**

PLANT SPECIES	PREPARATION	ADDITIONAL USES
Alcea setosa Boiss.	Leaf, flower, and root decoction	Stomach and intestinal pain, inflammation, and asthma
Ammi visnaga L.	Flower and seed decoction	Kidney inflammation and respiratory system (asthma)
Asphodelus microcarpus Salzm. and Viv.	Bulb and root juice	Ectoderm parasites and jaundice
Cyclamen persicum Mill.	Leaf and bulb decoction	Ear infections
Eruca sativa Miller	Seed oil	Sexual weakness and hair loss
Ficus sycomorus L.	Stem milky sap	Coughing, digestive system, and anemia
Glaucium corniculatum L.	Poultice of macerated roots	Cholesterol and acne
Inula viscosa L. Ait. Inula	Foliage macerated in oil	Muscle relaxation and infertility
Lavandula officinalis Chaix and Kitt	Leaf, flower, and seed infusion	Urinary system, asthma, and nerve system
Lycium europaeum L.	Root decoction	High blood pressure and diabetes
Malva nicaeensis All.	Whole plant decoction	Coughing and wounds
Myrtus communis L.	Leaf infusion	Stomach or intestinal pain and inflammation
Paronychia harmala L.	Seed infusion in olive oil	Wounds and lice
Sanguisorba minor Scop.	Whole plant decoction	Ulcer, burns, and wounds
Saponaria mesogitana Boiss.	Root decoction	Liver diseases, stones in kidneys, and joint inflammation
Scolymus maculatus L.	Stem decoction	Intestine and kidney inflammation
Solanum nigrum L.	Foliage decoction	Wounds and sun burn
Tamarix aphylla L. H. Karst.	Leaf decoction	Eye inflammation and fever
Thymelaea hirsuta L. Endl.	Foliage paste	Couching and respiratory system
Viola odorata L.	Foliage decoction	Respiratory system, stomach and intestinal inflammation

Data from Azaizeh H, Saad B, Khalil K, Said O. The state of the art of traditional Arab herbal medicine in the eastern region of the Mediterranean: a review. Evid Based Complement Alternat Med 2006;3:229-235.

- A strict system of licensing for medical practitioners was introduced in Baghdad in 931 AD, which included taking the Hippocratic Oath and specific periods of training for doctors.
- There was a system of inspection of drugs and pharmaceuticals—the equivalent of the U.S. Food and Drug Administration—in Baghdad 1,000 years ago.
- The European system of medicine was based on the Arabic system, and even as recently as the early nineteenth century, students at the Sorbonne had to read the *Canon of Avicenna* as a condition for graduating.
- Unani-Tibbi hospitals were, from the beginning, free to all without discrimination on the basis of religion, sex, ethnicity, or social status.
- Unani-Tibbi hospitals allocated different wards for each classification of disease.
- Hospitals had unlimited water supplies and bathing facilities.
- Before the advent of the printing press, there were extensive handwritten libraries in Baghdad (80,000 volumes), Cordova (600,000 volumes), Cairo (2 million volumes), and Tripoli (3 million volumes).
- All Unani-Tibbi hospitals kept patient records.
- A hospital was established for lepers. As many as six centuries later in Europe, they were still burning lepers to death by royal decree.
- In 830 AD, nurses were brought from Sudan to work in the Qayrawan hospital in Tunisia.
- A system of fountain-cooled air was devised for the comfort of patients with fever.
- Avicenna described the contamination of the body by "foreign bodies" before infection, and Ibn Khatima also described how "minute bodies" entered the body and caused disease—well in advance of Pasteur's discovery of microbes.
- Al Razi was the first to describe smallpox and measles. He was accurate to such a degree that nothing has been added since then.
- Avicenna described tuberculosis as being a communicable disease.
- Avicenna devised the concept of anesthetics. The Arabs developed a "soporific sponge" (impregnated with aromatics and narcotics and held under the patient's nose), which preceded modern anesthesia.
- The Arab surgeon, Al Zahrawi, was the first to describe hemophilia.
- Al Zahrawi was also the first surgeon in history to use cotton, which is an Arabic word, as surgical dressings for the control of hemorrhage.
- Avicenna accurately described surgical treatment of cancer, saying that the excision had to be radical and remove all diseased tissue, including amputation and the removal of veins running in the direction of the tumor. He also recommended cautery of the area if needed.
- Avicenna, Al Razi, and others formed a medical association for the purpose of holding conferences so that the latest developments and advancements in the field of medicine could be debated and passed on to others.*

So it seems ironic that "what began as an advanced medical system that set world standards has now come to be regarded as a system of folk medicine. This decline coincided with the decline of the Islamic Empire and the dissolution of the Caliphate, as these were directly responsible for the direction and impetus of Islamic scientific scholars in all fields."[27]

The decline of this ancient system of medicine also proves, if proof be needed, that "the achievements of the Unani-Tibbi practitioners of today bear little resemblance to those of their illustrious predecessors, and some of those claiming to practice traditional medicine are woefully ill-equipped"[27] to do so. Most individuals passing themselves off as Unani practitioners today would be labeled by most primarily as folk healers or country herbalists, but not hakīms of the Avicennan-type.

Today, it is in the Indo-Pakistani subcontinent or, more generally speaking, the sub-Himalayan regions of the Orient, that Unani medicine continues to thrive as a living school of medicine, competing with three other systems of health care: Ayurveda, Traditional Chinese Medicine, and modern Western medicine. Although current modern "Western antipathies to things-Arabic and Muslim"* seem to have stalled the advance of Unani medicine into the stadium of complimentary and alternative therapies in the West, it is slowly and gradually gaining ground as an optional health care system for many patients.

In India, the government has set up a Central Council for Research in Unani Medicine, which also has a licensing system for traditional practitioners.[27] India has 18 colleges of Unani medicine, about 100 Unani hospitals, and nearly 1,400 beds for inpatients. In addition, there are nearly 900 dispensaries of Unani medicines and about 30,000 registered practitioners. The number of persons serviced by Unani medicine, in India alone, is estimated to be at least 23,000,000 from over 220 villages.[36] Unfortunately, details of the overall medical situation in Pakistan and other countries are not as well known or are simply not available.[37]

One commentator wrote, "Since both Ayurveda and Greek Medicine are constitutionally based, it's not surprising that improving basic constitutional strength, resilience and resistance to disease should be a very important therapeutic objective in both systems. The methods and modalities employed are also quite similar: diet is first and foremost, followed by simple herbal remedies, lifestyle modification, massage and bodywork, hygienic purification treatments and exercise/gymnastics/yoga. Being humor-based, both systems consider self-poisoning, or auto-intoxication with toxic metabolic residues and superfluous morbid humors to be the primary cause of all disease and pathology, for which they prescribe various hygienic purification treatments and regimes. The Ayurvedic word for toxins, 'ama,' means, 'crude' or 'raw' - residues from faulty or incomplete pepsis that haven't been properly integrated into the body and its functioning, and therefore impede it. The word ama has its equivalent in the word 'crudities,' a common term for toxins in Greek Medicine."[38]

In the humble opinion of this author, there is no better time than the present in discovering the beauty and mystery of Unani medicine. This gift from the East—along with Ayurveda and Traditional Chinese Medicine—will reveal itself to serious seekers as a very real health care option offering natural, safe, and effective approaches to healing.

*From Fundukian LJ. Gale Encyclopedia of Alternative Medicine. 3rd ed. Detroit, MI: Gale, a part of Cengage Learning, Inc; 2008. Reproduced with permission. www.cengage.com/permissions.

*This was part of a statement made by Dr. Paul Bergner in an e-mail correspondence to an inquirer regarding the issue of Unani medicine.[35]

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SECTION 4

SYNDROMES AND SPECIAL TOPICS

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Careful study of the various diseases to which humans are heir indicates that a limited number of underlying problems either cause or significantly contribute to most diseases. The reductionist philosophy underlying most of modern medical research and practice results in better diagnosis and progressively more specific therapies for a given disease, but makes recognition of broad patterns of disease causation extremely difficult.

We believe the reader will find the syndromes discussed in this chapter interesting, relevant, and a compelling inducement for developing a more holistic approach to patients. Old-fashioned ideas such as "bowel toxemia" and "liver toxicity" not only are intuitively reasonable but now have solid scientific evidence to support their validity. As one reads the chapters in this section, a compelling concept of medicine emerges:

Poor diet + unhealthy lifestyle + toxin exposure

↓

Nutritional deficiencies + toxicity

↓

(In the context of genetic susceptibility)

Metabolic dysfunction + subacute disease

↓

Clinically recognizable diseases that are apparently unrelated to the underlying causes

CHAPTER 50

Cancer—Integrated Naturopathic Support

Paul Reilly, ND, LAc, FABNO

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DIAGNOSTIC SUMMARY

Cancer is not a single disease. It is a group of more than 200 individual diseases all characterized by uncontrolled growth, proliferation, and spread of abnormal cells. Diagnosis and treatment strategies vary depending on the type of cancer cells and their location, the extent of total tumor burden, the health and performance status of the patient, and previously administered treatments, as well as consideration of which conventional treatment regimens are currently considered the "standard of care."

GENERAL CONSIDERATIONS

Defining the Problem

One million four hundred thirty-seven thousand new cases of cancer were diagnosed in the United States in 2008, not including basal and squamous cell type skin cancers. The most common cancers are lung (214,000 cases), prostate (186,000 cases), breast (182,000 cases), and colorectal (148,000 cases). More than 562,000 cancer patients will die of this disease this year.[1]

The extent of the problem is reflected in the following sobering statistics:

- Cancer will affect one in three persons alive today.
- Cancer causes one in five deaths in the United States.
- Half of those diagnosed with cancer will eventually die of their disease, even with the best treatment available today.

The Role of Naturopathic Medicine

Naturopathic medicine has a role to play in each stage of cancer care. The simplest description of these stages can be generalized to include:

1. Primary prevention and risk reduction
2. Screening and early diagnosis
3. Integrative co-treatment during active cancer therapies
4. Post-treatment recovery support
5. Long-term secondary prevention

Prevention should obviously take precedence over treatment. The occurrence of disease is generally thought to involve two compounding factors, genetic susceptibility and environmental exposure to carcinogens. Research studies following 90,000 twins in Scandinavia suggested that lifestyle and environmental factors contributed more than half of the risk to the 11 most common cancers.[2] Naturopathic medicine can help patients to reduce most lifestyle-based risk factors and even counteract some genetic risk factors. Cancer has a long latency period and reducing risk factors, including diet, lifestyle, and environmental toxins, can either delay or prevent progression from preclinical cancer to clinical cancer. An example of the ability to reverse early cancer is demonstrated by studies comparing women who received annual mammography screening versus less frequent screening. Those who had less frequent screening actually had approximately 20% less breast cancer, leading the authors to determine that the lower diagnosis rates reflected spontaneous resolution of up to 20% of cancers.[3] Newer genetic tests and metabolic tests can identify risk factors for cancers. Many of these reflect metabolic aberrations that reduce DNA repair or increase abnormal cell signaling. Early identification can allow for correction or amelioration

of these risk factors with dietary, lifestyle, and supplemental modification. An example of this would be the link between hyperinsulinemia and breast cancer. Early identification of hyperinsulinemia can reverse the predisposing condition and reduce the risk of ever developing breast cancer. Even genetic factors are at least partially responsive to modification. This was demonstrated in a study looking at the incidence of breast cancer in carriers of the BRCA gene. Those women who lost 10 or more pounds between the ages of 18 and 30 had up to 65% lower risk of developing breast cancer between the ages of 30 and 40.[4]

As primary care providers, a focus on regular screening and sensitive diagnostic testing is necessary to detect some cancers in their early stages when they are more curable. Some types of cancer, like pancreatic cancer, are difficult to screen successfully. Once cancer has been diagnosed, the need for the support of naturopathic medicine both during and after treatment should be recognized. The roles that naturopathic medicine can play include, but are not limited to, the following:

- Help guide the patient in selecting the best oncology care team and facility
- Reduce the side effects of conventional therapies during active treatment
- Improve tumoricidal activity of conventional therapies to maximize benefit
- Change the environment that allowed the growth of the tumor (remove tumor promoting factors such as hyperinsulinemia, nutrient deficiencies, exogenous hormones, smoking, etc.)
- Support the patient metabolically while starving the tumor
- Slow or arrest abnormal cell division
- Promote normal cell differentiation and apoptosis
- Reduce metastasis and angiogenesis
- Enhance cell-to-cell communication and intracellular signaling
- Use natural antitumor, proapoptotic agents
- Block hormonal stimulation of tumors through normalizing hepatic clearance of hormones
- Support a healthy immune response
- Support secondary prevention for the patient after completing active treatment
- Deal with death and dying for those who eventually succumb to their disease
- Encourage primary prevention and aggressive screening for family members of the patient

This chapter addresses all of these roles. As in any specialty of medicine, there are terms and language specific to the practice of oncology. A brief review is included to help the reader understand discussions in clinical reports, textbooks, and research on oncology literature.

Cancer Overview

What Is Cancer?

Cancer is a general term applied to a group of diseases characterized by cells that have undergone a number of mutations, altering them from their normal phenotype. The normal healthy, mature, fully differentiated cell is responsive to a series of regulatory signals that limit cell division and invasiveness, whereas cancer cells are marked by insensitivity to a wide variety of extracellular and intracellular signaling, leading to alterations of behavior.

Transformation of a healthy cell into a cancerous one is a multistep process involving multiple mutations to cellular DNA over time. Recent research suggests that epigenetic alterations can also affect which portions of DNA are active or inactive, and can have an impact on cancer risk without actually requiring alteration of the underlying DNA.

The alteration of a healthy cell into a malignant one begins when mutations lead to an alteration of the ratio between cell growth and cell death, sometimes described as hyperplasia. The next stage is development of changes in cellular architecture, known as dysplasia. As the cell further mutates, it becomes a premalignant cell or carcinoma in situ. When sufficient mutations have accumulated, the cell crosses a border into the realm defined as cancer. These mutations generally include development of self-sufficiency in growth signals, insensitivity to normal antigrowth signals, evasion of normal apoptotic processes, limitless replicative potential, sustained angiogenesis, and loss of the need for basement membrane contact. The combination of these mutations produces cancerous cells. Further mutations allow the cancerous cells to develop the ability to perpetrate tissue invasion and metastasis.[5]

These processes are sometimes divided into three stages: initiation, promotion, and progression. Initiation is the stage of damage to cellular DNA, leading to mutations that eventually result in the original development of a cancerous cell. The promotion stage is the stage where factors in the cellular environment, such as free radicals, xenobiotic chemicals, and hormones "feed" the cancerous cell, allowing it to grow into a tumor. The progression stage is when a tumor continues to grow and then begins to metastasize and spread to other parts of the body.

The Cell Cycle

Normal cell division proceeds in an orderly manner through a series of phases. Each phase is characterized by certain chemical and genetic processes, and each must proceed properly for cell division to occur. The orderly succession in the cell cycle is controlled by a group of molecules known as cyclins and cyclin-dependent kinases that regulate the entrance into each phase of the cycle. The cell cycle is usually divided into four or five phases as follows:

G0 phase: This is the resting state, also known as the gap phase. Many cells spend most of their time in this phase and are either at rest or performing their assigned duties in the body. Cells in this phase are generally resistant to most types of chemotherapy.

G1 phase: This is also known as the gap 1 phase or the interphase. In this stage cells begin to synthesize RNA and to prepare for cell division.

S phase: This is also called the synthesis phase because the cell begins to duplicate the DNA in preparation for creating a daughter cell.

G2 phase: This is also called the gap 2 phase. In this phase DNA synthesis has been completed, and the microtubule members of the mitotic spindles are produced.

M phase: This phase, also known as mitosis, is the stage at which all the previously produced DNA and cellular proteins are divided into two daughter cells. After completing this phase, most cells return to the G0 or resting phase (Figure 50-1).

Certain chemotherapeutic agents work best in particular phases of the cell cycle. A rough breakdown is as follows:

- G1: Asparaginase
- S phase: antimetabolites, Procarbazine, Topotecan, and topoisomerase I inhibitors
- G2 phase: Etoposide, Bleomycin, Taxol, and topoisomerase II inhibitors
- M phase: vinca alkaloids and taxanes

Types of Cancer

Carcinomas are cancers deriving from cells of epithelial origin. Most common cancers, including breast cancer, prostate cancer, lung cancer, colon cancer, and melanoma, are carcinomas.

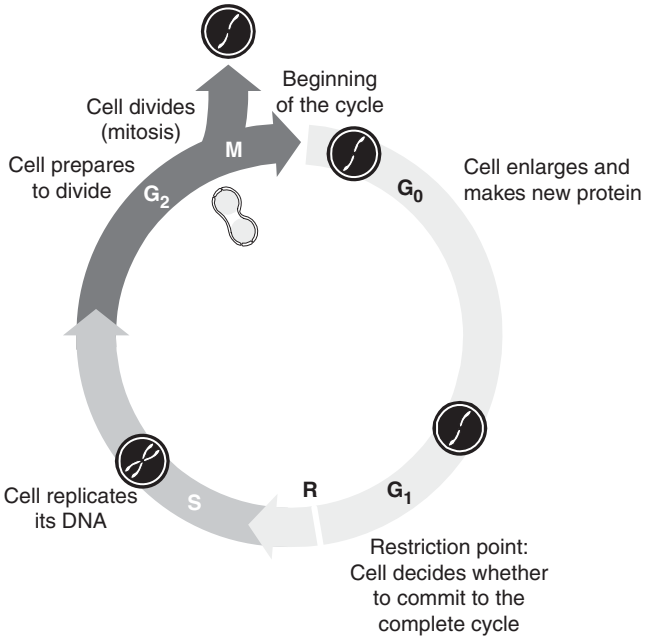


FIGURE 50-1 The cell cycle.

Sarcomas are cancers derived from cells of mesenchymal origin, such as bone, muscle, or fibrous tissue. Sarcomas can be further divided into those of bone origin and those derived from soft tissues. Examples include osteosarcoma and leiomyosarcoma.

Leukemias are cancers derived from white blood cell–producing tissues, such as the bone marrow. Leukemia types include chronic lymphocytic leukemia, chronic myelogenous leukemia, acute lymphocytic leukemia, and acute myelogenous leukemia. Other less common subtypes are not discussed due to space constraints.

Lymphomas are malignancies that develop in the lymphatic system. Most arise in lymph nodes. Lymphomas are generally divided into Hodgkin's disease and non-Hodgkin's lymphomas. Non-Hodgkin's lymphoma can be further subdivided by types of cells involved (e.g., T cell or B cell); physical form (e.g., follicular, diffuse, mantle cell); and their degree of indolence or aggressiveness.

Staging

Staging is a process of determining the extent of spread of disease. The purpose of staging is to provide information that can be used in making treatment decisions, evaluating responses, and making survival prognoses.

Most staging is based on the anatomic spread of disease, but certain cancers have other characteristics that affect staging. For example, in colon cancer, the depth of penetration through the wall of the colon is important in the staging of the disease.

A complete staging description should include information about the tumor and the host. Information necessary for staging includes origin of the tumor, as well as histologic type and grade. The extent of the spread of tumor and locations of metastatic lesions should be described, as well as the functional status of the patient.[6] The first step in staging is determination of the TNM rating. The TNM score gives a relatively precise description of the size of the tumor (T), the number of involved lymph nodes (N), and the presence or absence of distant metastatic disease (M). Each type of cancer has slightly different criteria for each characteristic, but in general one can expect a T1 lesion to be smaller, usually less than 1 or 2 cm, whereas a T4 lesion is larger and often extends into local tissues. Lymph node staging generally begins with N0, which signifies no nodal involvement detected; to N1, which signifies limited nodal involvement; on up to N3, which signifies involvement of distant nodes. The metastatic rating is limited to M0 for no detectable metastases or M1, which indicates positive findings for any metastatic disease. For example, the description of a breast cancer that has a primary tumor 2.5 cm in size, with positive lymph nodes in the ipsilateral axilla and no detectable metastatic lesions, would be T2,N1,M0.

After establishing a TNM score, the information can be simplified into a "Stage," the term with which most patients are familiar. Once again staging varies with cancer type but generally follows a pattern. Stage 0 is in situ or noninvasive disease. Stage I is small localized disease. Stage II generally is somewhat larger disease but still localized, perhaps involving a small number of local lymph nodes. Stage III disease is regionally advanced, and Stage IV is advanced metastatic disease. Note that staging is generally written using Roman numerals.

Description of the host characteristics include basics such as age, physical condition, comorbidities, etc., but should also include predisposing factors that can impact prognosis. Examples include hyperinsulinemia; immune status; redox function; risky behaviors such as smoking, or nutrient deficiencies or excesses; and more.

Doctors use TNM and staging information to help make decisions regarding the aggressiveness of treatment to suggest for the patient, as well as to answer general questions about prognosis. The two types of staging are (1) clinical staging, which is based on physical examination, radiographs, ultrasounds, and computed tomographic (CT) scans, and (2) surgical staging (also known as pathologic staging), which can determine the ultimate accuracy of the clinical staging. Often the staging is upgraded to the next level during surgery when it is found that the disease has extended farther or more lymph nodes are involved than were detectable on the clinical staging scans. In some cancers, surgical staging allows the final determination. In the example of colon cancer, this is because determination of the depth of penetration through the wall of the colon is critical to analysis.

Full details on the staging of all cancer types are available in reference manuals published by the American Joint Commission on Cancer and by the International Union Against Cancer. Simplified details are available in most textbooks on oncology.

Tumor Markers

Tumor markers are a group of proteins that can be measured in the blood to indirectly evaluate progression of cancer. These proteins are normally expressed in healthy tissue in small amounts, but the amount secreted is frequently increased in malignant tissue. Common examples of these would be markers like the prostate specific antigen (PSA) for prostate cancer, carcinoembryonic antigen for colon cancer, and CA 125 for ovarian cancer.

Although these markers can be useful in disease management, there are several caveats in their use. First, most are not considered useful as screening tests for cancer. This is because not all cancerous tissue expresses large amounts of the proteins and because the line between normal levels and cancerous levels is still under debate. Noncancerous tissue can also secrete higher amounts of these markers in conditions such as inflammation and infection. For example, many men with an elevated PSA have prostatitis or benign prostatic hypertrophy rather than prostate cancer. At the same time, up to 30% of men with prostate cancer show normal levels of PSA at the current normal range.

The second caveat is that although tumors have "classic" markers, they may express a different marker than that which is

TABLE 50-1 **Common Tumor Markers**

TUMOR MARKER	TYPICAL TUMOR TYPES
Carcinoembryonic antigen	Colorectal, breast, small cell lung
Prostate-specific antigen	Prostate, some breast
CA 15-3	Breast
CA 19-9	Pancreas, hepatic, biliary, gastric, colon
CA 27-29	Breast
CA 125	Ovarian
β-HCG	Testis, trophoblastic neoplasia
β 2 microglobulin	Multiple myeloma, lymphoma
Thyroglobulin	Thyroid

HCG, human chorionic gonadotrophin.

typically found in a tumor type. For example, a breast tumor may occasionally express PSA rather than the typical CA 27-29. This reflects the fact that tumor cells have become less differentiated and therefore less typical of their original cell type, and during this process they may begin to develop characteristics of other cells.

Tumor markers are most useful in monitoring response to a treatment or progression of disease. The direction and rate of change enable the provider to assess efficacy of treatment. It is often helpful to measure tumor markers before a patient has a tumor surgically removed to determine if there is a viable marker to follow for later evaluation. If the patient has a large tumor but all tumor markers are negative, there is less reason to follow those markers as a sign of recurrence after treatment. Table 50-1 lists common tumor markers and diagnoses.

The raw number of a tumor marker is generally less important than the direction of change. One person with a low tumor marker may have a larger disease burden than another patient with a higher tumor marker due to differences in the biology of their cancer. However, if the tumor marker drops, the assumption can be made that treatment is working. Conversely, if the marker rises, the assumption is that the current treatment plan needs modification.

Performance Indexes

Oncologists use a series of performance indexes to indicate the level of a patient's health. The most commonly used indexes are the Karnofsky and Eastern Cooperative Oncology Group (ECOG) scores. These indexes are based on the patient's ability to perform daily activities, need for assistance, and need for medical treatment. Such tools are useful because they reflect the level of vitality remaining in a patient and suggest a potential ability to withstand and respond to further treatment. Two patients with similar stages of disease but radically different performance indexes (based on variables such as previous treatments, organs involved, and pain levels) may have very different outcomes. Examples of the Karnofsky and ECOG systems are compared in Table 50-2.

Tumor Response Criteria and Terminology

Tumor response criteria are often quoted in research studies and journal articles. Although they do give some understanding of the therapeutic potential of a treatment, it is important to understand that a tumor response does not always equate with a cure or even an improvement in survival. When a tumor responds initially to a treatment, it often reflects a susceptible clone of tumor cells being killed by the treatment. However, just as antibiotic treatments eventually select for resistant strains of bacteria, cytotoxic therapy selects for resistant clones of tumor cells, which over time no longer respond to a treatment. A newer theory suggests that chemotherapy may kill tumor stromal cells without destroying the tumor stem cells, which can trigger a relapse.

TABLE 50-2 **Comparison of Karnofsky and Eastern Cooperative Oncology Group (ECOG) Scoring**

KARNOFSKY SCORE	DESCRIPTION	ECOG SCORE
100	Asymptomatic	0
90	Normal activity, minor disease signs	1
80	Some disease signs with exertion	1
70	Cares for self, unable to do active work	2
60	Requires occasional assistance, in bed >50% of day	2
50	Requires considerable assistance and medical care	3
40	Disabled; requires special assistance; in bed >50% of day	3
30	Severely disabled; hospital indicated	4
20	Very ill; requires active supportive traction, bedridden	4
10	Moribund	4
0	Deceased	5

Modified from Murray M, Birdsall T, Pizzorno JE, et al. How to prevent and treat cancer with natural medicine. New York: Riverhead Books, 2002.

When reading about complete response, partial response, etc., in a journal article, it is important to know exactly what those terms imply. A cure is defined as a treatment that allows the patient to live as long as an age-matched cohort or to allow the patient to die of other causes, even if some disease was still present. For example, if a prostate cancer patient had a radical prostatectomy and later developed metastases to the bone, but died of a stroke, that could be considered a cure because the patient died of another cause than the cancer.

Remission is complete disappearance of all detectable tumors. Even in a remission with no detectable disease, it is possible to have millions of tumor cells present, and thus remission is probably a better term than cure, until there is a better way of identifying residual tumor cells that may be lying dormant.

A complete response is the term used to reflect the complete disappearance of all evidence of disease for at least two measurement periods at least 4 weeks apart.

A partial response is a decrease of 50% or more in the diameter of all measurable lesions with no appearance of new lesions for at least 4 weeks.

Stable disease is a decrease of less than 50% up to an increase of 25% in measurable lesions.

Progression is an increase of more than 25% or the appearance of new lesions.

Palliation is treatment not aimed at curing a patient but at the reduction of symptoms, such as obstruction or pain by reducing the size of the tumor, or a transient extension of life for a brief period without real hope of achieving a cure.

THERAPEUTIC CONSIDERATIONS

When the author first began to learn more about the actions of natural agents and cancer cells, he became optimistic that with the proper combination of agents, most patients would need little or

no conventional therapy. Unfortunately, despite a few remarkable successes, for the majority of patients, natural therapies alone were unable to completely control the disease process. Judiciously combining naturopathic therapies with conventional treatments did lead to greater success and significantly improved survival and quality of life. It is not unusual for patients to report actually feeling better than they had in many years, even in the midst of integrated cancer therapy. Using an integrated approach also reduces the need for patients to make the difficult choice of either doing natural therapy and declining any potential benefit of conventional treatments or vice versa.

The majority of patients diagnosed with cancer in this country use one or more forms of conventional therapy. This chapter assumes that the patient is receiving conventional therapy for their disease along with naturopathic support. The treatment of patients with natural therapies alone is controversial and evaluation of its efficacy is limited by the absence of quality research with documented results. When making therapeutic decisions, it is the author's contention that it is necessary to be able to show results at least as good as those of conventional therapies to justify declining those therapies. In most cases, those statistics are just not available. Cancer is not a self-limiting disease, and it must be remembered that our advice may determine whether a patient lives or dies. In such a situation it is incumbent on the naturopathic physician (as well as all other providers) to make recommendations on the basis of hard data, not theory, anecdote, or opinion.

Abundant evidence indicates that individual nutrients and botanicals can affect tumor growth both in vitro and in vivo. Many conventional chemotherapy agents are derived from natural compounds. However, to be reliably cytotoxic, most natural compounds must be strong enough to also be toxic to healthy cells. A better way to use the natural therapies is to support the normal healthy processes of cellular communication, differentiation, and apoptosis, thereby changing the environment that allowed cancer cells to develop and survive in the first place, rather than focusing on killing cancer cells directly. This theory was eloquently discussed in a paper entitled "Shifting the paradigm: must we kill to cure?" in the *Journal of Clinical Oncology*. Schipper et al[7] argued that the killing hypothesis has had some success, such as the treatment of testicular cancer, but in general has not led to dramatic changes in survival rates of more common cancers. The authors argued instead for a concerted effort to affect the regulatory imbalance rather than attempting to kill all cancer cells.[7]

This is exactly where the use of natural therapies can be most beneficial. Nutrients and herbs can affect the cell cycle and cell division, angiogenesis, cell-to-cell communication, metastatic processes, growth signaling (e.g., tyrosine kinases), and many other aberrant processes in cancer. However, in most cases, this is not enough in itself to guarantee a cure. Combining this approach with rationally selected conventional care can improve outcomes while reducing side effects, and this integrated approach is advocated here for most patients as giving the best opportunity for remission and increased survival, along with good quality of life.

In cases where it is known that conventional therapies have no further meaningful benefit or if the patient chooses to adamantly refuse all conventional treatment, then the use of natural therapies alone may be justified. However, it is incumbent on the practitioner to discuss the lack of solid research supporting "natural cures for cancer" and to continue conventional monitoring to evaluate treatment success and make changes as indicated.

Several large peer-reviewed articles reported that two thirds to three fourths of all cancer patients make use of one or more alternative or complementary therapies while undergoing treatment for cancer.[1,2,5] Many of these patients make decisions on the basis of information on the Internet or from well-meaning but uninformed relatives or health food store employees. An important part of our role as naturopathic physicians is to help patients sort through the overwhelming amounts of promotional literature to identify treatments that are not cost or clinically effective from those with well-established benefit.

Goals of Naturopathic Oncology Support During Active Treatment

The goals of active treatment vary significantly depending on the wishes of the patient, the stage of the disease, and the type of treatment. Some patients only want help with controlling the symptoms of treatment, whereas others seek a comprehensive management approach. Equally important is to help the patient select the best goals in his or her case. Late-stage patients may primarily need support for pain relief or appetite stimulus. Putting late-stage patients on a severely restricted diet is more likely to hasten their demise than improve their health. Early-stage patients are most likely to benefit from dramatic changes in lifestyle and aggressive supplemental and botanical support.

In brief, the goals of naturopathic oncology co-treatment include the following:

- Improve nutrition
- Selectively starve the tumor
- Inhibit metastasis
- Reduce side effects of conventional treatments
- Maximize tumor kill from conventional therapies
- Support normal cell division and cellular signaling
- Remove tumor promoters such as inflammatory signals, hormones, etc.
- Use antitumor and/or proapoptotic herbs and nutrients to help patients make wise choices and avoid purchasing worthless "cures" off the Internet
- Support healthy, balanced immune function
- Support positive attitude and healthy lifestyle
- Encourage regular secondary cancer screening after completion of treatment

Stages of Clinical Care

A typical clinical pattern occurs in most cases of cancer:

1. The first step is detection of an abnormality suggestive of a possible cancer. Symptoms vary with the type of tumor but may include a mass, lymphadenopathy, pain, bleeding, unexplained weight loss, or some other abnormal finding on physical examination or in laboratory results.
2. The next step is evaluation of the suspicious finding with imaging studies such as CT scans, ultrasounds, etc., to determine if cancer is a likely diagnosis. In almost all cases, some type of biopsy is taken to make the final determination of malignancy versus benign tissue and to establish the type of tumor and degree of abnormality. The biopsy also allows for histologic grading of the tumor and assessment of receptors and molecular markers that may affect diagnosis and treatment decisions.
3. Once the diagnosis is made and the staging process completed as previously described, most patients with solid malignancies have surgery to remove the tumor or debulk its mass. In some cases, the tumor is inoperable, and this step is bypassed. In other cases, neoadjuvant chemotherapy is administered before surgery to shrink the tumor, thus making more conservative surgery possible.

4. The next stage may include one or more types of chemotherapy, radiation, hormones, or biological response modifiers.
5. After completion of these therapies, most patients are monitored for recurrence. They may also receive additional therapy in the form of biological response modifiers based on the type of cancer. An example might be to use antiestrogen therapies after surgery, chemotherapy, and radiation to reduce risk of a recurrence of estrogen receptor (ER) positive breast cancer.

The specifics of each individual cancer and clinical oncology are too complex to be covered adequately in the limited space available here. This chapter covers some of the issues related to each of the previously mentioned conventional therapies and how best to improve the response to those therapies. For more specific details on conventional treatment refer to an oncology textbook.

SURGERY

Surgery is the first treatment in approximately 75% of cancers. In some cases the surgery is done diagnostically in the form of a biopsy, but most often it is done with a curative intent. In later stages of disease, the surgery may be intended only to debulk a tumor or to remove an obstruction or painful lesion. Of all the conventional treatments available, surgery has the greatest potential for true cure. If it is possible to remove all cancerous tissue and associated stem cells with adequate tumor-free margins before the tumor has had time to metastasize, then a patient can truly be considered "cured." The biggest difficulty is determining if all malignant cells have been fully removed. A 1-cm tumor has more than 1 billion cells. Clusters of cells or micrometastases are so small that they are impossible to detect by current methods. It is therefore impossible to say with certainty that "we got it all," and all that can be said with certainty is that "we removed all visible signs of diseased tissue." A newer test for circulating tumor cells has been shown to have some predictive value for risk of recurrence.[8]

The benefits of surgical tumor removal come at the risk of complications. The most common potential problems encountered in the surgical and postoperative period include bleeding, anesthesia reactions, infections, blood clots, dissemination of cancer cells during the procedure, suppression of cell-mediated immunity,[9] and damage to nearby nerves or tissues during surgery. Postsurgical adhesions can cause various complications as late sequelae and may lead to the necessity for further surgical interventions to release the adhesions if they cause intestinal obstruction. Other potential complications vary depending on the tumor location, tissues involved, and skill of the surgeon.

The goals of natural therapies include reduction of all the previously mentioned complications, improved rates of healing and recovery, and support for formation of healthy scar and connective tissue. All licensed naturopathic physicians have been well trained in the support of surgical patients, and many have their favorite nutritional, botanical, and homeopathic regimens. In addition to the usual treatments, several specific things are important to keep in mind when dealing with cancer patients. Most important is that these patients may already be quite weakened or debilitated by their disease or their previous treatments and may therefore need more aggressive support than one usually provides.

A second concern when dealing with surgery in cancer patients is the potential for spread of tumor cells during the perioperative period. Several studies have shown that patients with no tumor cells detectable in circulation before surgery frequently have detectable levels of micrometastases in the general circulation after surgical removal of the tumor.[10,11] This means that one or more of those circulating cells can attach to a new site, penetrate the basement membrane, and begin to grow into a new tumor. This is one of the reasons that adjuvant chemotherapy is given, because it is impossible to predict with 100% certainty that every single tumor cell has been removed by surgery alone.

To reduce the potential for the spread of micrometastases, one can use several natural agents, including fractionated citrus pectin (FCP), larch arabinogalactans, fish oils, and proteolytic enzymes. FCP, also known as modified citrus pectin (MCP), is a complex of polysaccharides derived from seeds and skins of citrus fruits. The pectin fractions are rich in galactose residues with the ability to bind to receptors on tumor cells known as galactan 3 receptors. These receptors normally enable tumor cells to attach to each other and to healthy tissues, assisting the metastatic process. By binding to the galactan 3 receptors, MCP has been shown to significantly reduce the aggregation of cancer cells and the adhesion of prostate, breast, and melanoma cells to healthy epithelium.[12,13] Fractionation of the pectin molecules breaks them down into the correct size to specifically bind to galactan 3 receptors. Whole pectins from fruits and vegetables are less efficient at this process due to their large molecular size. All cancer patients are strongly advised to use FCP preoperatively and postoperatively to minimize the possibility of tumor cell adhesion. One situation where this is most advisable is during biopsy procedures. Disturbance of the tumor bed during the biopsy may allow dissemination of a previously localized tumor, and it is desirable to do everything possible to avoid this.[14]

General Preoperative Guidelines (Begin 2 Weeks Presurgery)

Patients should be advised to avoid the following:

- Alcohol
- Recreational drugs
- Tobacco (women who abstained from smoking for at least 3 weeks before breast reconstruction had one half the complications of smokers)[15]
- Sugar
- Fried foods
- Coffee (taper slowly to minimize withdrawal headaches)
- Anything capable of causing increased bleeding, such as aspirin, *Ginkgo biloba,* high doses of garlic, and high doses of fish oil

Use caution with any drugs or herbs that might react with anesthesia, including kava, hypericum, and valerian. These should be discontinued at least 5 days before surgery unless there is a pressing need for their continuation. Patients should be advised to increase the following:

- Fiber
- Protein (1 to 2 g/kg body weight)
- Vegetables
- Fresh fruit
- Fluids
- Probiotic agents
- Vitamin C with bioflavonoids

Some specific suggested doses for several nutrients are included as examples (Box 50-1). This is not to suggest that other nutrients may not be equally helpful.

Postoperative Nutrition

Nutritional support may be resumed as soon as the patient can consume foods. The patient should not be started on vitamins or herbs if he or she can receive nothing by mouth, meaning that the patient should not be consuming any foods. Once patients can consume liquids, then herbal teas and homeopathic remedies can be added, and once patients are allowed foods without restriction, they may

BOX 50-1 **Preoperative Nutritional Support**

Diet high in protein, fruits, and vegetables; low in alcohol, caffeine, saturated fats, and junk foods.

Avoid blood thinning herbs and nutrients.

Avoid herbs that can alter liver metabolism of anesthesia or pre- and postoperative medications.

Stop smoking 3 weeks before surgery.

Fractionated citrus pectin 8 g twice daily (to inhibit micrometastases).

Gotu kola to reduce adhesions, three cups tea daily.

High-potency multivitamin.

- Vitamin C 2000 to 5000 mg/day. Vitamin C promotes healing, supports immunity, and helps to build strong collagen.
- Zinc (60 mg/day) speeds healing, localizes to healing tissues, and is most active in the second phase of healing.* A study of 10 random healthy young men receiving surgical excision of pilonidal cysts showed zinc supplementation sped up healing time almost 300% in the zinc group over the control group.*
- B vitamins (20 to 100 mg) are generally included in the multivitamin formula.

Immune support as desired to reduce probability of infection, including hospital-acquired respiratory infections.

Protein powder or free-form glutamine and arginine supplementation has been shown to speed postoperative recovery and promote protein synthesis necessary for collagen formation. Glutamine supplementation also reduced total hospital costs, rates of infection, and nitrogen balance in bone marrow transplantation patients.†

Arnica and Traumeel are two homeopathic remedies that have been traditionally used to speed recovery from injury or trauma. Although no studies have evaluated the effectiveness of these remedies, their long history of use, low cost, and apparent clinical benefit justify their addition to a postsurgical support protocol.

*Pories WJ, Henzel JH, Rob CG, et al. Acceleration of wound healing in man with zinc sulphate given by mouth. Lancet. 1967 Jan 21;1(7482):121-4.

†Ziegler TR. Glutamine supplementation in cancer patients receiving bone marrow transplantation and high dose chemotherapy. J Nutr. 2001 Sep;131(9 Suppl):2578S-84S; discussion 2590S.

also resume all indicated medications. The naturopathic physician must be aware of all prescription medications the patient is taking and verify that there are no adverse interactions between the natural medications and the prescription items. Multiple sources of information on drug–nutrient interactions are available. Several websites now have extensive lists of the specific cytochrome p450 enzyme families and drugs metabolized via those pathways. One excellent site is http://medicine.iupui.edu/flockhart. By comparing hepatic clearance pathways for current medications, one can predict the likelihood of negative interactions and avoid those combinations.

Continue all presurgical support medications for at least 6 weeks postoperatively or until the patient has fully recovered. Particularly important at this time is the continued use of the MCP/FCP to inhibit aggregation and attachment of any tumor cells that might have been released into circulation during the surgical procedure. This product should be continued for 3 to 6 months afterward whenever possible.

Additional nutrients that may be beneficially added postoperatively include the following:

- Vitamin E and fish oils to reduce the risks of thromboses and adhesions
- Bromelain and other proteolytic enzymes to reduce inflammation, pain, and the risk of thrombophlebitis
- Protein drinks or smoothies to provide easily assimilated amino acids necessary for tissue repair and collagen formation

The patient should be encouraged to ambulate as soon as possible to reduce the risk of blood clots, constipation, and muscle atrophy. Patients should also be encouraged to return home as soon as safely possible to reduce the risks of hospital-acquired infections, sleep disruptions, and medication errors that can occur in busy hospitals. Conversely, if patients feel something is not right, they should not leave the hospital just because they have reached some statistical average-stay length. It is better to remain an extra 1 or 2 days until all infections or problems are resolved than to go home early, have a complication, and then spend additional days or weeks in intensive care dealing with that problem. Patients should report any unusual symptoms such as fever, swelling, and excessive pain. Although hospital stays are generally limited according to diagnostic codes, attending doctors can override these guidelines for medical reasons or complications.



CHEMOTHERAPY AND TARGETED BIOLOGICAL AGENTS

Chemotherapy is the use of chemical agents that affect rapidly dividing cells. Technically, this category includes both cytotoxic therapies and biological response modifiers such as hormones, vaccines, monoclonal antibodies, and tyrosine kinase inhibitors. For clarity, this group is divided into two sections: cytotoxic chemotherapy agents and targeted biological agents.

Cytotoxic Chemotherapy Agents

Chemotherapy agents are developed for their toxicity to rapidly dividing cells. This damage ultimately leads to cell death through apoptosis (programmed cell death). Unfortunately, most chemotherapy drugs cannot distinguish between cancer cells and normal cells and thus attack any rapidly dividing cell, including healthy cells in the bone marrow, hair follicles, and lining of the gastrointestinal (GI) tract. This inability to distinguish between cancer and healthy cells produces most of the side effects associated with chemotherapy.

Chemotherapy as it is currently practiced began in the late 1940s, after World War II. Louis S. Goodman made the observation that mustard gas caused bone marrow suppression and that this effect might be used therapeutically in a disease marked by hyperactive bone marrow, such as leukemias. The first scientific paper on the use of nitrogen mustard for treatment of cancer was published in 1946. Over time, newer agents known as antimetabolites and alkylating agents were added, and the role of chemotherapy gradually evolved from that of an experimental procedure to a standard of care. Today, more than 50 chemotherapy agents are commonly used, and new agents are approved on a regular basis.

Chemotherapy has enabled the high rates of cure for several cancers, including testicular cancer, some forms of childhood leukemia, Hodgkin disease, some non-Hodgkin lymphomas, and some cases of ovarian cancer. Unfortunately, for many of the more common cancers, such as breast, prostate, colon, and lung cancers, chemotherapy has had a more limited success. This is due to the high frequency of side effects limiting dosage and the fact that many cancer cell types begin to develop drug resistance after multiple courses of treatment, eventually no longer responding to

available agents. Newer timing schedules such as "metronomic chemotherapy," using smaller doses of chemotherapy more frequently, have been shown to be better tolerated and at times, more effective than conventional timing.[15a-15c] Other modifications such as intrahepatic chemotherapy and chemoembolization procedures have also enabled treatment of tumors that would previously have been considered untreatable.

Clinical Uses of Chemotherapy

Chemotherapy is used clinically in a number of situations with different objectives. These include the following:

1. Neoadjuvant treatment is the use of chemotherapy before other treatments such as surgery or radiation. The goal in this situation is to shrink a tumor, making it more easily treatable with less extensive surgery or radiation, thus reducing the surgical mutilation or long-term post-radiation complications. Examples of disease that receive this type of treatment are breast cancers, some rectal cancers, bladder cancer, and esophageal cancer.
2. Adjuvant treatment is chemotherapy used after control of visible tumor with treatments such as surgery or radiation. The goal in adjuvant treatment is to destroy any undetectable cancer cells and reduce the likelihood of recurrence of the disease. Conditions where this type of chemotherapy is commonly used include breast cancer and colon cancer. Adjuvant chemotherapy can be divided into induction chemotherapy, which is a first-line treatment, and consolidation therapy, where another agent combination is used to further "consolidate" improvements from the first treatment.
3. Second-line chemotherapy is treatment given on evidence of a tumor recurrence. Treatment at this time generally attempts to put the patient into remission, but generally uses agents different from the first time the tumor was treated, on the presumption that the remaining cells frequently have developed resistance to the first agents.
4. Palliative treatment is chemotherapy given with the intention to reduce symptoms such as pain by temporarily shrinking a tumor that is pressing on a vital organ or nerve. Palliative treatment is not intended to cure a patient. In some cases it may extend life for a short period, but the primary goal is improving quality of life by reducing pain, obstruction, or other symptoms.
5. High-dose chemotherapy, also called "myeloablative chemotherapy," is given with the intention of delivering enough chemotherapy to kill all cancer cells. Unfortunately, the side effect is loss or complete destruction of bone marrow capacity as well, and the patient needs some form of "rescue" therapy, either a bone marrow or stem cell transplantation. High-dose chemotherapy is generally used in hematologic malignancies such as leukemia and multiple myeloma. The study of bone marrow and stem cell transplantation is beyond the scope of this chapter.

Actions of Chemotherapeutic Drugs

Chemotherapeutic agents can be divided into various subcategories, but all tend to work in one of two general manners. They are either cytotoxic, meaning they are intended to kill all dividing cells, or cytostatic, meaning they slow cell division, allowing reestablishment of check point regulation, but do not necessarily cause cell death. Some agents have other secondary effects, such as being antiangiogenic when given in metronomic dosages. Chemotherapy is usually given in combinations of two or more agents to take advantage of differences in metabolism or specific activities against particular tumor types. In general, chemotherapy is also given in cycles that consist of a specific number of infusions followed by a rest period. The number and timing of the infusions vary widely with the type of agent being used, as well as the type of tumor and health of the patient. The specifics are determined by the oncologist in each case.

Families of Chemotherapy Drugs

Alkylating Agents and Platinum Compounds

Alkylating agents substitute an alkyl group for hydrogen to produce defects in DNA. The effects are similar in many ways to the DNA damage caused by radiation. Members of this group include chlorambucil and cyclophosphamide. Platinum drugs work similarly by causing DNA cross linking.

Antitumor Antibiotics

Antitumor antibiotics bind between DNA base-pairs, interfering with normal mitosis. Many also generate free radicals. Common examples of this group include Adriamycin, Mitomycin, and Bleomycin.

Antimetabolites

Antimetabolites substitute structural analogs of normal metabolites, thus interfering with replication of DNA. Common examples include Methotrexate (MTX), Fluorouracil (5-FU), Gemcitabine, and Hydroxyurea.

Microtubule and Chromatin Inhibitors

Microtubule inhibitors and topoisomerase inhibitors work by interfering with the normal intracellular mechanisms necessary for mitosis. They work by blocking either topoisomerase enzymes used in DNA replication or binding to tubulin and blocking assembly or disassembly of microtubules necessary for mitosis. Examples of microtubule inhibitors include Vinblastine, Vinorelbine, Taxol, and Taxotere. Examples of topoisomerase inhibitors include Irinotecan and Etoposide.

Targeted Biological Agents

Targeted biological agents comprise a large, diverse group of medications with many actions. In general, the group can be divided into several subgroups, including antiangiogenic agents, immune modulators, hormones and hormone blockers, and "new breed" agents such as monoclonal antibodies and tyrosine kinase inhibitors.

Antiangiogenic

Antiangiogenic agents inhibit the growth of new blood vessels. Because tumors require increased vasculature to support their high metabolic rate, agents that prevent the development of blood vessels theoretically inhibit the ability of tumors to grow. Many of these agents block growth signals by inhibiting epidermal growth factor receptors. Examples of these include Thalidomide, Avastin, Tarceva, and matrix metalloproteinase inhibitors. Many other agents, including taxane-based chemotherapy at low doses, can also have a weak antiangiogenic action when given metronomically since they inhibit replication of endovascular cells.[15d-15e]

Immune Response Modulators

Immune modulators, vaccines, and monoclonal antibodies all work by increasing or focusing the immune response directly or indirectly. This category includes commonly used agents like

interferon and interleukins. Included in this group for simplicity are various bone marrow–stimulating agents such as Neupogen, Epogen, and Leukine, although these could also be included in the group of hormones and hormone inhibitors. Monoclonal antibodies such as Herceptin and Rituxan also work via targeting the immune system against specific markers on tumor cell surfaces.

Hormones and Hormone Inhibitors

Hormones and hormone inhibitors are used to manipulate the signals that regulate cell growth. A well-known example of a hormone inhibitor is Tamoxifen, which blocks estrogen receptors to slow growth of estrogen receptor–positive breast cancer. Newer antiestrogen agents called aromatase inhibitors work by blocking the synthesis of estrogen in fat cells rather than blocking estrogen receptors on tumors. Similar agents like Casodex inhibit the binding of testosterone in prostate cancer.

Gonadotropin Releasing Hormones. Agonists such as Lupron are commonly used in prostate cancer to inhibit the production of testosterone. An example of a hormone used therapeutically is prednisone in the chemotherapy combination of Cyclophosphamide, Doxorubicin Hydrogen Chloride, Oncovin, and Prednisone used for hematologic malignancies, or the use of Megace to stimulate the appetites of advanced cancer patients.

Mechanism of Action

These newer agents (e.g., Imatinib [Gleevec], Thalidomide, and photosensitizing agents[16]) work by various methods. For some, like Imatinib, their strength is the specificity of their action, which limits the majority of their effects to the target tumor cells. Others, such as photosensitizing agents like psoralen, have less toxicity than most systemic chemotherapy agents and allow for specific activation in the areas desired with a laser light source (Box 50-2).

BOX 50-2 **Common Chemotherapeutic Agents**

Alkylating Agents	
Nitrogen mustard	Chlorambucil, Cyclophosphamide, Estramustine, Ifosphamide, Melphalan
Metal salts	Carboplatin, Cisplatin
Nitrosourea	Carmustine, Lomustine
Antibiotics	Adriamycin, Doxil, Epirubicin, Mitomycin, Bleomycin
Antimetabolites	
Antifolates	Methotrexate, Trimetrexate
Pyrimidine analogs	Fluorouracil, Fluorodeoxyuridine, Xeloda
Purine analogs	Thioguanine, Mercaptopurine, Fludarabine
Microtubule and Chromatin Inhibitors	
Mitotic inhibitors	Vinblastine, Vincristine, Vinorelbine
Microtubule stabilizer	Paclitaxel, Docetaxel, Abraxane
Topoisomerase I inhibitors	Irinotecan, Topotecan
Topoisomerase II inhibitors	Etoposide, Teniposide
Biologic Response Modifiers	
Hormones	Dexamethasone, Prednisone, Diethylstilbestrol, Megestrol acetate
Hormone antagonists	Lupron, Tamoxifen, Raloxifene, Flutamide, Bicalutamide
Aromatase inhibitors	Anastrozole, Letrozole, Aminoglutethimide
Immune modulators	Interferon, Interleukin-2, Neupogen, Epogen, Neulasta, Leukovorin, Leukine
Monoclonal antibodies	Herceptin, Rituxan, Bevacizumab, Panitumumab, Cetuximab
Tyrosine kinsae inhibitors	Erlotinib, Lapatinib, Gefitinib

Modes of Administration

Most chemotherapy agents are given intravenously, although a few are oral agents (e.g., Xeloda, Tamoxifen) or intramuscular agents (e.g., Lupron). The intravenously administered agents can be given in various schedules. Typically, drugs are given in "cycles"; the chemotherapy is given for several sessions, and then the patient takes a drug holiday to recover. The most common protocol is an intravenous (IV) bolus of chemotherapy once every 3 weeks, but some agents can also be administered daily for up to a week or given in a 24-hour continuous infusion pump. Some more progressive oncologists use "fractionated chemotherapy," also known as metronomic chemotherapy, in which the total dose is "fractionated" or broken into multiple smaller doses given more frequently, such as once weekly. Using this method, patients generally have fewer side effects and equal or better tumor responses.[17] The length of treatment depends on many variables, including the subtype of tumor, its stage and grade at the time of diagnosis (more aggressive tumors are generally treated longer and with more agents), and the type of chemotherapy being used. Another important variable is how well the patient tolerates treatment without excessive side effects, such as bone marrow depression.

An interesting variable is chronotherapy, the study of how timing the dose of chemotherapy during the 24-hour circadian rhythm affects response and side effects. For example, chemotherapy given early in the day seems to cause a smaller drop in white blood cells. Because breast cancer cells tend to be more active in the evening, chemotherapy given at that time might prove to be more effective with fewer side effects than the same treatment given at another time.[18] One problem with chronotherapy is the logistical difficulty of administering different agents at different times of day. This would necessitate having treatment centers open around the clock, with an attendant on such a schedule. For this reason, and the fact that the field of chronotherapy is still young with much additional research necessary, it is likely to be a long time before conventional oncologists incorporate this information into standard treatment protocols.

Side Effects of Chemotherapy

These vary depending on the chemotherapy agent used, the timing and dosage administered, and what protective measures are available and used to reduce side effects. Individual factors, including the general health of the patient, efficiency of liver enzymes, and the amount of previous treatment (which can cause bone marrow suppression) also affect the degree of side effects. Each chemotherapy agent has specific side effects that occur more commonly. For example, Paclitaxel often causes significant myalgia and arthralgia, whereas a similar drug, Docetaxel, causes fewer of these symptoms but more bone marrow depression. Common short-term side effects caused by chemotherapy agents are listed in Box 50-3. Anyone working with these agents should acquire several references and review them regularly.

Long-term side effects are those that persist after completion of chemotherapy. Late side effects are those that may occur months

BOX 50-3 Common Short-Term Side Effects Caused by Chemotherapy

- Nausea/vomiting
- Neuropathy
- Mucositis
- Pneumonitis
- Diarrhea
- Nephropathy
- Fatigue
- Tinnitus
- Hair loss
- Infections
- Anemia
- "Chemo brain"
- Leukopenia
- Hand–foot syndrome
- Thrombocytopenia
- Alterations of taste and smell
- Bruising
- Anorexia
- Cardiac damage

BOX 50-4 Common Long-Term Side Effects Caused by Chemotherapy

- Development of tumor resistance to chemotherapy
- Increased risk of secondary cancers
- Increased risk of leukemia/lymphoma
- Infertility and premature menopause
- Persistent unexplained fatigue
- Persistent bone marrow suppression or myelodysplasia
- Persistent "chemo brain" or short-term memory dysfunction

to years after treatment as a result of the chemotherapy. Some potential long-term problems are listed in Box 50-4.

Chemotherapy Resistance Testing

A new and intriguing option, which is still in early developmental stages, is the testing of tumor tissue for resistance to common chemotherapeutic agents. Currently, chemotherapy is given to patients based on results of treatment to large groups of patients with the same type of tumor, assuming that all similar tumors are likely to respond to the same chemotherapy agents. Whether an individual patient's tumor is responsive to a particular agent is determined by measuring shrinkage of visible tumors, or if there is no measurable tumor after surgery, is assumed based on previous studies. Unfortunately, a large percentage of tumors are resistant to one or more common chemotherapy agents, leading to needless side effects and delay of treatment with an appropriately effective agent.

In resistance testing, a small amount of the fresh, unpreserved tumor tissue taken from the patient during biopsy or surgery is sent to a research laboratory that grows cell cultures from the sample and then tests the patient's cell lines for resistance to chemotherapeutic agents typically used for that tumor type. The underlying assumption is that if concentrations of chemotherapy much higher than those achievable in the body do not slow tumor growth in vitro, then they are unlikely to do so in the patient, and there is little reason to expose the patient to the risks, expense, and side effects of treatment with that particular chemotherapy agent. This allows oncologists to make decisions about therapies most likely to benefit the patient.

The technique of chemotherapy resistance testing is still controversial but makes sense and can help avoid the cost and potential medical complications of treatment with a toxic agent that is unlikely to provide any benefit. The test, which costs approximately $3000 to $4000, is not generally covered by insurance companies at this time, but the potential benefit of knowing that one's treatment is appropriate for one's specific cancer seems to justify the expense if at all possible. This test is most useful for later cases where first-line therapies failed to deliver expected results.

An emerging technique is the use of genetic or molecular fingerprint testing of the tumor tissue to determine specific characteristics that may indicate the best therapeutic agents, as well as predict the risk of recurrence more accurately to help in determining who may need a specific type of treatment and who might not need any chemotherapy at all.

General Recommendations for Chemotherapy

To Improve Effectiveness

Although chemotherapy can be life saving at times, it has many limitations. Tumors sometimes do not respond completely or respond at first but later become resistant to chemotherapy. Some researchers question whether medicine has really made any significant progress against the most common cancers that affect Americans.[19] Other "breakthroughs" may add only a few months to actual survival. For example, when the chemotherapy drug Gemzar was introduced, it was hailed as a breakthrough in the treatment of pancreatic cancer. In reality, the increases in survival were modest, generally adding 3 months or less to overall survival compared with current therapies.[20] A meta-analysis of studies of breast cancer treatment found that for most early-stage patients with minimally aggressive cancers, chemotherapy added 10.3 months of relapse-free survival and 5.4 months of overall survival for premenopausal women and 6.8 months relapse-free survival with 2.9 months overall survival for postmenopausal women.[21] Obviously, there is a need to improve the effectiveness of chemotherapy, leading to more significant changes in survival times. Fortunately, there are ways to improve the potential benefits from standard treatment. In addition to appropriate timing and dosage schedules, one can select specific nutrients to enhance specific chemotherapy agents. These nutrients are best taken for at least 2 weeks before beginning chemotherapy until completion of treatment. They may have various actions, including normalizing cell division, increasing apoptosis, increasing uptake of chemotherapy into cells, reducing development of drug resistance, and stimulating normal cell differentiation. It is important to match the nutrients to the planned chemotherapy agents for best effects and to minimize negative interactions with chemotherapy.

The broad range of chemotherapy agents and the even broader range of potential natural support makes an exhaustive review of this topic impossible in a summary chapter. However, a few examples can illustrate the potential benefits of using this approach.

Melatonin. A study of 250 Stage IV cancer patients with various tumor types who were treated with conventional therapies or with the same therapies and 20 mg of melatonin nightly found that the response rates to chemotherapy and survival at 1 year were doubled.

Moreover, the addition of melatonin to the chemotherapy regimen reduced the incidence of toxicity symptoms, such as thrombocytopenia, neurotoxicity, and cardiotoxicity.[22]

Green Tea. In a similar fashion, the simple addition of green tea enhanced the inhibitory effects of Adriamycin 2.5-fold against Ehrlich ascites tumors in mice. Interestingly, this effect was seen only in tumor cells and not the healthy cells.[23]

These studies illustrated that although chemotherapy alone has some benefit, the addition of appropriate nutrients to the protocol can significantly increase therapeutic efficacy.

To Reduce Side Effects

Due to variations in their mode of action and path of elimination, each chemotherapy agent can cause damage to certain organs. For example, Adriamycin has been implicated in causing severe cardiac damage at high doses, and even lower doses appear to affect heart function negatively.[24] Taxol can cause neuropathy and myalgias. Taxotere causes less neuropathy but greater marrow suppression. Cisplatin can cause neuropathy and cystitis. Each of these side effects can be avoided or minimized with nutritional support. Using the appropriate support throughout the patient's treatment is particularly important, because, in some cases, once the damage has occurred, it is irreversible. Equally important is that excessive side effects may cause reduction in dosage of therapeutic agents, potentially reducing therapeutic effectiveness.

Certain general measures should be emphasized in all cases to reduce side effects from chemotherapy. Some, such as encouraging the patient to stay adequately hydrated and eat a healthy diet, are basic and obvious. Even a simple, broad-based, high-potency multiple vitamin, along with good diet, goes a long way toward reducing complications. Finding open-minded oncologists who support the patient in making wise dietary and supplement choices makes the job of supporting patients easier.

Specific Recommendations for Chemotherapy

Entire books have been written on the actions, effects, and side effects of chemotherapy agents. It is not the intention here to replace a thorough understanding and knowledge of that information. Rather, the following highlights a few of the more commonly used agents and demonstrates the type of information that must be understood about any agent before treating a patient receiving that drug. The fact that some drugs used in combination may have contradictory requirements is noteworthy. In these cases, contraindications are the trump card and nutrients contraindicated by any of the agents in a chemotherapy protocol should be avoided. For example, in the commonly used combination Cytoxan, MTX, and 5-FU for breast cancer, the use of additional folate could support the actions of Cytoxan but might potentially interfere with the benefits of MTX. Therefore, high doses of folate are not recommended at this time.

The selection of appropriate nutrients and botanicals for support during chemotherapy is a complex discussion. Each case must be evaluated on the basis of many factors, and the full complexity cannot be covered here. Instead, a basic support protocol appropriate for virtually all outpatient chemotherapy treatments is presented, as well as a discussion of specific nutrients to consider adding to the most common chemotherapy agents used today.

General recommendations safe for virtually all chemotherapy regimens include a high-potency multivitamin (Box 50-5), fish oil capsules, melatonin, green tea, and some form of immune support.

BOX 50-5 **Basic Support Program for Chemotherapy**

Multivitamin

Melatonin: 20 mg at bedtime

Vitamin C: 3000–10,000 mg/day in divided doses according to bowel tolerance

Fish Oils: 2 g total combined eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) daily

Mushroom Extracts/Immune Support: Use various immune modulators and switch them regularly to avoid downregulation of receptors. Standard doses for polysaccharide krestin mushrooms are 3 g of the extract daily. Suggested dose for Maitake D or MD fractions is 0.5–1 mg of extract per kg body weight. Other botanical immune modulators may be used as desired.

Enzymes: Use pancreatic enzymes with meals and mixed enteric-coated enzymes between meals.

Green Tea: Capsules and beverages should total the equivalent of 5–10 cups green tea daily. Caffeinated form is preferred if caffeine is tolerated, since there is some possibility of removing the desirable EGCG in the decaffeinating process.

Whey Protein Shake with Fruit Daily: This is a source of easily assimilated protein and amino acids, particularly glutamine.

Melatonin

Melatonin is a pineal hormone that is secreted in response to darkness. It is thought to serve as a synchronizer of biological rhythms. Melatonin has been shown to slow the development of a wide variety of tumor types. including breast, endometrial, nonsmall cell lung, hepatocellular, renal, colon, and prostate cancers. For a full discussion of the topic, see *Melatonin after Four Decades.*[25] Low levels of melatonin have been associated with increased risks of cancers, including breast cancer.[26] Multiple studies have confirmed the antiproliferative action of melatonin when given alone and when combined with chemotherapy or radiation. The actions have been attributed to the fact that melatonin is a potent antioxidant; may inhibit the action of hormones such as prolactin, estrogen, and testosterone; and it may inhibit the transformation of linoleic acid into tumor growth–promoting metabolites.[27,28] Melatonin used alone in late-stage patients refractory to other treatments led to increased survival and improved well-being in more than one third of subjects.[29] Addition of melatonin to hormonal therapy protocols improved responses, even in some cases that were no longer responsive to hormonal treatments alone.[30] Melatonin added to conventional treatment with Doxorubicin, reduced the drug's known cardiotoxic effects, and at the same time produced better responses as measured by long-term survival.[31]

A study mentioned earlier in this chapter evaluated the efficacy of chemotherapy in 250 advanced cancer patients with various tumor types. Half of the group received appropriate conventional chemotherapy, and half received appropriate chemotherapy with the addition of 20 mg of melatonin. Tumor response rates were observed in 42 of 124 patients receiving melatonin versus in 19 of 126 receiving chemotherapy without melatonin. Survival responses were equally impressive: 63 of 124 patients receiving melatonin plus chemotherapy were alive at 1 year versus 29 of 126 in the chemotherapy group. Melatonin was not a cure-all, but it essentially doubled responses to conventional treatment and doubled survival.[32]

Melatonin is appropriate in almost all solid tumor types, but there are a few safety considerations to keep in mind. Research on the safety or efficacy in hematologic malignancies is scant, and

some of what is available suggests negative outcomes when using melatonin in malignancies like leukemia, lymphoma, and myeloma.[33] At this time, melatonin is not recommended for these tumor types. The majority of melatonin research has used 20 mg at bedtime, and this is the suggested dosing schedule until further research is done on the question of melatonin given at other times of day. Finally, if a patient is taking a selective serotonin reuptake inhibitor–type medication (e.g., Zoloft, Paxil, Celexa), lower doses of melatonin should be used to avoid any potential interactions or development of serotonin syndrome, although this is unlikely.

Green Tea

Green tea, particularly the polyphenol components, inhibits the initiation, promotion, and progression stages of carcinogenesis. The cancer preventive aspects of green tea are well documented and thus are not reviewed here.[34,35] Of more interest in this situation are the effects of green tea in promoting cell cycle arrest and even apoptosis.[36] Recall that apoptosis is critical to adequate antitumor response to chemotherapeutic agents. When given with chemotherapy, green tea extracts have shown the ability to reduce drug resistance and increase the concentration of chemotherapy agents within tumor cells.[37,38]

Green tea catechins have also been shown to inhibit angiogenesis, the process of blood vessel growth that is crucial for tumor growth and metastasis.[39] Green tea polyphenols have a profound growth inhibitory effect on cancer cells without inhibiting the growth of healthy cells. This differential effect is thought to be due to the fact that differential modulation of genes regulating cell signaling may be involved, leading to death in cancer cells.[40] Green tea in high doses has been shown to reduce the effectiveness of Bortezomib (Velcade) and should be avoided when patients are using this agent until further information clarifies this issue.

Multiple Vitamin

A high-potency multiple vitamin is essential to provide additional nutritional support during cancer therapy. Patients have multiple physiologic stresses, including the demands of surgery, chemotherapy and radiation, difficulty eating due to nausea or fatigue, and increased susceptibility to infection caused by leukopenia. Maintaining adequate levels of nutrients not only improves overall patient health but can improve responses to chemotherapy. For example, simply increasing levels of folic acid in rats improved response to cyclophosphamide from 53% to 97%, with 5-FU from 46% to 66%, and from Doxorubicin from 25% to 61%.[41]

Eicosapentaenoic Acid/Fish Oils

Fish oils are a concentrated source of ω-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These fatty acids are important precursors to protective prostaglandins and are associated with reduced risks of numerous cancers, including breast, prostate, and colon cancers.[42-44] EPA and DHA have been demonstrated to improve levels of regulatory molecules such as *bcl-2,* leading to apoptosis of tumor cells in various in vitro models.[45] EPA and DHA improve response rates to some chemotherapy agents, including Irinotecan and Doxorubicin.[46]

Fish oils in some studies demonstrated the ability to slow, or even reverse, the wasting syndrome of advanced cancer known as cachexia. In one study, 6 g/day of EPA halted weight loss in pancreatic cancer patients who had previously been losing an average of 2 kg monthly, leading to stabilization of weight for the duration of the 12-week study period.[47]

Another advantage to fish oils is their well-documented ability to reduce platelet aggregation. Cancer patients are more prone to thromboses than the average person, and it has also been postulated that reduction of thromboses can indirectly reduce metastases because many micrometastases are encased in platelet aggregates, effectively masking the tumor cells from the immune system.[48]

Flax oil is sometimes considered a vegetarian alternative to fish oils because it also contains ω-3 fats. Although flax oil is beneficial in cancer, the majority of studies used the preformed EPA/DHA of fish oils, the currently recommended form, since conversion of the flax oil ω-3 into EPA and DHA is limited.

Vitamin C

Vitamin C has been well documented to reduce the incidence of most cancers in humans.[49] What has been hotly debated is whether vitamin C has any therapeutic effect in the treatment of cancer. Pauling and Cameron reported in 1976 that high-dose ascorbic acid (typically 10 g/day via IV infusion) increased average survival of advanced cancer patients by a factor greater than 4, and for a small group of responders, survival was increased up to 20 times longer than that of controls.[50] Similar results were reported by Murata et al with ascorbate-treated terminal patients surviving six times longer than matched controls, with 3 of 55 terminal patients still alive after more than 4 years.[51] Two follow-up studies did not find similar results,[52,53] but various methodological differences called their results into question. Most significant was the fact that the positive studies looked at survival in terminal patients, whereas the 1985 negative study compared time to progression before starting chemotherapy rather than overall survival.

Tumor cells take up vitamin C and, due to lower catalase activity, produce high levels of intracellular hydrogen peroxide. Some studies suggest that high-dose ascorbic acid may have active antitumor activity,[54-56] but it should be noted that oral dosing is unlikely to achieve the millimolar concentrations needed to produce cytotoxic activity. IV infusions of 30 to 100 g may show some benefit, but have not been shown to be a replacement for conventional therapy. Rather, it may be therapeutic in extending periods of remission and promoting healing and recovery after treatment. (*Editor's note*: A well-designed study of high dosage IV vitamin C is now underway to determine efficacy in late-stage cancer patients in whom all conventional treatment has failed.[57])

This discussion is directed more to the reduction of toxicity and improvement of tumor kill when combining vitamin C with conventional therapy. Vitamin C has been shown to reduce the general toxicity and cardiotoxicity of Adriamycin with no reduction in the antitumor activity, producing a prolongation of life.[58] Vitamin C has been shown to increase the tumoricidal action of Cisplatin, Dacarbazine, Adriamycin, and Paclitaxel.[59,60] Combined administration of vitamins C and K simultaneously potentiated the therapeutic effect of six different chemotherapy agents.[61]

The combined use of vitamin C with chemotherapy is even more desirable when one considers all the beneficial actions of vitamin C on immune function, tissue repair, detoxification, and the fact that cancer patients are diagnosed with frank scurvy at a rate more than 10 times greater than noncancer patients.[62]

Mushroom Extracts

Many various botanical and nutritional agents may be useful for immune support during chemotherapy treatment. Some of the best studied are mushroom extracts, including Maitake and Coriolus.

Both mushrooms are high in β-glucan rich molecules shown to support healthy immune function.

Polysaccharide krestin (PSK) is an extract of the *Coriolus versicolor* mushroom, which has been studied in Japan since the early 1970s. When PSK was combined with conventional surgery and radiation for lung cancer patients, those receiving the PSK extract had a 5-year survival of 39% for Stages I and II and 22% for Stage III, versus survival of 16% for Stages I and II and 5% for Stage III without the PSK.[63] PSK also improved 5-year survival in gastric cancer when combined with surgery and chemotherapy, producing a 73% survival versus 60% in the control group.[64] Improvements were also seen in studies looking at breast cancer, leukemia, and colorectal cancer.[65] In total, more than 400 studies have evaluated PSK extracts for cancer. Most studies indicated that the primary benefit of PSK is due to immunomodulating activity, but there is also evidence that the extract may act to suppress metastases.[66] PSK has also been shown to reduce the development of cancer in vulnerable cell lines by protecting against oxidative stress.[67]

Maitake mushrooms *(Grifola frondosa)* have also been shown to be rich in β-glucan molecules and to have immunostimulating activity.[68] Maitake extracts have the benefit of being more easily found in the United States than PSK, but overall there have been fewer studies of these products combined with conventional therapy than there have been with PSK. The two products will likely be found to be more or less equivalent in activity as further studies are completed. Maitake extracts have been shown to potentiate the activity of Carmustine against prostate cancer cells in vitro.[69]

Enzymes

Pancreatic enzymes have been used as cancer support since the works of John Beard were published in the early 1900s. The best-known modern advocate of pancreatic enzymes for cancer therapy is Nicholas Gonzalez, MD. In an unblinded study of 10 patients with Stage II to IV pancreatic cancer, 81% survived for 1 year, 45% survived for 2 years, one patient survived for more than 3 years, and one was alive and well at 4 years. This is compared with a 10% typical 2-year survival with conventional chemotherapy.[70]

A recently published study failed to demonstrate benefit of the Gonzales protocol compared with conventional chemotherapy. The patients who chose chemotherapy lived almost three times longer than those following the Gonzalez program.[71]

Clinical studies have compared the survival of patients when enzymes have been added to conventional chemotherapy, with improved results in lung cancer, gastric cancer, ovarian cancer, colon cancer, and multiple myeloma. The results indicated fewer side effects of treatment, and most studies also demonstrated increased survival in the patients receiving the enzyme preparations.[72] Some studies indicated that enzyme preparations may produce beneficial effects by their impact on production and release of cytokines, such as tumor necrosis factor.[73] Enzymes also have anti-inflammatory activity, and it is being discovered that anti-inflammatory drugs inhibit the progression of cancer via multiple pathways, including blockade of cyclooxygenase-2, nuclear factor-κB, and inhibition of metastases.

Cancer patients often have difficulty with digestion, due to side effects of treatment as well as the disease process, and to assure adequate assimilation of foods and supplements, some form of digestive support is desirable. When using enzymes for digestive support, they should be taken with meals; however, when using enzymes for their anti-inflammatory activity, antimetastatic activity, or synergy with chemotherapy, they should be taken between meals on an empty stomach (see Box 50-5).

Recommendations for Specific Individual Chemotherapy Agents

Each chemotherapeutic agent has a typical side effect profile, as well as certain nutrients that can enhance effectiveness while reducing undesirable side effects. Individual agents are discussed as follows with notes regarding nutrients to be considered in addition to the basic protocol mentioned previously. Unless there is reason to give larger doses of a nutrient already mentioned under General Recommendations, it is not repeated or discussed in this section. For a more complete resource on individual chemotherapy agents, their actions, and side effects, the reader is referred to Chu and DeVita's *Physician's Cancer Chemotherapy Drug Manual 2010*.[74]

Anthracyclines, Including Adriamycin, Epirubicin, and Doxil

Adriamycin (Doxorubicin) is an antitumor antibiotic agent isolated from the *Streptomyces* species. It inhibits DNA synthesis and RNA polymerases, as well as having a secondary action of inhibiting topoisomerase II.[74] Side effects include hair loss, leukopenia, nausea and vomiting, and cardiotoxicity. Evidence indicates that Doxorubicin may increase the risk of secondary leukemia.

The biggest concern with anthracyclines is the potential for irreversible cardiotoxicity. Several studies suggest this damage to be due to free radical injury to the mitochondria. By the time symptoms manifest clinically, the damage may be irreversible.[75] Fortunately, several nutrients can protect against this damage, including vitamin C, vitamin E, L-carnitine, and Coenzyme Q10 (CoQ10).[76-78] Fortuitously, several of these agents were also found to increase the beneficial effects of Doxorubicin.

When patients receive anthracyclines, they should drink additional green tea, which has been shown to enhance 2.5-fold the inhibitory effects of Doxorubicin on tumor growth by increasing the concentration of the chemotherapy agent in tumor cells, but not in healthy cells.[79] Genistein also increased the antitumor effects of Doxorubicin and was noted to be effective in both ER positive breast cancer cells and in ER-negative cells, which tend to be more difficult to treat.[80]

Cytoxan

Cytoxan (cyclophosphamide) is an alkylating agent that is inactive until transformed by the p450 enzyme system into cytotoxic metabolites, which are active in all phases of the cell cycle.[81] It is notable for being orally active and not requiring IV administration. Cytoxan is used in several common chemotherapy combinations for the treatment of breast and ovarian cancers, leukemias and lymphomas, and several types of sarcoma. The major side effects of cytoxan include myelosuppression, nausea and vomiting, bladder toxicity, and alopecia. There is also an increased risk of bladder cancer and acute leukemia's long-term side effects. Cytoxan also has some cardiac toxicity that can be synergistic when combined with Adriamycin, as it is often used for breast cancer.

Natural products of benefit with this agent include fish oils, folic acid, vitamin E, *Withania somnifera* (ashwagandha), and mushroom extracts. Fish oils have been shown to enhance the antitumor efficacy of cytoxan while simultaneously exerting a protective effect against side effects, possibly due to changes in liver p450 enzyme activity.[82] The benefits of folic acid with cytoxan were mentioned previously and included decreased side effects, as well as an increase of antitumor response from 53% in folate-deficient animals to 97% in folate replete rats. Vitamin E combined with cyclophosphamide produced a stronger antitumor

response than the chemotherapy alone in rats with fibrosarcoma and in rats with prostate cancer.[83] Mushroom extracts from *Coriolus versicolor* have been shown to be helpful in partially reversing the immunosuppression induced by cytoxan.[84]

Because of the tendency to cause cystitis, it is important to keep the patient well hydrated when taking cytoxan. Patients should consume at least 2 quarts of fluids daily while on this drug.

Cisplatin, Carboplatin, and Oxaliplatin

Platinum-based agents cause cross-linking of DNA leading to inhibition of DNA synthesis and cell replication. Cisplatin is used primarily for ovarian cancer and testicular cancer. Its use is limited by the side effect profile and higher degree of toxicity, particularly nephrotoxicity, neurotoxicity, and myelosuppression. Carboplatin is used for similar treatments but is generally better tolerated, especially when given in lower weekly doses.

One of the best studied natural supports during treatment with platinum agents is the concurrent use of glutathione. Combining IV glutathione immediately before administration of cisplatin was shown to reduce side effects, including nephrotoxicity, neurotoxicity, and myelosuppression without reducing the effectiveness of the chemotherapy against tumors. Most studies showed slight trends toward increased response to chemotherapy. In some cases, this was attributed to the fact that dose reductions due to side effects were not required, and therefore patients received a larger total cumulative dose.[85-87] Similar results have recently been published demonstrating similar benefits with a newer platinum compound, Oxaliplatin, which was recently approved for use in the United States.

Simultaneous co-administration of selenium with cisplatin allowed for higher doses with less toxicity and a higher therapeutic index.[88,89] Milk thistle extracts can also reduce the toxicity of cisplatin, but should probably be avoided on the day of treatment to prevent overly rapid clearance of the chemotherapy.

Vitamin A showed a synergistic effect when combined with cisplatin for head and neck cancers. Beta-carotene supplements are not recommended at this time except in dietary sources because of research suggesting it may actually increase death rates in cancer patients, particularly smokers. Vitamin C also improves the antineoplastic activity of cisplatin, as does vitamin E.[90] Spleen extracts used in combination with cisplatin demonstrated a stabilizing effect on white blood cells, body weight, and fatigue.[85,91] PSK enhanced cytotoxicity of cisplatin against human ovarian cancer cells, but not normal cells.[92]

Fluorouracil and Capecitabine (Xeloda)

Fluorouracil and related drugs, capecitabine (Xeloda) and fluorodeoxyuridine, are pyrimidine analog antimetabolites. 5-FU is primarily used for colorectal cancers and as part of the combination of cytoxan, MTX, and 5-FU used for breast cancers. It is also used to treat pancreatic cancer, ovarian cancer, head and neck cancers, and basal cell cancers of the skin.

Toxicity and side effects include mucositis (mouth sores), diarrhea, and bone marrow depression. An unusual symptom is hand–foot syndrome, which is characterized by redness, swelling, and numbness in the hands and feet. Neurologic symptoms may include confusion and seizures. 5-FU can also cause inflammation and blockage of the tear ducts and chronic conjunctivitis. It can cause cardiac changes, although not as frequently or severely as those from Adriamycin.

Vitamin E has been demonstrated to increase the antitumor activity of 5-FU against colorectal cancer both in vitro and in vivo by causing an upregulation of the proapoptotic enzyme p21.[93] Other studies have suggested an augmentation of the proapoptotic protein "Bax" in response to vitamin E combined with 5-FU.[94] Vitamin B_6 at 100 mg/day has shown some benefit in reducing the incidence and severity of hand–foot syndrome.[95] Other studies have used up to 100 mg B_6 three times daily with benefit.

Methotrexate

MTX is an antifolate analog that works via inhibition of the enzyme dihydrofolate reductase, blocking the conversion of folic acid into its active metabolite folinic acid. Without adequate folinic acid, cells cannot duplicate their DNA. Folic acid in the levels of a multivitamin do not interfere with the action of this drug, but higher doses should be avoided.

The primary toxicity of MTX is myelosuppression. Other toxic symptoms include mucositis, which can be severe enough to limit dosage. Nausea and vomiting are dose dependent. MTX can lead to acute renal failure, and both liver enzymes and kidney functions must be monitored regularly during treatment. Less common side effects include lung inflammation or pneumonitis and severe headaches. Patients can also develop skin rashes, itching, photosensitivity, and hyperpigmentation. An unusual condition known as "radiation recall" can occur where areas previously irradiated again develop redness and pain. Both men and women can experience gonadal failure after treatment with MTX.

Several interactions with common medications should be avoided while receiving treatment with MTX. The first is to avoid aspirin and other anti-inflammatory medications. These medications can reduce the renal elimination of MTX, leading to higher blood levels and higher toxicity. Penicillin can also produce a similar effect and should be avoided during treatment.

The amino acid glutamine has been shown to increase the intratumoral levels of MTX in rats. This may be due to the effect of glutamine in decreasing the intratumor levels of glutathione, making tumors more susceptible to the MTX.[96] Glutamine is a primary nutrient for enterocytes lining the GI tract, and using glutamine during chemotherapy appears to reduce incidence of mucositis and diarrhea caused by the MTX. Vitamin A has also been demonstrated in animal studies to limit the GI damage from MTX without reducing the antitumor benefit of the drug.[97]

Paclitaxel (Taxol), Docetaxel (Taxotere), and Abraxane

The taxanes are semisynthetic isolates from Yew species (Pacific yew for paclitaxel [Taxol] and European yew for docetaxel [Taxotere]). Both drugs bind tubulin, resulting in microtubule polymerization and inhibition of mitosis and cell division. First approved for ovarian cancer, taxanes are now used for a wide variety of tumor types, including breast, lung, gastric, bladder, prostate, esophageal, and head and neck cancers. Both agents can also be used as radiosensitizers, making tumors more sensitive to radiotherapies.

Side effects include hypersensitivity reactions, neuropathy, arthralgia and myalgias, mucositis, onycholysis, and myelosuppression. Taxol tends to cause greater arthralgia and myalgia, whereas Taxotere causes greater myelosuppression.

Nutrients helpful with these agents include vitamin C, glutamine, and essential fatty acids (EFAs). Vitamin C has been demonstrated in vitro to improve the response to Taxol in a partially synergistic manner.[90] Glutamine 10 g three times a day is helpful in reducing the myalgias and neuropathy associated with the taxanes.[98] EFAs, including γ-linolenic acid, α-linolenic acid, EPA, and DHA, all enhanced the cytotoxic activity of Taxol against human breast cancer cells in an in vitro model. Of these EFAs,

γ-linolenic acid was the most active and linoleic acid was found to have no benefit.[99]

Many other nutrients are potentially beneficial with the agents mentioned, as well as many other chemotherapy agents, but space limitations prohibit more extensive discussion of this topic.

RADIATION

Along with surgery and chemotherapy, radiation completes the triumvirate of standard therapies for most cancers. Radiation works by causing ionizing damage to the DNA of cells. In most cases this does not cause immediate cell death but leads to apoptosis the next time the cell tries to divide. The effects of radiation are more localized than that of chemotherapy. This can be either an advantage or a disadvantage depending on the situation. It does limit side effects to the region being radiated but misses any malignant cells outside the field of treatment.

Radiation can be used as primary therapy to shrink tumors or postoperatively to limit survival of any malignant cells potentially missed by the surgical procedure. Radiation can also be used for management of metastatic lesions and for palliative reduction of tumors that are causing symptoms such as bone metastases.

Types of Radiation Therapy

Radiation therapy (RT) generally refers to the use of ionizing radiation from a machine source or a radioactive isotope, but in the broadest sense, the term could also be used to refer to other forms of radiant energy such as photodynamic therapy and hyperthermia treatments. This section deals only with forms of ionizing radiation.

Ionizing radiation generated from machine sources can be divided into several types, including photon radiation, neutron therapy, and proton therapy. Neutrons have mass but no charge, whereas protons have mass and a positive charge. Particle radiation has some advantages, including the ability to be effective even in low-oxygen environments.

Machine-Generated Beams

Machine-generated beams come in several forms, including two-dimensional (2-D) external beam therapy, three-dimensional (3-D) conformal therapy, intensity-modulated radiation therapy (IMRT), and tomotherapy. The degree of sophistication and control of field shape increases with each of the listed types. The 2-D external beam is the oldest form and causes the most collateral damage to healthy tissues. The 3-D conformal therapy and IMRT use more angles of treatment and field-shaping collimators to reduce radiation exposure of healthy tissues. The newest and most sophisticated form of treatment is tomotherapy, in which the field and dose are administered according to results of a simultaneous CT scan, thus permitting a degree of targeting accuracy impossible to achieve until recently. Another precise form of RT is gamma-knife surgery, used primarily for intracranial neurologic lesions.

Brachytherapy

Brachytherapy is the use of localized radiation sources placed within the tumor. This may include permanent placement of seeds such as is now common in prostate cancer or temporary placement of a high-intensity source within a tumor or operative site. Examples include high-dose brachytherapy for the prostate, in which the radioactive seeds are placed within the prostate for short periods, or the newer procedure of brachytherapy within a lumpectomy site immediately after surgery. In both cases the advantage is that a precise dose can be administered to the areas of greatest concern, while less radiation reaches healthy tissue.

Radioimmunotherapy

Radioimmunotherapy, the final form of radioactive treatment, includes the use of radioactive moieties linked to a monoclonal antibody, forming radioimmunoconjugates that are then injected into the bloodstream. The monoclonal antibody targets the appropriate abnormal tissue marker and delivers the bulk of the dose to specific tumor tissues while sparing most other tissues. An example of this therapy is Bexxar, which uses radioactively linked monoclonal antibodies to treat lymphoma. A similar treatment, without the monoclonal antibodies, is the use of radioactive iodine-11, which is used to treat thyroid cancer. Because most of the iodine is taken up by the thyroid, the majority of the radioactivity is also delivered to the tumor.

Side Effects of Radiation Therapy

In general, most patients find RT more tolerable than chemotherapy, but the type and extent of side effects is quite variable. Factors affecting this include the location of the tumor, the size of the treatment field (and the organs or tissues within the field), previous or concurrent chemotherapy (which may act as a radiosensitizer), and the presence or absence of radioprotective agents.

Radiation side effects can be divided into early and late effects. Typical early side effects include localized superficial burning, discoloration and desquamation, fatigue, reduced blood counts, and collateral damage to adjacent nerves, organs, and tissues within the field of treatment. Late or long-term side effects can include increased risk of secondary cancers, permanent scarring or fibrosis of tissues, and impaired organ function.[100] All side effects are variable according to the location of treatment and which adjacent tissues may experience direct or collateral damage. This is why it is important to use the newest and most sophisticated machinery available, because of its ability to limit radiation exposure to uninvolved tissues.

When designing a treatment program for a patient undergoing RT, it is important to ascertain the type of radiation being planned, the areas in the treatment field, and the adjacent organs. For example, only radiation to the abdomen is likely to cause nausea, whereas radiation to the prostate can lead to either proctitis or cystitis if either tissue is within the field. Early effects of head and neck radiation include severe mucositis and pain, often resulting in dehydration and inability to eat, but late effects are more likely to include dry mouth due to damage to salivary glands. Radiation to the outer portions of the breast are unlikely to damage the heart, lungs, or esophagus, but treatment to the medial breast may damage these tissues.

Naturopathic Support During Radiotherapy

Naturopathic support during RT has four goals:

1. Help the patient to decide if radiation is appropriate by reviewing all the relevant survival data with the patient. An example is reviewing data for radiation versus surgery versus hormonal therapy for a prostate cancer patient. Each choice has advantages and disadvantages, so patients appreciate help in understanding the pros and cons of each.
2. If a patient undergoes radiotherapy, help him or her identify the most advanced equipment available to maximize tumor destruction while reducing collateral damage to healthy tissues.

3. Consider radiosensitizing support to increase the degree of tumor death after treatment.
4. Consider whether radioprotective agents are appropriate and which ones to use.

The first two steps require some previous understanding by the provider of treatment options for common tumor types and which local or regional centers may offer those options. For example, as of this writing, very few centers in the entire United States offer tomotherapy or proton beam therapy.

Radiopotentiation

Various conventional and natural therapies can improve the tumoricidal benefits of RTs. Certain pharmaceutic agents, including 5-FU, paclitaxel, gemcitabine and cisplatin are sometimes administered concurrently with radiation to increase the damage to tumor DNA. Radiation is also known to be less effective in hypoxic tissues, so radiation oncologists use various methods to increase oxygenation, including hyperthermia (increases local circulation via vasodilation), carbogen gas inhalation, and hemoglobin-inducing therapies, including either erythropoietin or transfusions.

Natural therapies to potentiate radiation benefits can act by two methods: by directly enhancing of tumoricidal action or by preventing the need for dose reduction due to excessive side effects. Because the second action is actually a radioprotective one, it is discussed later in the radioprotection section.

Research on natural radiopotentiators is limited. One agent shown to have benefit is melatonin. In a study of 30 patients with glioblastoma multiforme randomized to receive either RT alone or RT plus melatonin, those receiving melatonin along with RT had significantly higher survival at 1 year. In addition, the melatonin group had fewer side effects than those treated by RT alone.[101]

Flavonoids including Genistein and quercetin were also shown to increase tumor cell death in combination with RT, with Genistein being most active. Although RT alone reduced surviving hepatoma cell population by a factor of 20, RT plus continuous Genistein during radiation led to a reduction by a factor of 10,000.[102]

Ashwagandha, mentioned earlier, is a well-known Ayurvedic medicinal herb that has also shown radiosensitizing properties. A small in vivo study in hamsters indicated that withaferin A, isolated from Withania, increased sensitivity to radiation by approximately 50% with no untoward toxicity.[103]

PSK has also been shown to improve survival in a number of cancers, most likely due to enhancement of immune function. In a study of 185 nonsmall cell lung cancer patients treated with combined RT and PSK versus RT alone, patients receiving the combined treatment had significantly improved survival. Patients with Stages I and II disease had a 5-year survival of 39% with combined RT and PSK versus only 22% in the RT only group. For patients with Stage III disease, the 5-year survival was 16% with combined RT and PSK versus 5% in the RT only group.[104]

Radioprotection

Many nutrients have shown radioprotective activity, and not all can be discussed here due to space constraints. In most cases, all antioxidants seem to have some degree of radioprotective activity. At massive doses (i.e., 1400 to 2800 mg CoQ10 daily), modest reductions of RT-induced tumor kills have been seen. However, at normal or mildly elevated doses (i.e., 700 mg CoQ10 daily), no reduction of tumor kill was seen.[105]

Similar results have been noted with vitamins E and C. Typical doses given during or immediately before RT led to normal or enhanced tumor responses to RT.[106,107] Similar conclusions were reached about other antioxidants, including *N*-acetylcysteine (NAC), in that "clinically relevant concentrations of NAC are incapable of protecting tumor cells against clonogenic killing by x-rays …"[108] A clinical trial done at Cancer Treatment Centers of America looked at the effect of nutritional supplements on tumor response rates in prostate cancer patients who underwent RT. The therapeutic response to radiation did not appear to be inhibited by antioxidant activity.[109] The safest conclusion to be made is that standard doses of antioxidants, such as those in a high-potency multiple vitamin minerals, do not reduce the efficacy of RT, but do appear to have protective activity for normal cells. Furthermore, because antioxidants are a crucial factor in the apoptotic cascade, they may enhance the secondary response to RT by triggering greater rates of apoptosis after treatment.[110] However, until we know conclusively that megadoses of antioxidants do not interfere with radiation benefits, it seems reasonable to focus more on other botanicals with known benefits and to limit use of antioxidants such as vitamin E to doses found in multivitamins. If nothing else, this will minimize conflicts with radiation oncologists who routinely advise avoiding all antioxidants during RT.

Glutamine has shown benefit in protecting mucus membranes during RT and in healing radiation-induced enteritis and proctitis after RT. When given in combination with RT, glutamine protects the patient and increases the selectivity of therapy for the tumor.[111,112]

Alkylglycerols and squalene have also demonstrated radioprotection, in particular helping to maintain bone marrow function and white blood cell counts during RT. Squalene has also demonstrated the ability to prolong survival after lethal doses of whole body radiation.[113]

Various topical agents can be applied to reduce burning of the skin surface during RT. These include aloe vera gel (the fresh leaf is most effective), vitamin E, methylsulfonylmethane creams, glutathione gels, and calendula creams.[114] These may be applied nightly throughout the treatment but must be completely washed off each morning before treatment so as to not alter the penetration or scattering of the radiation beams. A degree of redness and peeling is common, particularly in fair-skinned individuals, but the agents mentioned here do seem to help with healing and discomfort.

Summary

RT is a critical part of the treatment plan for many cancer patients at some time during the course of their disease. Even when not curative, RT can improve quality of life by spot treatment to metastatic lesions in bone and brain tissue. If patients will be undergoing RT, they can safely take typical doses of vitamins and minerals without concerns about interference, but should probably avoid megadoses. Radioprotective agents such as glutamine and radiopotentiators such as quercetin, ashwagandha, and PSK can be used to maximize therapeutic benefit of RT. Topical burn creams may be used but must be removed before receiving each dose of RT.



ANTIOXIDANTS DURING CHEMOTHERAPY AND RADIATION

The use of antioxidants with chemotherapy is one of the most controversial aspects of natural support during cancer treatments. The thinking of conventional oncologists is that most chemotherapeutic agents work via oxidative damage to the DNA of cancer

cells. Therefore, anything that protects the cells from oxidative damage might interfere with the action of the chemotherapy.[115] However, looking at the published research on this topic, the results typically showed that most antioxidants not only reduced the side effects of chemotherapy but actually improved the tumoricidal action. This finding appears to be consistent across a wide range of chemotherapy agents and types of antioxidants. Extensive reviews of this topic are available.[116-121]

How is it possible to have a theoretic problem but no apparent negative actions in reality? A review article in *Scientific American* explained the seeming contradiction in the following way: "[F]or many years it was assumed that radiation therapy and many chemotherapeutic drugs killed malignant cells directly by wreaking widespread havoc in their DNA. We now know that the treatments often harm DNA to a relatively minor extent. Nevertheless the affected cells perceive that the inflicted damage cannot be easily repaired and they actively kill themselves."[122] This process of active cell death is also known as apoptosis. An article in the journal *Cell* stated that cancer cells often fail to undergo apoptosis in response to treatment, and those agents that stimulate apoptosis would be beneficial.[123] This is exactly the action of the antioxidants. This ability of antioxidants to promote apoptosis in cancer cells probably explains the apparent contradiction.

Another possible explanation for the apparent contradiction is that the original theory is wrong and that oxidative damage is not the primary mediator of the actions of chemotherapy. In experimental studies, co-administration of free radical scavengers did not reduce the antitumor effect of Doxorubicin and cisplatin, and survival of animals was increased in the group receiving the antioxidants with treatment compared with those receiving chemotherapy alone.[124] Another recent experiment demonstrated that the commonly used chemotherapy agents cisplatin and VP-16 induced tumor cell death in the absence of any detectable lipid or protein oxidation. Furthermore, it appeared that oxidative stress actually reduced the effectiveness of the chemotherapy agents, and that addition of antioxidants enhanced the tumor killing action.[125,126]

In addition to damaging organs and increasing the risk of secondary cancers, oxidative byproducts of chemotherapy may be counterproductive because free radicals and reactive oxygen species increase processes such as production of vascular endothelial growth factor, which has been implicated as crucial for growth and invasiveness of tumors.[127]

On the basis of all these data it is this author's opinion that the benefits of appropriately chosen and dosed antioxidants outweigh any theoretic concerns. This conclusion is based on the following logic:

1. Many patients are forced to discontinue or delay chemotherapy due to side effects that can be significantly reduced with nutrition.
2. Many other patients refuse to even consider starting chemotherapy because of fear of side effects.
3. Chemotherapy and radiation have been implicated in causing increased rates of secondary cancers and late complications, many of which are theoretically preventable with nutrition.
4. Approximately 50% of tumors have been found to have abnormal p53 enzymes, making them less responsive to chemotherapy. This abnormality is partially reversible with antioxidants. Increasing p53 activity improves apoptotic response to chemotherapeutic agents.
5. Chemotherapy for common cancers has a limited ability to produce meaningfully significant improvements in survival when used alone. Combination with antioxidants allows the use of higher, and potentially more effective, doses without the benefit-limiting results of dose reductions and dose interruptions caused by excessive side effects.

Antioxidants, when combined with chemotherapy and radiation, have been shown to reduce negative side effects, increase tumor responses, and increase survival times in numerous studies. Therefore, with a few specific exceptions, there is no reason to advise patients against the use of a nutrient merely because it is an antioxidant when undergoing conventional cancer treatment; they should be considered an important part of any naturopathic treatment regimen. However, at the same time, there are generally better and more specific nutrients for almost all treatments that can benefit patients more than merely throwing massive doses of antioxidants at them. It makes more sense at this point in time to use nutrients shown to improve responses to specific agents regardless of whether or not they are antioxidants, rather than just loading patients with antioxidants alone.

DRUG–NUTRIENT INTERACTIONS

An area that is largely ignored and yet has substantial potential to interfere with the therapeutic benefits of conventional treatment is the possibility of drug–nutrient interactions. Interference (or benefit) can occur at the level of absorption, at the level of hepatic activation or clearance, or at the level of intracellular pathways within the tumor.

All medications, both natural and conventional, that the patient is using should be assessed for potential interactions. For example, it was just recently accepted that common antidepressants given for reduction of hot flashes can interfere with the therapeutic benefit of tamoxifen by inhibiting the activity of cytochromes p450, 2C9, and 2D6, which are necessary for the hepatic activation of tamoxifen into its active metabolite.[128]

DIET FOR CANCER PATIENTS

The central role of diet in increasing the risk and preventing the occurrence of cancer is well documented.[129] Research indicates that 30% to 40% of all cancers can be prevented by lifestyle and dietary measures. Although no diet has been demonstrated to cure cancer, eating a diet known to prevent cancer and avoiding foods and dietary behaviors known to increase the risk of cancer is an extremely important component of comprehensive care.

In general, the diet should be high fiber, whole food based (the foods organically grown), rich in fruits, vegetables, beans, seeds, and cold water fish. It should be low in high-calorie, low-nutrient foods, such as junk foods, candy, and soft drinks. Allium and cruciferous vegetables, especially broccoli sprouts, are beneficial. For a complete discussion and a useful resource for patients, see *How to Prevent and Treat Cancer with Natural Medicine*.[130]

SECONDARY PREVENTION

Active conventional cancer treatment can be as simple as surgery alone, surgery plus 6 weeks of radiation, or 12 weeks of adjuvant chemotherapy after surgery. It can also be an extended process over many years with periods of treatment followed by remissions and recurrences that are then treated again with chemotherapy or radiation.

As should be completely clear from the previous discussion, the author does not believe that natural medicine alone is adequate treatment for most cancers. However, by understanding newer concepts of cancer biology, we can apply these understandings to

modify physiology in ways to reduce tumor progression and enhance natural defenses against cancer.

Most recent research leads us to realize that cancer is more than just accumulated genetic alterations. Another way to think about cancer is as a breakdown in cellular signaling and regulation. Research has shown derangements in one or more of the following in most cancers:

- Altered hormonal status (increased estrogen, altered estrogen clearance or ratios, or changes in testosterone)
- Hyperinsulinemia and metabolic syndrome
- Chronic inflammation
- Altered intracellular signaling
- Altered signaling from the host environment. Differences in the regulatory signaling from surrounding tissues can even impact the behavior of cancer cells
- Increased cell division
- Decreased apoptotic signaling and caspases
- Oxidative stress, hypoxia inducible factor, and angiogenesis
- Mitochondrial dysfunction
- Epigenetic changes leading to altered activity of DNA regardless of mutations
- Nutrient deficiencies (reduced levels of vitamin D, antioxidants, essential fatty acids, etc.)
- Differences in activity of tumor stem cells versus tumor stromal cells

Recognizing these differences and identifying ways to beneficially modify them with natural medicines and lifestyle will be helpful at all stages of cancer treatment, but perhaps is most important in extending remission or controlling the growth from microscopic disease to more active disease. In some cases like prostate cancer, modifying these factors may be the only treatment needed. Studies have shown that active lifestyle modification can frequently control or even regress some early and nonaggressive prostate cancers.[131]

Developing a long-term program for secondary prevention involves identifying and modifying as many risk factors as possible in the patient. Some can be determined by history (use of hormone replacement therapy, smoking, alcohol, exposure to radiation, xenobiotic chemicals, etc.). Others will be noted on physical examination (obesity, abdominal adiposity, nodular prostate, lymphadenopathy), and most risk factors will be identified on laboratory evaluation. Testing will vary with type of cancer risk, family history, sex of patient, etc., but in most cases should at least include complete blood count, comprehensive chemistry, 25-hydroxy vitamin D levels, markers for inflammation (C-reactive protein, cytokines, etc.), markers for hormonal and metabolic derangement (2:16 estrogen ratios, insulin levels, hemoglobin A_{1c}, lipids) as well as individual risk factors, such as levels of heavy metal or xenobiotics if suspected as risk factors.

The naturopathic concept of the body as an integrated ecosystem fits well with this part of cancer therapy. Each derangement of homeostasis can lead to other alterations and the ripple effects can cumulatively become clinically significant. Conversely, each modification that improves cellular communication, signaling, cell cycling, etc., can reduce risk of cancer progression.

This author often tells his patients that it is not our goal to destroy every single cancer cell in their body, but rather to make their internal ecology such that any stray cancer cells that are present find it difficult or impossible to grow and spread.

SUMMARY

Cancer therapy can be divided into several broad phases: the first is prevention and risk factor reduction with healthy diet and lifestyle along with regular examination and screening tests. With newer information about genomics and epigenetics, prevention may also become more proactive in identifying individual risk factors and correcting for these before cancer ever occurs. The second phase would be active treatments, including surgery, chemotherapy, and radiation supported with natural therapies. Naturopathic therapies should be carefully selected to support and magnify the benefits of conventional therapies, while reducing side effects. During this phase it is critical to avoid any drug–nutrient interactions that could reduce or negate the benefits of treatment. The next phase might include "maintenance therapy," including treatments such as antiestrogen drugs after treatment of breast cancer, but also including newer drugs such as tyrosine kinase inhibitors as well as antiangiogenic diets. The final phase is secondary prevention after patients have completed active treatment. At this stage, naturopathic therapies will often be the most important component of protection, utilizing all the newest understandings of cancer biology, nutrients as biological response modifiers, and lifestyle modification as a way to alter cell biology and immune function.

Those interested in treating more cancer patients are well advised to embark on an ongoing study plan to keep updated on the ever evolving understanding of cancer biology and how this understanding can be filtered through naturopathic knowledge and training to design appropriate treatments for each stage of cancer care.

Treating cancer is more complex than many other conditions because the clinical situation changes rapidly, treatments change frequently, and the volumes of information to digest continue to grow exponentially. The key to success in this endeavor is not to have the "cookbook answer" of what nutrient to match with what disease or chemotherapy agent. Rather, it is to understand the disease process, the treatments, and the patient enough to manage every eventuality as successfully as possible. Once again, it is comforting for the patient to work with oncologists who have the therapies and experience to deal with the occasional crisis, while using the naturopathic treatments to reduce the likelihood of crisis occurring at all. In the integrated cancer center where the author works, it is unusual for patients to need hospitalization due to side effects of their treatments.

Naturopathic medicine can play a large role in improving the quality of life and success of cancer treatments and should be a critical part of any oncology treatment protocol.

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CHAPTER 51

Chronic Candidiasis

Michael T. Murray, ND

CHAPTER CONTENTS

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INTRODUCTION

In the past 30 years overgrowth in the gastrointestinal (GI) tract of the usually benign yeast *Candida albicans* has become increasingly recognized as a complex medical syndrome known as chronic candidiasis, or the yeast syndrome.[1,2] Specifically, the overgrowth of *C. albicans* is believed to cause a wide variety of symptoms in virtually every system of the body, with the GI, genitourinary, endocrine, nervous, and immune systems being most susceptible.[3]

Although chronic candidiasis has been clinically defined for a long time, it was not until Orion Truss published *The Missing Diagnosis* and William Crook published *The Yeast Connection* that the public and many physicians became aware of the magnitude of the problem.[1,2]

GENERAL CONSIDERATIONS

Normally, *C. albicans* lives harmoniously in the inner warm creases and crevices of the digestive tract (and vaginal tract in women). However, when this yeast overgrows, immune system mechanisms are depleted, or when the normal lining of the intestinal tract is damaged, the body can absorb yeast cells, particles of yeast cells, and various toxins.[3] As a result, there may be significant disruption of body processes, resulting in the development of the "yeast syndrome."

This syndrome is generally characterized by patients saying they "feel sick all over." Fatigue, allergies, immune system malfunction, depression, chemical sensitivities, and digestive disturbances are just some of the symptoms patients with the yeast syndrome may experience.[3]

The typical patient with the yeast is female, as women are eight times more likely to experience the yeast syndrome compared with men due to the effects of estrogen, birth control pills, and the higher number of prescriptions for antibiotics (Box 51-1).[4]

Causal Factors

Chronic candidiasis is a classic example of a "multifactorial" condition, as shown in Box 51-2. Therefore, the most effective treatment involves addressing and correcting the factors that predispose to *C. albicans* overgrowth. It involves much more than killing the yeast with antifungal agents, whether synthetic or natural.

Antibiotics

Prolonged antibiotic use is believed to be the most important factor in the development of chronic candidiasis in most cases. Antibiotics, through suppressing normal intestinal bacteria that prevent yeast overgrowth and suppression of the immune system, strongly promote the overgrowth of *Candida*.

There is little argument that, when used appropriately, antibiotics save lives. However, there is also little argument that antibiotics are seriously overused. Although the appropriate use of antibiotics makes good medical sense, what does not make sense is reliance on them for such conditions as acne, recurrent bladder infections, chronic ear infections, chronic sinusitis, chronic bronchitis, and nonbacterial sore throats. Relying on antibiotics in the treatment of these conditions does not make sense, since either the antibiotics rarely provide benefit or these conditions are effectively treated with natural measures.

BOX 51-1 Typical Chronic Candidiasis Patient Profile

Sex: **Female**

Age: **15 to 50 years**

General Symptoms
- Chronic fatigue
- Loss of energy
- General malaise
- Decreased libido

Gastrointestinal Symptoms
- Thrush
- Bloating, gas
- Intestinal cramps
- Rectal itching
- Altered bowel function

Genitourinary System Complaints
- Vaginal yeast infection
- Frequent bladder infections

Endocrine system complaints
- Primarily menstrual complaints

Nervous System Complaints
- Depression
- Irritability
- Inability to concentrate

Immune System Complaints
- Allergies
- Chemical sensitivities
- Low immune function

History
- Chronic vaginal yeast infections
- Chronic antibiotic use for infections or acne
- Oral birth control usage
- Oral steroid hormone usage

Associated Conditions
- Premenstrual syndrome
- Sensitivity to foods, chemicals, and other allergens
- Endocrine disturbances
- Eczema
- Psoriasis
- Irritable bowel syndrome

Other
- Craving for foods rich in carbohydrates or yeast

BOX 51-2 Predisposing Factors to *Candida albicans* Overgrowth

- Decreased digestive secretions
- Dietary factors
- Impaired immunity
- Nutrient deficiency
- Drugs (particularly antibiotics)
- Impaired liver function
- Underlying disease states
- Altered bowel flora
- Prolonged antibiotic use

Syndromes Related to the Yeast Syndrome

Eventually the "yeast syndrome" will likely be replaced by a more comprehensive term to include small intestinal bacterial overgrowth and the leaky gut syndrome. Both conditions are often associated with *C. albicans* overgrowth and may produce identical symptoms to the yeast syndrome. For further discussion of small intestinal bacterial overgrowth and leaky gut syndrome, see Chapters 10 and 20.

DIAGNOSIS

Questionnaire

One of the most useful screening methods for determining the likelihood of yeast-related illness is a comprehensive questionnaire (see Appendix 1).

Although the *Candida* questionnaire can help, the best method for diagnosing chronic candidiasis is clinical evaluation by a physician knowledgeable about yeast-related illness. More than likely, the manner in which the doctor will diagnose the yeast syndrome will be based on clinical judgment from a detailed medical history and patient questionnaire. He or she may also employ laboratory techniques such as stool cultures for *C. albicans* and measurement of antibody levels to *C. albicans* or *C. albicans* antigens in the blood. Although these laboratory examinations are useful diagnostic aids, they should be used to confirm the diagnosis. In other words, the diagnosis is best made by evaluation of a patient's history and clinical picture.

The Comprehensive Digestive Stool Analysis

Rather than simply culture a stool sample for the presence of *C. albicans*, the comprehensive digestive stool analysis (CDSA) is more clinically useful (discussed in detail in Chapter 27). This battery of integrated diagnostic laboratory tests evaluates digestion, intestinal function, intestinal environment, and absorption by carefully examining the stool. It is a useful tool in determining the digestive disturbance that is likely to be the underlying factor responsible for *C. albicans* overgrowth. In addition, the CDSA may determine that the symptoms are not related to *C. albicans* overgrowth but rather to conditions such as small intestinal bacterial overgrowth and the leaky gut syndrome.

Antibody and Antigen Levels

Another laboratory method to confirm the presence of *C. albicans* overgrowth is measuring the level of antibodies to *Candida* or the level of antigens in the blood.[3,5] However, these tests are rarely necessary, as the results typically only confirm what the patient history, physical examination, and CDSA reveal. Hence, the test does not change the course of action. Nonetheless, some patients and physicians may desire confirmation that *C. albicans* is a responsible factor in the patient's health equation. In this situation, blood studies can be helpful and can also be used as a way of monitoring therapy.

THERAPEUTIC CONSIDERATIONS

A comprehensive approach is more effective in treating chronic candidiasis than simply trying to kill the *C. albicans* with a drug or

natural anti–*C. albicans* agent. Drugs like nystatin, ketoconazole, and Diflucan, as well as various natural anti–*C. albicans* agents, rarely produce significant long-term results because they fail to address the underlying factors that promote *C. albicans* overgrowth. The pharmaceutical approach is a bit like trying to weed a garden by simply cutting the weeds, instead of pulling them out by the roots. Nonetheless, in many cases it is useful to try to eradicate *C. albicans* from the system, preferably with the help of natural anti–*C. albicans* therapies such as timed-release caprylic acid preparations, enteric-coated volatile oil preparations, or fresh garlic preparations. A follow-up stool culture and *C. albicans* antigen determination will confirm if the *C. albicans* has been eliminated. If it has and symptoms are still apparent, it is likely that the symptoms patients are experiencing are unrelated to an overgrowth of *C. albicans*. Similar symptoms to those attributed to chronic candidiasis can be caused by small intestinal bacterial overgrowth. In this scenario, pancreatic enzymes and berberine-containing plants like goldenseal can be helpful.

In addition to using natural agents to eradicate *C. albicans*, it is important to address predisposing factors, recommend a *C. albicans* control diet, and support various body systems according to the individual patient's need.

Diet

A number of dietary factors appear to promote the overgrowth of *C. albicans*. The most important factors are a high intake of sugar, milk, and other dairy products; foods containing a high content of yeast or mold; and food allergies.

Sugar

Sugar is the chief nutrient of *C. albicans*. It is well accepted that restriction of sugar intake is an absolute necessity in the treatment of chronic candidiasis. Most patients do well by simply avoiding refined sugar and large amounts of honey, maple syrup, and fruit juice.[1-4]

Milk and Other Dairy Products

Several reasons to restrict or eliminate the intake of milk in patients with chronic candidiasis are the following:

- High lactose content promotes the overgrowth of *Candida.*
- Milk is one of the most frequent food allergens.
- Milk may contain trace levels of antibiotics, which can further disrupt the GI bacterial flora and promote *Candida* overgrowth.[1-4]

Mold and Yeast-Containing Foods

Many experts generally recommend that individuals with chronic candidiasis avoid foods with a high content of yeast or mold, including alcoholic beverages, cheeses, dried fruits, and peanuts. Although many patients with chronic candidiasis may be able to tolerate these foods, we think it is still a good idea to eliminate them from the diet. At the least, they should be avoided until the situation is under control.[1-4]

Food Allergies

Food allergies are another common finding in patients with the yeast syndrome.[3] Enzyme-linked immunosorbent assay tests, which determine both immunoglobulin-E and immunoglobulin-G mediated food allergies, are often helpful in identifying food allergies.

Hypochlorhydria

An important step in treating chronic candidiasis in many cases is improving digestive secretions. Gastric hydrochloric acid, pancreatic enzymes, and bile all inhibit the overgrowth of *C. albicans* and prevent its penetration into the absorptive surfaces of the small intestine. Decreased secretion of any of these important digestive components can lead to overgrowth of *C. albicans* in the GI tract. Therefore, restoration of normal digestive secretions through the use of supplemental hydrochloric acid, pancreatic enzymes, and substances that promote bile flow is critical in the treatment of chronic candidiasis. The CDSA can provide valuable information in identifying which factor is most important.

People on antiulcer drugs like Tagamet (cimetidine) and Zantac (ranitidine) actually develop *C. albicans* overgrowth in the stomach.[6] This occurrence highlights the importance of hydrochloric acid in the prevention of *C. albicans* overgrowth. Restoring proper levels of gastric acid by supplemental hydrochloric acid is often quite useful in chronic candidiasis.

Pancreatic enzymes can also be useful in the treatment of chronic candidiasis. As well as being necessary for protein digestion, the proteases serve several other important functions. The proteases are largely responsible for keeping the small intestine free from parasites (including bacteria, yeast, protozoa, and intestinal worms).[7,8] A lack of proteases or other digestive secretions greatly increases an individual's risk of having an intestinal infection, including chronic *C. albicans* infections of the GI tract.

Enhancing Immunity

Recurrent or chronic infections, including chronic candidiasis, are characterized by a depressed immune system. What makes it difficult for these people to overcome chronic candidiasis is a repetitive cycle—a compromised immune system leads to infection, and infection leads to damage of the immune system, further weakening resistance.

The importance of a healthy immune function protecting against *C. albicans* overgrowth is well known by any physician who has seen a patient having acquired immunodeficiency syndrome (AIDS) or taking drugs that suppress the immune system. In either case, severe overgrowth of *C. albicans* is a hallmark feature. The occurrence of *C. albicans* overgrowth in these conditions provides considerable evidence that attaining better immune function is absolutely essential in the patient with chronic candidiasis.

In addition, patients with chronic candidiasis often have other chronic infections, presumably due to a depressed immune system. Typically, this depression of immune function is related to decreased thymus function presenting primarily as depressed cell-mediated immunity. Although expensive laboratory tests can document this depression, it is better to rely on the history of repeated viral infections (including the common cold), outbreaks of cold sores or genital herpes, and prostatic (men) or vaginal (women) infections.

Causes of Depressed Immune Function in Candidiasis

The patient with chronic candidiasis is typically stuck in a vicious cycle (Figure 51-1). With regard to the immune system, a triggering event such as antibiotic use or nutrient deficiency (Box 51-3) can lead to immune suppression, allowing *C. albicans* to overgrow and become more firmly entrenched in the lining of the GI tract. Once the organism attaches itself to the intestinal cells, it competes with the cell and ultimately the entire body for nutrition—potentially robbing the body of vital nutrition. In addition, *C. albicans* secretes a large number of mycotoxins and antigens.[9,10] *C. albicans* is referred to as a "polyantigenic" organism because more than 79 distinct antigens have been identified. Because of

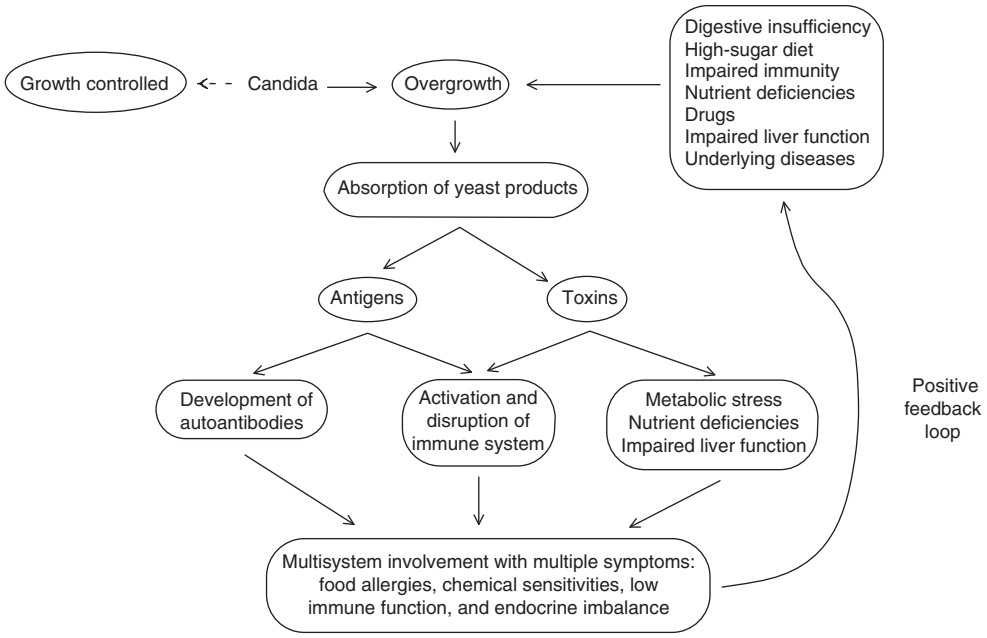


FIGURE 51-1 The vicious cycle of chronic candidiasis.

BOX 51-3 Triggers to Impaired Immunity in Candidiasis

- Antibiotic use
- Corticosteroid use
- Other drugs that suppress the immune system
- Nutrient deficiency
- Food allergies
- High-sugar diet
- Stress

this tremendous number of antigens, an overgrowth of *C. albicans* greatly taxes the immune system.

Restoring Proper Immune Function

Restoring proper immune function is one of the key goals in the treatment of chronic candidiasis. No single magic bullet exists to immediately restore immune function in patients with chronic candidiasis. Instead, a comprehensive approach involving lifestyle, stress management, exercise, diet, nutritional supplementation, glandular therapy, and the use of plant-based medicines is used.

Perhaps the most effective intervention in reestablishing a healthy immune system is employing measures designed to improve thymus function. The clinical remission of oral candidiasis has been shown to be critically dependent on T-cell function.[11,12] Not surprisingly, oral candidiasis occurs in roughly 90% of human immunodeficiency virus positive individuals. Presumably, improving thymus-mediated immunity is critical in the remission of chronic candidiasis as well. Promoting optimal thymus gland activity involves the following:

- Prevention of thymic involution or shrinkage by ensuring adequate dietary intake of antioxidant nutrients, such as carotenes, vitamin C, vitamin E, zinc, and selenium
- Use of nutrients that are required in the manufacture or action of thymic hormones

Promoting Detoxification

Patients with chronic candidiasis usually exhibit multiple chemical sensitivities and allergies, an indicator that detoxification reactions are stressed. Therefore, their liver function must be supported. Improving the health of the liver and promoting detoxification may be one of the most critical factors in the successful treatment of candidiasis.

Damage to the liver is often an underlying factor in chronic candidiasis, as well as chronic fatigue. When the liver is even slightly damaged by chemical toxins, immune function is severely compromised.

The immune system suppressing effect of nonviral liver damage has been repeatedly demonstrated in experimental animal studies and human studies. For example, when the liver of a rat is damaged by a chemical toxin, immune function is severely hindered.[13] Liver injury is also linked to *C. albicans* overgrowth, as evident in studies with mice demonstrating that when the liver is even slightly damaged, *C. albicans* runs rampant through the body.[14]

A rational approach to aiding the body's detoxification involves the following:

- A diet focused on fresh fruits and vegetables, whole grains, legumes, nuts, and seeds
- A healthy lifestyle, including avoiding alcohol and exercising regularly
- A high-potency multiple vitamin and mineral supplement
- Lipotropic formulas and silymarin to protect the liver and enhance liver function
- A 3-day fast at the change of each season

If any of the factors in Box 51-4 apply to the patient, enhancing detoxification is a major therapeutic goal.

Lipotropic Factors

The nutrients choline, betaine, and methionine are often beneficial in enhancing liver function and detoxification reactions. These compounds, referred to as lipotropic agents, promote the flow of fat and bile to and from the liver. In essence, they produce a "decongesting" effect on the liver and promote improved liver

BOX 51-4 Indications of the Need for Detoxification

- More than 20 lb overweight
- Diabetes
- Presence of gallstones
- History of heavy alcohol use
- Psoriasis
- Natural and synthetic steroid hormone use
 - Anabolic steroids
 - Estrogens
 - Oral contraceptives
- High exposure to certain chemicals or drugs
 - Cleaning solvents
 - Pesticides
 - Antibiotics
 - Diuretics
 - Nonsteroidal anti-inflammatory drugs
 - Thyroid hormone
 - History of viral hepatitis

function and fat metabolism. Formulas containing lipotropic agents are useful in enhancing detoxification reactions and other liver functions. Lipotropic formulas have been used for a wide variety of conditions by nutrition-oriented physicians, including a number of liver disorders such as hepatitis, cirrhosis, and chemical-induced liver disease. The daily dosage should be 1000 mg of choline and 1000 mg of methionine or cysteine, or both.

Lipotropic formulas appear to increase the levels of two important liver substances: S-adenosyl-methionine, the major lipotropic compound in the liver, and glutathione, one of the major detoxifying compounds in the liver.[15,16]

Promoting Elimination

In addition to directly supporting liver function, proper detoxification also involves promoting proper elimination. A diet that focuses on high-fiber plant foods should be sufficient to promote proper elimination by supplying an ample amount of dietary fiber. If additional support is needed, fiber formulas can be prescribed. These formulas are composed of natural plant fibers derived from psyllium seed, kelp, agar, pectin, and plant gums like karaya and guar. Alternatively, they can be purified semisynthetic polysaccharides like methylcellulose and carboxymethylcellulose sodium. Psyllium-containing laxatives are the most popular and usually the most effective. Fiber formulas approximate most closely the natural mechanism that promotes a bowel movement. In the treatment of candidiasis, 3 to 5 g of soluble fiber at bedtime should be recommended, especially if antiyeast therapies are employed, to ensure that dead yeast cells are excreted and not absorbed.

Probiotics

Intestinal flora plays a major role in the health of the host, especially in the battle against GI tract infection.[17,18] Intestinal flora is intimately involved in the host's nutritional status and affects immune system function, cholesterol metabolism, carcinogenesis, and aging. Due to the importance of *Lactobacillus acidophilus* and *Bacterium bifidum* to human health, probiotic supplements can be used to promote overall good health. However, probiotics have several specific uses. The four primary uses related to chronic candidiasis are promotion of proper intestinal environment, postantibiotic therapy, vaginal yeast infections, and urinary tract infections.

The dosage of a commercial probiotic supplement is based on the number of live organisms. The ingestion of 5 to 10 billion viable *L. acidophilus* or *B. bifidum* cells daily is a sufficient dosage for most people. Amounts exceeding these may induce mild GI disturbances, whereas smaller amounts may not be able to colonize the GI tract.

See Chapters 115 and 116 for a more comprehensive discussion of these useful agents.

Natural Antiyeast Agents

A number of natural agents have proven activity against *C. albicans*. Rather than relying on these agents as a primary therapy, however, it is important to address the factors that predispose one to chronic candidiasis, especially lack of either hydrochloric acid or pancreatic enzymes. The five approaches we feel most comfortable in recommending as natural agents against *C. albicans* are as follows:

- Caprylic acid
- Berberine-containing plants
- Garlic
- Enteric-coated volatile oil preparations
- Propolis

Most, but not all, patients can achieve benefits from the natural agents described here rather than the drug approach. Use of any effective antiyeast therapy alone likely results in the Herxheimer ("die-off") reaction due to the rapid killing of the organism and subsequent absorption of large quantities of yeast toxins, cell particles, and antigens. The Herxheimer reaction refers to a worsening of symptoms as a result of this dying off. The Herxheimer reaction can be minimized by the following measures:

- Following the dietary recommendations for a minimum of 2 weeks before taking an antiyeast agent
- Supporting the liver by following the recommendations made earlier
- Starting any of the previously described antiyeast medications in low doses and gradually increasing dosages over 1 month to achieve full therapeutic dosage

Caprylic Acid

Caprylic acid is a naturally occurring fatty acid that has been reported to be an effective antifungal compound in the treatment of candidiasis.[19,20] Because caprylic acid is readily absorbed in the intestines, it is necessary to take timed-release or enteric-coated caprylic acid formulas to allow for gradual release throughout the entire intestinal tract.[21] The standard dose for these delayed-release preparations is 1000 to 2000 mg with meals.

Berberine-Containing Plants

Berberine-containing plants include goldenseal *(Hydrastis canadensis),* barberry *(Berberis vulgaris),* Oregon grape *(Berberis aquifolium),* and goldthread *(Coptis chinensis).* Berberine, an alkaloid, has been extensively studied in both experimental and clinical settings for its antibiotic activity. Berberine exhibits a broad spectrum of antibiotic activity, having shown antibiotic activity against bacteria, protozoa, and fungi, including *C. albicans*.[22–28]

Berberine's antibiotic action against some of these pathogens is actually stronger than that of antibiotics commonly used for the diseases these pathogens cause. Berberine-containing plants should be considered in infectious processes involving the previously mentioned organisms. Berberine's action in inhibiting *C. albicans*, as well as pathogenic bacteria, prevents the overgrowth of yeast, which is a common side effect of antibiotic use.

Diarrhea is a common symptom in patients with chronic candidiasis. Berberine has shown remarkable antidiarrheal activity in even the most severe cases. Positive clinical results have been shown with berberine in relieving diarrhea in cases of cholera, amebiasis, giardiasis, and other causes of acute GI infection (e.g., *Escherichia coli, Shigella, Salmonella,* and *Klebsiella*) and may also relieve the diarrhea seen in patients with chronic candidiasis.[29–35]

The dosage of any berberine-containing plant should be based on berberine content. Since there is a wide range of quality in goldenseal preparations, standardized extracts are preferred. Three times a day dosages are as follows:

- Dried root or infusion (tea), 2 to 4 g
- Tincture (1:5), 6 to 12 mL (1.5 to 3 tsp)
- Fluid extract (1:1), 2 to 4 mL (0.5 to 1 tsp)
- Solid (powdered dry) extract (4:1 or 8% to 12% alkaloid content), 250 to 500 mg

Note that the dosage recommendations for berberine would be 25 to 50 mg three times daily or a daily dose of up to 150 mg. This dosage is consistent with the dosage range in the positive clinical studies in patients with GI infections. For children, a dosage based on body weight is appropriate. The daily dose would be the equivalent of 5 to 10 mg of berberine/kg (2.2 lb) body weight.

Berberine and berberine-containing plants are generally nontoxic at the recommended dosages; however, berberine-containing plants are not recommended for use during pregnancy, and higher dosages may interfere with vitamin B metabolism.[36]

Allium Sativum. Garlic has demonstrated significant antifungal activity. Its inhibition of *C. albicans* in both animal and test tube (in vitro) studies have shown it to be more potent than nystatin, gentian violet, and six other reputed antifungal agents.[37-39] The active component is allicin—the pungent and odorous principle of garlic.

The modern clinical use of garlic features the use of commercial preparations designed to offer the benefits of garlic without the odor. These preparations are prepared in such a manner that the allicin is not formed until the enteric-coated tablet is delivered to the small and large intestine.

The treatment of chronic candidiasis requires a daily dose of at least 10 mg allicin or a total allicin potential of 4000 mcg. This amount is equal to approximately one clove (4 g) of fresh garlic. Going beyond this dosage with these preparations usually results in the odor of garlic being detectable.

Enteric-Coated Volatile Oils

Volatile oils from oregano, thyme, peppermint, and rosemary are all effective antifungal agents. One study compared the anti–*C. albicans* effect of oregano oil with that of caprylic acid.[40] Although the minimum inhibitory concentration of oregano oil was less than 0.1 mg/mL and the 0.1% survival of *C. albicans* occurred at a concentration of 45 mg/mL, the minimum inhibitory concentration of caprylic acid was less than 500 mg/mL and 0.1% survival occurred at a concentration of 5000 mg/mL. These results indicate that the anti–*C. albicans* activity of oregano oil is more than 100 times more potent than caprylic acid. Because volatile oils are quickly absorbed and associated with inducing heartburn, an enteric coating is recommended to ensure delivery to the small and large intestine. An effective dosage for an enteric-coated volatile oil preparation is 0.2 to 0.4 mL twice daily between meals.

Melaleuca Alternifolia. Tea tree oil is another option, especially in the topical treatment of *Candida* infections such as thrush or vaginal yeast infection. In one open study, 27 patients with AIDS and oral candidiasis clinically refractory to fluconazole were randomized to receive either an alcohol-based or alcohol-free *Melaleuca alternifolia* oral solution 4 times daily for 2 to 4 weeks. Overall, 60% of patients demonstrated a clinical response to this oral solution (seven patients were cured and eight patients clinically improved) at the 4-week evaluation.[41]

Propolis

Propolis has shown considerable in vitro antimicrobial activity against *C. albicans*, as well as an ability to enhance the effectiveness of conventional antifungal drugs.[42–45] Its cytotoxic activity against *C. albicans*, along with its immune-enhancing effects, make propolis a strong candidate for treatment of chronic candidiasis.



THERAPEUTIC APPROACH

The following is a comprehensive step-by-step approach to the successful elimination of chronic candidiasis.

Step 1. Identify and address predisposing factors:
- Eliminate the use of antibiotics, steroids, immune-suppressing drugs, and birth control pills (unless there is an absolute medical necessity)
- Perform a CDSA
- Follow the specific recommendations if the identifiable predisposing factor is dietary factors, impaired immunity, impaired liver function, or an underlying disease state

Step 2. Recommend the *C. albicans* control diet:
- Eliminate refined and simple sugars
- Eliminate milk and other dairy products
- Eliminate foods with a high content of yeast or mold, including alcoholic beverages, cheeses, dried fruits, melons, and peanuts
- Eliminate all known or suspected food allergies

Step 3. Provide nutritional support:
- A high-potency multiple vitamin and mineral formula
- Additional antioxidants
- 1 Tbs of flaxseed oil daily

Step 4. Support immune function:
- Promote a positive mental attitude
- Help patients deal with stress by teaching positive stress-coping techniques
- Recommend avoiding alcohol, sugar, smoking, and elevated cholesterol levels, which can impair immune function
- Recommend plenty of rest and good sleep
- Follow supplement recommendations given in Chapter 56 on Immune Support.

Step 5. Promote detoxification and elimination:
- Recommend 3 to 5 g of a water-soluble fiber source, such as guar gum, psyllium seed, or pectin at night
- If necessary, recommend lipotropic factors and silymarin to enhance liver function

Step 6. Recommend probiotics:
- Dose: 5 to 10 billion viable *L. acidophilus* and *B. bifidum* cells daily

Step 7. Use appropriate antiyeast therapy:
- Ideally, use the recommended nutritional or herbal supplements, or both, to help control against yeast overgrowth and promote a healthy bacterial flora
- If necessary, use prescription antiyeast drugs appropriately

These simple steps should take care of chronic candidiasis in most cases. If a patient follows these guidelines and fails to achieve significant improvement or complete resolution, further evaluation is necessary to determine if chronic candidiasis is the underlying factor. Repeat stool cultures and antigen levels are often helpful in this goal. If the organism has not been eradicated, stronger prescription antibiotics can be used, along with the other general recommendations.

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CHAPTER 52

Dietary Fiber

Michael Lyon, BSc, MD

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INTRODUCTION

Anthropology

With the possible exception of ice age hunters, most primitive cultures consumed very large quantities of dietary fiber. Early humans obtained fiber principally in the form of soluble fiber from fruits, vegetables, and root vegetables. With the advent of grain cultivation, the human diet shifted more towards insoluble fiber, which has less beneficial metabolic effects, particularly in the context of a higher carbohydrate intake. Although the original Inuit diet of the far north was, calorically speaking, very high in animal fat and, to a lesser extent, animal protein, they supplemented their diet extensively with seasonal berries, roots, various plants, and seaweeds; thus, they consumed relatively large amounts of fiber. Further south, aboriginal peoples made extensive use of numerous plant foods that contributed to a large intake of dietary fiber.[1] Around the world, there are few examples of indigenous peoples whose traditional diet did not provide very high quantities of fiber. Only with the advent of commercial food processing and refining has the human diet been so characteristically meager in dietary fiber.

History

Although we are experiencing a contemporary revival in medical interest surrounding fiber, references to dietary fiber have long existed in the medical literature in the writings of such historical figures as Hippocrates, the ninth century Persian physician Hakim, and the Kellogg brothers of the United States.[2] However, our contemporary interest in fiber as physicians as well as the widespread understanding of fiber's importance among the general public began with a zealous campaign instituted by the missionary surgeon, Denis Burkitt (also the discoverer of Burkitt's lymphoma), beginning in the early 1970s. Over his 20 year career in Africa, Dr. Burkitt observed a dramatic difference in the incidence of many diseases, such as coronary heart disease, diabetes, diverticulosis, and gallstones among the local tribesmen. He noted that the largely agrarian Africans consumed very large amounts of dietary fiber, often more 100 g/day. He determined that as a result of this diet, their stool transit time was far more rapid than that of Westerners, and their stools were more frequent and bulky. On the basis of his research, he launched a worldwide campaign to raise awareness of the importance of dietary fiber among medical professionals and the general public. Without a doubt, Dr. Burkitt's zeal was an important factor that catalyzed a veritable revolution in research surrounding dietary fiber.[3] During Burkitt's campaign, contemporaries such as Jenkins et al[4] published the first studies on fiber-related concepts such as the glycemic index. Today, we have begun to recognize the complex mechanisms by which fiber exerts its many health effects beyond just its impact on laxation.

FIBER

Classification

In the simplest definition, dietary fiber is a nonstarch polysaccharide in (mostly) plant food that is poorly digested by humans. Based on a recent government consensus report, fiber can exist as either dietary fiber (naturally occurring in food), or functional fiber (added during the processing or preparation of food).[5] Fiber can be

either insoluble or soluble in water. Insoluble fibers include cellulose, hemicellulose, and lignins, whereas soluble fibers include various gums, pectins, β-glucans, oligosaccharides, resistant dextrans, and resistant starches. Chitin and chitosan are indigestible amino-polysaccharides that are found in or are derived from the exoskeletons of arthropods such as crabs and lobster, as well as the cell walls of most fungi, and could functionally be regarded as fiber, although they are not recognized as fiber by most regulatory authorities. The distinction between soluble and insoluble fibers is due to the chemical properties of the fiber, resulting in its tendency to absorb water. Various physicochemical properties of fiber (viscosity, water holding capacity, cation exchange capacity, adsorption of organic materials, and fermentability) are now thought to be fundamental to its beneficial physiologic effects. The Institute of Medicine has proposed a new definition of dietary fiber that will encompass both its physical characteristics and its physiologic effects in humans.[6] A fiber's viscosity, its water holding capacity, and its fermentability are the chief determinates of fiber's physiologic effects.

The regulatory classification of fiber varies considerably in different countries. In the United States, dietary fiber is defined based upon analytic methods rather than its physical or physiologic characteristics.

Sources

The typical Western diet is largely devoid of dietary fiber, being composed principally of refined grains and other highly digestible sources of starch, sugar, various fats, and animal products. Children in particular are commonly fiber deficient, with daily intakes often under 5 g and with nearly no soluble fiber. Likewise, many adults in Western society consume 5 to 10 g of fiber daily as opposed to the 35 to 50 g that is considered desirable or at least minimal for optimal health. Moreover, because most fiber in the Western diet is derived from cereal grains, the intake of viscous soluble fiber is typically highly inadequate.

A whole foods based diet focusing on a large intake of vegetables and fruits as well as unrefined whole grains and legumes should be the foundation of a healthy lifestyle. With a whole foods based diet, it is certain that dietary fiber intake will substantially increase.[7] Unfortunately, only a minority of the population, particularly children, are likely to adopt a largely whole foods diet anytime in the near future. Because of this, efforts are underway to establish effective means to fortify the Western diet with dietary fiber through the use of various fibers as food additives or ingredients as well as the use of readily accepted fiber supplements.

Health Effects

There is compelling epidemiologic and experimental data associating numerous disorders, at least in part, to a lack of dietary fiber. Ischemic heart disease, stroke, atherosclerosis, type 2 diabetes, overweightness and obesity, insulin resistance, hypertension, dyslipidemia, as well as gastrointestinal disorders such as diverticulosis, irritable bowel disease, colon cancer, and cholelithiasis, are just a few of the many conditions that seem to be influenced by the adequacy of dietary fiber intake.[8]

Numerous studies demonstrated that certain fibers decrease the glycemic response to food, promote satiety, lower serum cholesterol, promote bowel regularity, positively influence colonic microflora, provide nutritional substrates for colonic mucosal cells, improve mucosal barrier function, as well as sequester and eliminate toxic and carcinogenic dietary and environmental compounds. These and other effects constantly interplay to increase or decrease the development of a wide range of health conditions.

Viscous dietary fibers are now clearly correlated with moderation in blood glucose and cholesterol concentrations, prolonged gastric emptying, and slower transit time through the small intestine.[9] Among viscous fibers, fermentability is mostly associated with large bowel function. Rapidly fermented fiber sources provide substrates for short-chain fatty acid (SCFA) production by microflora in the large bowel, whereas slowly or incompletely fermented fiber sources improve bowel health by promoting laxation, reducing colonic transit time, and increasing stool weight.[10]

MECHANISMS OF ACTION OF DIETARY FIBER

Dietary fiber exerts its effects through an interaction between the physical properties it imparts to foods accompanied by a complex array of microbiological, biochemical, and neurohormonal influences. Dietary fiber has a strong influence on the palatability of food, thus influencing ingestive behavior. In the stomach, fiber affects the volume and viscosity of food, which has a highly significant effect on satiety. This "volumetric" effect on food promotes a sense of fullness and a delay in gastric emptying, which tends to naturally result in a decrease in caloric intake. Various fibers differ dramatically in their ability to impart volume and viscosity to foods. Becoming familiar with the use of highly viscous soluble fibers enables health care providers to teach patients to choose an eating strategy that promotes and maintains satiety while consuming a diet that is lower in caloric density.

Viscosity of Fiber

Viscosity as related to dietary fiber refers to the ability of some polysaccharides to thicken or form gels when mixed with fluids, resulting from physical entanglements and hydrophilic interactions among the polysaccharide constituents within the fluid or solution.[11] Gums, pectins, and β-glucans make up the majority of viscous dietary fibers. The viscosity that a fiber imparts to the gastric and small intestinal contents is directly correlated with the ability of the fiber to reduce postprandial glycemic response, promote satiety, decrease serum cholesterol, and decrease serum uric acid.[12] The viscosity of fiber is also thought to play an important role in the augmentation of gut mucosal protection through the stimulation of enteral mucus production and goblet cell hypertrophy and replication.[13] Additionally, those viscous fibers that are largely fermented by colonic microflora exert a wide array of physiologic effects through the production of SCFAs (the principle energy substrates of colonocytes), the promotion of beneficial colonic microbial populations, and the augmentation of important gut-derived peptide hormones.

The viscosity of fiber is best measured by methods that quantify a hydrated fiber's internal friction and its ability to resist flow. Viscosity is usually expressed in units of millipascal seconds or centipoise.[14] Other factors, such as shear stress (e.g. mastication, peristalsis), acid pH, dilution, and chemical components of food determine the real viscosity that a fiber will impart to food rather than just its in vitro viscosity.

The concept of the glycemic index came about through the work of Jenkins et al as they examined the impact of viscous fiber ingestion on glucose tolerance.[15] It is now generally accepted that the glycemic index of a carbohydrate containing food is directly correlated to the viscosity of that food after ingestion.

More recently, one research group was involved in several studies looking at the effects of adding a novel, highly viscous

functional fiber (Polyglycoplex [PGX]) to various foods on glycemic index, serum cholesterol, hunger, and satiety in healthy humans. The novelty of this fiber relates to its viscosity, which is higher than that of any other fiber thus studied. Unlike some viscous fibers, such as psyllium, which are not fermented, PGX is highly fermentable and prebiotic.[16] This composition, made from glucomannan, sodium alginate, and xanthan gum, is taken through several steps of processing, and the resultant modified fiber is approximately three times the viscosity of glucomannan, a naturally occurring fiber from the Konjac root that may possess the highest viscosity of any naturally occurring fiber. In addition, it was demonstrated that PGX is a novel and stable molecular entity with viscosity that is several-fold higher than its constituent ingredients, through a wide range of pH and sheer stress conditions, and when added to a variety of foods and beverages.[17,18] In addition, this fiber is tasteless, and disperses readily when added to food or mixed with beverages. Its viscosity evolves several minutes after initial hydration, making it very easy to consume the small amounts needed to create a highly viscous gastric milieu, leading to its resultant physiologic effects.

This study demonstrated that substantial reductions in postprandial glycemia along with reduced hunger and increased satiety can be achieved with a very modest quantity of this highly viscous fiber. These findings support the contention that the viscosity that a fiber imparts to the gastric contents is more important than simply the grams of the fiber consumed.[19-23] In a study of Zucker Diabetic Fatty (ZDF) rats, the effects of diets supplemented with nonviscous, insoluble fiber (cellulose); nonviscous, prebiotic fiber (inulin, oligofructose); and with a highly viscous, prebiotic fiber (PGX) were compared. In this study, only the diet supplemented with highly viscous fiber substantially decreased postprandial blood glucose and insulin secretion, decreased hepatic fatty infiltration, and preserved pancreatic β cell mass. These effects were accompanied by an increase in the production of the important glucoregulatory incretin hormone, glucagon-like peptide-1 (GLP-1) and, in a human clinical trial, the appetite reducing hormone peptide YY (PYY).[24] Human clinical trials are currently underway to see if this novel, highly viscous fiber has utility in the management of obesity and diabetes, but the substantial glycemic index modifying effects have been well confirmed in human studies.[18-20]

Water Holding Capacity

The ability of a fiber to absorb and hold on to water as it transits the gut is another factor that contributes to its functional effects. Soluble fibers have the capacity to create a stable gel that results in stomach volume being occupied and a sense of satiety being created without the addition of significant calories. The "volumetric" properties of a food consist of a food's volume and viscosity per net quantity of calories. Those who work in the field of obesity management believe that teaching patients strategies that promote a high consumption of low calorie-density, highly volumetric foods are mainstays in the dietary management of overweightness and obesity.[25-27]

Laxation

The most common clinical application of fiber is in the maintenance of bowel regularity. Insoluble fiber, perhaps in combination with soluble fiber, is most effective in increasing stool bulk, reducing gut transit time, and increasing the frequency of defecation.[28] The health promoting effects of insoluble fiber from the bran of grains is well documented and certainly extends beyond just its laxative effects,[29] but the benefits of reduced stool transit time and increased fecal frequency may have more profound long-term benefits simply beyond the comfort that accompanies bowel regularity.[30-32]

Prebiotics

It is increasingly recognized that certain forms of fiber are fermentable, providing an important substrate in the metabolism of gut flora. By definition, humans lack the enzymes specific to digest fiber. In the case of insoluble fiber, most gut microbes cannot utilize it as an energy source, and so it is typically excreted without any molecular alteration other than by forming a surface for the adsorption of organic matter and cations. Soluble fibers vary in their fermentability and in the specific microbes that can utilize them as substrates. The term "prebiotic" was coined by Gibson and Roberfroid in 1995, and was defined as an indigestible carbohydrate that is fermentable in the lower gastrointestinal tract that selectively promotes the growth of desirable (prebiotic) microflora and is associated with a positive health outcome.[33,34] Although there may be exceptions, prebiotics tend to reduce populations of potentially pathogenic flora while promoting desirable commensals such as *Bifidobacteria*.

Recent evidence suggested that this effect might play an important role in both the reduction in adiposity as well as a reduction in the contribution of adipocytes to inflammation. It was demonstrated that prebiotic supplementation might reduce the development of large adipocytes (those that predominate in the visceral compartment), which are highly involved in the over activation of a wide variety of inflammatory processes that may contribute to overeating, obesity, diabetes, cardiovascular disease, and pain.[35,36]

Pathways of inflammation associated with atopic disease are also intimately associated with gut flora. Both prebiotics and probiotics are believed to hold significant promise in the prevention and treatment of allergies and atopic disorders, such as eczema.[37-40]

Lack of sufficient intake of prebiotics early in life has lasting ill effects on glucoregulation, which may result in a substantial predilection towards obesity, diabetes, and cardiovascular disease later in life.[41] Unfortunately, there is little effort being made to increase fermentable soluble fiber intake in infants and children. This may have serious consequences and may be one of the reasons for the current obesity epidemic. The food industry has just begun to respond to this with the introduction of prebiotic fortified infant formulas. Because breast milk contains significant quantities of prebiotic oligosaccharides, adding analogous agents to infant formulas would help to make these more closely mimic the natural diet. This strategy results in a gut flora predominated by *Bifidobacteria*, rather than potential pathogens such as *Clostridia* and *Enterobacter* that tend to predominate in formula fed infants.[42]

Prebiotics, namely lactulose, have been used for many years in the management of hepatic encephalopathy.[43] It has long been a marvel for modifying the colonic flora, and giving lactulose can restore sanity to a delirious patient with liver failure. It is now recognized that the prebiotic effects of this treatment result in a reduction in neurotoxic bacterial metabolites that can normally be eliminated by the healthy liver. Similarly, prebiotics have begun to find their place in the treatment of HIV patients[44] and allergy prevention and treatment.[45]

Prebiotics may play an important role in the modification of carcinogens and in the promotion of substances that reduce cancer risk at least in the gastrointestinal tract.[46] Dietary fiber has the capacity to sequester and increase the elimination of a wide range of organic molecules as well as metal ions. This effect, along with the resultant

decrease in colonic transit time, results in reduced colonocyte exposure to potentially harmful xenobiotics and endogenously produced, but potentially harmful, compounds. Fermentable soluble fiber is metabolized anaerobically into SCFAs such as butyrate, acetate, and propionate. These simple molecules are the principle energy substrates of colonocytes, and an adequate and ongoing supply of these may reduce the risk of colon cancer and other colonic disorders, such as diverticulosis and inflammatory bowel disease.[47,48]

Neuroendocrine Effects of Fiber

The most intriguing discovery of late is related to the role played by dietary fiber in the modulation of important neuroendocrine physiology, which may be related fundamentally to the etiology of a number of serious disorders. Of particular interest is the impact of fiber on the density and activity of a specialized enteroendocrine cell known as the L-cell.[49] The L-cell is located throughout the terminal ileum and colon, and it is responsible for the secretion of the peptide hormones GLP-1, PYY, and oxyntomodulin.[50] After a meal, oxyntomodulin and PYY are released synchronously; both act as potent anorexigens. The rapid rise of circulating hormone levels signals a change in energy status to the brain and also acts locally to enhance digestive processes. GLP-1 is an incretin hormone that is also secreted by the L-cell and, as well as being an anorexigen, it plays a pivotal role in glucoregulation through the stimulation of accurately timed insulin secretion and suppression of glucagon secretion from the pancreas. It has been established that diminished GLP-1 production plays a central role in the etiology of diabetes, a discovery that has led to the development of the most important class of diabetes drugs (the incretin analogues) since the discovery of insulin.

It was recently shown that (bariatric) gastric bypass surgery results in rapid amelioration of diabetes that is out of proportion with and precedes significant weight loss.[51] Current evidence points to a rapid and sustained increase in circulating GLP-1 and PYY after this procedure that has profound effects on appetite and glucoregulation. It is now thought that the malabsorption of carbohydrates and rapid gastrointestinal transit after gastric bypass results in an increased delivery of carbohydrate fermentation products (SCFAs) and bile acids, both of which activate L-cells via free fatty acid (FFA) receptors and bile acid receptors.[52-56]

It is most interesting that fermentable soluble fiber has the potential to generate a significant supply of SCFAs that might mimic, on a lesser scale, the mechanism of gastric bypass surgery through stimulation of FFA receptors with a resultant increase in GLP-1 and PYY.[57] Because viscous soluble fiber also effectively sequesters bile acids, reducing their usual absorption through the jejunum and delivering them to the same L-cells, viscous soluble fiber that is also fermentable may exert an appetite reducing and glucoregulating effect through L-cell activation via both FFA receptors and bile acid receptors as well as by suppression of the orexigenic (appetite stimulating) hormone ghrelin.[58,59]

Sequestration of bile acids by viscous soluble fiber is also known to be a principle mechanism by which viscous fiber lowers serum cholesterol, because sequestration of bile acids decreases the enterohepatic recycling of bile acids, a major cholesterol reservoir for the human.[60]

CLINICAL APPLICATIONS

With the abundant and ever growing evidence that has elevated the role of fiber well beyond its place in the promotion of bowel regularity, dietary fiber should now be respected by health care providers as an important prophylactic and therapeutic agent. The importance of viscous, fermentable soluble fiber in the prevention and management of obesity and diabetes is of particular importance to clinicians who are on the front lines facing the obesity epidemic.

It is clear that fiber, especially viscous and (prebiotic) fermentable soluble fiber, plays a key role in the risk of obesity, diabetes, cardiovascular disease, cancers, atopic illness, and a wide range of gastrointestinal disorders. It is also clear that the lack of adequate dietary fiber, particularly prebiotic and viscous fibers in childhood and infancy, may set the stage for a higher risk of the same array of disorders, and that some of that increased risk may linger for the remainder of life. Clinicians must develop effective strategies to educate their patients and assist them in the incorporation of much higher levels of fiber in their daily diet. In particular, because the greatest benefits from fiber are derived from highly viscous, prebiotic fibers, clinicians should become especially knowledgeable in the effective use of these agents, particularly when treating patients who are obese or exhibit dysglycemia.

Dosage and Administration

The dietary fiber intake for typical Americans is usually less than desirable, with typical intakes averaging only 14 to 15 g/day and children consuming less than 5 g/day.[61] The American Dietetic Association currently recommends that healthy adults should consume 20 to 35 g of fiber per day and children should consume at least 5 g/day plus 1 g for every year of their age.[62] The American Dietetic Association points out that insoluble, nonfermentable, and low viscosity fiber is principally consumed to promote laxation and other aspects of colon health, whereas viscous soluble fibers are necessary to reduce serum cholesterol, blunt postprandial glycemic response, and promote satiety. A fiber-rich meal, particularly a meal high in viscous, soluble fiber, is processed more slowly, promoting earlier satiety, and is frequently less calorically dense and lower in fat and added sugars. All of these characteristics are typical of a dietary profile optimized to treat and prevent obesity. Unfortunately, viscous soluble fiber is not easily incorporated into the regular diet, but fiber supplements may provide a practical means to insure that most meals contain optimal quantities of viscous fiber. Pal et al[63] at Curtin University in Australia demonstrated the utility of high-dose psyllium given as a premeal supplement as an adjunct to a calorie-reduced weight loss program. However, the dosage of psyllium used in this application was very large (12 g with each meal) and might pose a compliance problem for many subjects. Using very high viscosity fiber (such as PGX) may overcome this limitation, since the dosages required to achieve a reduction in postprandial glycemia and an increase in satiety may be much less than fibers with lesser viscosity.[19,64]

DRUG INTERACTIONS

Clinicians prescribing higher doses of supplementary fibers should be aware of the potential drug–food interactions in those patients requiring pharmaceuticals. Most fiber, especially viscous fibers, has the potential to modify the rate or total absorption of various drugs.[65] In most cases, taking medications 1 hour before or 2 hours after consumption of the supplementary fiber will reduce the impact of this phenomenon.

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CHAPTER 53

Functional Toxicology

Michael Lyon, BSc, MD

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INTRODUCTION

The wide array of persistent toxicants in our environment has undoubtedly caused or contributed to a great diversity of health threats. Prominent biologists Colborn and Myers[1] documented the precarious state of the human as a species in the best-selling book *Our Stolen Future*. Although the environment–cancer connection has been acknowledged for many years, this book documented the increasing evidence that chemical pollutants pose a significant threat to our fertility, our intelligence, and many other aspects of health as well. Furthermore, the scientific literature is beginning to reflect an increasing awareness that polysymptomatic disorders such as multiple chemical sensitivity syndrome, sick building syndrome, chronic fatigue syndrome, and the Gulf War syndrome are all strongly associated with toxic chemical exposures.[2,3] Recently, the Collaborative on Health and the Environment formed an initiative to bring together researchers, clinicians, government officials, environmental activists, educators, and others with common concerns about the impact of the environment on human health. This initiative, with over 6000 individual and organizational members, is becoming a catalyst to raise awareness of the growing evidence linking environmental chemical influences to a wide array of human health conditions.[4] This organization maintains a database of chemicals and related health conditions. It has also established numerous working groups to bring together researchers and other professionals for focusing on the relationship between environment and specific health conditions, along with solutions to address these issues.

Humans reside on the top of the food chain and are subject to the phenomenon of bioconcentration or biomagnification, as are other species near or at the top of the food chain.[5] Additionally, long lives, occupational exposures, household chemicals, prescription drugs, and dental amalgams are some of the many reasons why humans are in a class of their own for magnitude and diversity of chemical exposure.

Chemical threats to human health exist in both organic and inorganic forms. The actual number of xenobiotic chemicals that are encountered on a daily basis is vast. It is becoming clear that few, if any, of these toxicants act alone but, instead, generally act in synergy with other chemicals.[6] Chemical synergy can increase a chemical's toxicity by several hundredfold, resulting in "superinteractions" far exceeding even those of an additive nature.[7] Synergistic chemical reactions may occur even before the toxicants enter the human body, changing the chemical's nature and complicating their toxicologic evaluation even further.[8] In addition, many toxins are now known to exert toxic effects at levels vastly lower than originally assumed. For example, cadmium was shown to have estrogen-mimicking effects in tissue at a level of 100,000th of a part per billion.[9]

COMMON TOXINS THAT AFFECT HUMAN HEALTH

Organohalogens

Organohalogens are chemicals that are generally highly persistent in the natural environment, as well as the human body. The major categories of organohalogens are the organochlorine pesticides, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), plastic residues, dioxins, and organic byproducts of water chlorination. All of these agents are subject to bioaccumulation in the food chain and are highly persistent within the human body.[10,11]

One of the first man-made chemicals to be recognized as a persistent contaminant of the food chain with a distinct presence in human tissues was the organochlorine dichlorodiphenyltrichloroethane (DDT). Several other organochlorine pesticides, as well as the family of PCBs and fire retardants (PBDEs), have been established to be highly persistent and widely distributed as human contaminants. These agents were introduced and strongly promoted, in part, because they have minimal short-term toxicity. However, they have been established to be highly disruptive to the endocrine system and have been linked to problems such as breast cancer, infertility, and premature onset of puberty.[12,13] More subtle effects of endocrine-disrupting organohalogens, particularly effects on behavior and neuropsychological function, have been well described.[14,15] The ubiquitous and highly persistent nature of this group of chemicals makes them of grave concern to human health.

Organophosphates

In the 1930s, Nazi scientists synthesized the organophosphate nerve agents Tabun and Sarin while looking for more effective pesticides. Although Sarin and Tabun are now classified as weapons of mass destruction and are officially banned from most nations, they formed the prototypes for the currently used organophosphate pesticides. Pesticides in use today are acutely less toxic than their parent chemical warfare agents. However, they use the same basic mechanism for exerting toxicity, and they have no known safe dose at which no neurologic effects occur. Although their half-lives are short in the environment, because they are so ubiquitous in our diets and used so frequently in homes, on pets, and in the environment, they pose a significant risk to humans.[16] Symptoms of long-term organophosphate pesticide toxicity can be subtle and cumulative. Mental and emotional dysfunction may develop so gradually that it can go unnoticed for years, or it may be attributed to aging.[17]

Organic Solvents

Numerous solvents are used occupationally and in the home for a multitude of purposes. Benzene, toluene, and various petrochemical solvents (e.g., gasoline) are all significantly neurotoxic in long-term, low-level exposure, and are of particular concern for pregnant women and children.[18,19] Solvents have also been shown to carry significant carcinogenic potential.[20]

Heavy Metals

Numerous hazardous metals are part of daily life. The potential effects of toxic metals on human function are so vast that toxicity may manifest as almost any symptom humans are capable of experiencing. Although acute heavy metal poisoning is relatively rare, long-term, low-grade heavy metal toxicity may actually be one of the most pervasive antecedents contributing to chronic disease.

Except for the past 100 years, toxic metals were virtually absent from the general population. Adaptive physiologic mechanisms are phylogenetically unprepared for more than small trace quantities of toxic metals. Metals are not biodegradable and thus accumulate in the environment and enter the food chain. The recognition of heavy metal toxicity as a primary cause of chronic illness may be impaired by the vast economic importance of metals to the economy of all nations. The 30 years of intense fighting between scientists and industrial lobbyists over lead in gasoline illustrates the effort required to bring about changes in public health policy when it comes to metals.[21] The hot debate over mercury in dental amalgams is becoming an even more intense war of vested interests.[22] The reclassification of sewage sludge from a toxic waste to an acceptable source of nitrogen for fertilizers is an example of how money drives unsustainable environmental practices that are leading to a rapid accumulation of toxic metals in the environment.[23] Because of their ubiquitous distribution and their well-documented toxicity, lead, mercury, arsenic, aluminum, and cadmium are of particular importance to the general population. The discussion of toxic metals in this chapter is limited to lead and mercury.

Lead

Lead has been known to affect workers for at least 1000 years, and its hazards to the reproductive process have been known for at least a century. Childhood lead poisoning was first described in Australia 100 years ago, and for 50 years it was believed that if lead did not kill the child, he or she would be not affected by any residual problems.[16] However, careful follow-up of children who recovered from lead poisoning showed that most failed in school and had behavioral problems. More recent evidence confirmed that subclinical levels of lead cause measurable deficits in neuropsychological function.

Despite reduced use of lead-based paints and gasoline, lead continues to be a worldwide public health hazard. The marked effects of lead toxicity on the central nervous system (CNS)—lowering IQ and impairing memory, reaction time, and the ability to concentrate—are well known.[24,25]

Lead is also a significant health threat to adults. Several studies found that the bones of modern humans contain lead on the order of 1000 times greater than bones of preindustrial humans.[26] Apart from its effect on the brain, lead affects the function of the kidneys and the cardiovascular system.[27] Lead, at low levels, may act in synergy with other common toxicants to subtly suppress the immune system and impair health.[28]

Mercury

Mercury is one of the most toxic of all elements, far more toxic than lead.[29] Mercury is the deadliest and most pervasive pollutant in aquatic ecosystems, and its presence is steadily rising in most regions throughout North America, primarily due to coal burning power plants and mining activities. Humans are exposed to mercury through consumption of fish (methylmercury), occupation (ionic mercury and mercury vapor), vaccinations (ethylmercury), and dental amalgams (mercury vapor). Except for populations that consume large amounts of seafood or workers in industries where mercury exists as an occupational hazard, the majority of the population is exposed to mercury through dental amalgams.[30]

The basic premise for regarding the amalgam filling as safe was the assumption that the amalgamation process resulted in a stabilization of the normally volatile mercury. This premise has since been proven entirely false. Since the 1980s, it has been well established that mercury vapor is continuously released from amalgam fillings. The release of this vapor into the mouth increases immediately after chewing[31] or tooth brushing[32] and can result in a daily absorbed dose of mercury that exceeds the excretory capacity via the urine and stool. It has now been well established and published by several authorities, including the World Health Organization (WHO), that amalgam tooth fillings are, by far, the major source of mercury exposure for the general population.[30] According to the WHO's expert committee, the daily human exposure to mercury vapor from amalgam fillings ranges from 3 to 17 mg, compared with a maximum of 2.6 mg from all other sources.

Mercury vapor released from dental amalgams is efficiently absorbed through the alveoli. After absorption through the lungs, elemental mercury vapor (Hg^0) is only found transiently in the blood. Due to its high lipid solubility, elemental mercury is rapidly transported through cell membranes (including membranes of the cells comprising the blood–brain barrier). Once inside metabolically active cells, Hg^0 is then oxidized by catalase to form ionic mercury (Hg^{2+}). Hg^{2+} is not lipid soluble and therefore results in a high degree of retention of absorbed mercury and a tissue half-life ranging from days to decades depending on the particular organ.[33,34]

This phenomenon clarifies why studies repeatedly demonstrated that after placement of amalgam fillings, blood, hair, and urinary mercury levels remain relatively low, although many organs develop concentrations of mercury many times greater than that of the blood.[35,36] Thus, blood, hair, or nonchallenged urinary mercury levels bear little relationship to the total body burden of mercury gradually acquired from amalgam fillings.

Once mercury enters the cell, it ultimately becomes bound covalently to the sulfhydryl groups found in glutathione and, to a lesser degree, to cysteine, biotin, lipoic acid, and coenzyme A, as well as to other protein sulfhydryl groups. The major intracellular sulfhydryl compound in mammals is the tripeptide glutathione. Glutathione and the enzyme glutathione peroxidase are probably the most important antioxidant defenses in humans.[37] Mercury was shown to cause a marked reduction in glutathione production and glutathione peroxidase activity, and thus it might result in a marked rise in oxidative stress within the brain and other organs. Apart from the loss of antioxidant protection from mercury-induced inhibition of glutathione and glutathione peroxidase, mercury results in a marked increase in free radical generation through Fenton reactions and other mechanisms.[38]

In addition to its key role in antioxidant defenses, glutathione is also a critical component in the liver's detoxification mechanisms. Enzymes within the liver must form conjugates between glutathione and certain toxic metabolites, organic xenobiotics, and heavy metals to enable these toxins to be eliminated from the body. This process of glutathione conjugation makes toxic molecules more water soluble and enables their excretion via bile or through the kidney. If liver glutathione production is markedly inhibited, as occurs when mercury accumulates within hepatocytes, mercury and numerous other toxic substances may more readily accumulate throughout the body because the excretion of such substances is significantly impaired.[39] Furthermore, because most mercury is excreted through the stool and urine as a glutathione conjugate, individuals with long-standing body burdens of mercury (and thus depleted glutathione production) may not demonstrate elevated levels of mercury in the urine, blood, or stool when specimens are gathered in the absence of a challenge with an appropriate metal chelating agent. Thus, tissue biopsy of target organs or a provocation test measuring urinary mercury after the administration of a chelating agent may currently be the only valid means to assess long-term mercury body burden.[40]

Numerous studies demonstrated the body tissue uptake and distribution of mercury from dental amalgams. Studies using whole body imaging in primates with dental amalgams clearly demonstrated that the amalgams resulted in high levels of mercury in the kidney, intestinal tract, brain, liver, and other organs.[41]

The impact of long-term, low-level mercury exposure is now known to adversely affect numerous other cellular and organ system processes. Ionic mercury may contribute significantly to autoimmune processes.[42] Of particular concern to the natural medicine practitioner is the impact that low levels of inorganic mercury have on gut flora. Research demonstrated that multiple strains of antibiotic-resistant bacteria developed rapidly in the gut and oral cavity of both humans as well as nonhuman primates after placement of amalgam fillings.[43] Furthermore, subclinical levels of inorganic mercury were shown to markedly impair the immune system's ability to suppress the growth of *Candida albicans*.[44]

Amalgam fillings were shown to contribute to mercury accumulation in human and animal kidneys, and this was associated with a significant decrease in renal function.[45] Human fertility was also shown to be significantly affected by low-level exposure to mercury vapor. A recent study that examined 7000 dental assistants demonstrated that this group experienced a fertility rate approximately 40% less than that of women who had no occupational exposure to mercury.[46]

Of perhaps greatest concern is the potential role of low-level, long-term mercury exposure on CNS function. It is now well established that amalgam-derived mercury accumulates in human brain tissues.[47] Mercury was shown to concentrate selectively in human brain regions involved with memory function, and it might play a significant role in the etiology of Alzheimer's disease.[48] Other reports showed subclinical motor and neuropsychological deficits among dentists and dental workers compared with control subjects.[49] Mounting evidence led some researchers to suggest that mercury from amalgams might play a highly significant role in the etiology of numerous mental illnesses and neuropsychological disorders (Table 53-1).[50-52]

TABLE 53-1 **Examples of Toxic Metal Contaminants in Humans**

TOXIC METAL	SOME COMMON SOURCES	EFFECTS OF LOW-LEVEL CHRONIC ACCUMULATION
Aluminum	Drinking water, antiperspirants, antiperspirant crystals, antacids, baking powder, bentonite	Immune suppression, cognitive dysfunction, dementia
Arsenic	Preserved wood (playgrounds and garden borders), drinking water, pesticides, fish	Gastrointestinal irritation, fatigue, cardiovascular damage, peripheral nerve damage, skin changes, cancer
Cadmium	Cigarette smoke, welding or grinding, air pollution, food from contaminated soils, chocolate	Kidney damage, cardiovascular damage, cognitive impairment
Lead	Old paint, lead solder water pipes, contaminated soil, car batteries, sewage sludge, chocolate, popular calcium supplements	Brain and nervous system damage, decreased intelligence, high blood pressure, cardiovascular disease
Mercury	Dental amalgam fillings, freshwater fish and larger predatory ocean fish, vaccines (thimerosal preservative), broken thermometers, spilled liquid mercury	Depression, anxiety, intellectual impairment, severe fatigue, chronic pain, immune suppression, autoimmune disorders, dementia, peripheral neuropathies

MECHANISMS OF TOXIC INJURY

Targets of Toxicity

Xenobiotic-initiated injury may be largely described as affecting three possible targets[53]:

1. Toxicant agents may alter, remove, or impair the synthesis of specific molecules (e.g., phospholipids, fatty acids, proteins, nucleotides, or glutathione).
2. Toxicants may alter structural entities (e.g., mitochondria, cytoskeleton, plasma membrane, or nucleus).
3. Toxicants may create disturbances in cell signaling (e.g., cytokines, eicosanoids, hormones, calcium channels, or neurotransmitters).

Biotransformation

Most drugs, metals, and xenobiotics undergo biotransformation before being excreted through the stool, urine, or sweat. Although not every molecule is processed in this way, biotransformation typically involves phase 1 and phase 2 modifications in the liver. Most phase 1 modifications involve oxidation, but can involve demethylation, hydroxylation, or dehalogenation. Phase 2 modifications result in conjugation of xenobiotic or metal ions with a carrier molecule, such as glutathione, cysteine, sulfate, or glycine. The cytochrome P450 enzymes are essential molecules involved in the metabolism of drugs, foreign chemicals, arachidonic acid, cholesterol, steroids, and other important lipids. However, xenobiotic biotransformation by cytochrome P450 mixed function oxidases is a two-edged sword.[54] On one hand, many xenobiotics are highly toxic when entering the body, and phase 1 oxidation can change the "molecular identity" of the molecule, rendering it less toxic (phase 1 detoxification).[55] Also, P450 oxidation can render a xenobiotic more water soluble (more readily excreted and less prone to penetrate cell membranes). Because a significant proportion of xenobiotics are lipid soluble, they readily pass through cell membranes (and the blood–brain barrier) and may accumulate in fatty tissues, causing prolonged toxic effects. Thus, adequate activity of phase 1 liver detoxification is critical in protecting humans from toxic stress.

However, biotransformation by cytochrome P450 enzymes may play a significant role in establishing or increasing the toxic nature of a xenobiotic. Cytochrome P450 enzymes oxidize the xenobiotic entity and transform it into a reactive electrophile. This reactive intermediate, if not immediately transformed further by one of several conjugating enzymes (phase 2 detoxification), may exert toxic effects within the liver, or systemically, if it escapes from the hepatocyte. These effects may include one or more of the following reactions[53]:

1. Covalent binding of the reactive metabolite to:
 - Proteins (e.g., cross linking of structural proteins; change in conformation of receptors, membrane pumps, enzyme carrier proteins, or peptide hormones)
 - Lipids (e.g., cell membrane phospholipid binds to reactive, intermediate-forming, lipid-soluble xenobiotics, initiating lipid peroxidation)
 - Nucleic acids (e.g., irreversible binding to DNA, initiating carcinogenesis)
2. Creating oxidative stress by one of three mechanisms:
 - Cytochrome P450 enzymes are oxidases that, in the process of xenobiotic biotransformation, generate reactive oxygen species (superoxide, peroxide, or hydroxyl radicals) exceeding the normal flux of reactive oxygen species generated by mitochondrial respiratory activity.
 - Xenobiotics, once biotransformed, are reactive electrophiles that are quenched by cellular antioxidant defenses (superoxide dismutase, catalase, glutathione peroxidase). This oxidative stress can lead to depletion of cellular antioxidant defenses.

Hormone Disruption

The homeodynamic balance of virtually any of the body's hormonal systems may be disrupted through toxic stress. Such disruptions may occur through effects upon the hypothalamic, pituitary, endocrine gland axis or peripherally on hormone production or hormone receptors. The estrogenic effect of environmental agents has been a major focus in toxicology research.[56] It has been recognized for some time that a number of chemicals in the environment possess estrogenic activity in various biological systems. These compounds include plant and fungal products, pesticides, plasticizers, estrogenic agents administered to livestock, and various other chemicals. It was originally postulated that estrogenic agents interacted with the estrogen receptor in an "on–off switch" fashion. This is now considered to be overly simplistic or even incorrect.[57]

Different estrogenic agents bind to a wide variety of estrogen receptors and create hormone-receptor complexes with variable life spans and molecular conformation. The hormone-receptor complex then binds to one of several dozen nucleotide estrogen response elements. This trimolecular complex binds to various target genes in the nucleus and either activates or suppresses transcription. Depending on the "flavor" of the hormone-receptor-estrogen response element complex, a wide variety of specific hormonally mediated effects may occur. This phenomenon helps to explain how certain estrogenic agents can be carcinogenic (organochlorine pesticides), whereas others can be anticarcinogenic (phytoestrogens). The wide variety of responses of different tissues to estrogenic influences also helps to understand how some agents, for example, affect the risk of cancer, whereas others affect behavior or sexual responsiveness.[58]

Chemical contaminants are now known to play a significant role in the etiology of obesity. Hormone disruption can impact adipogenesis, insulin sensitivity, mood and appetite, and may be one of the most significant influences behind the obesity and diabetes epidemics.[59] Particularly surprising is the very strong dose–response relationship that has been seen between concentrations of persistent organic pollutants and diabetes.[60]

Toxicity of Heavy Metals

Toxic metals share many of the deleterious effects of organic xenobiotics, particularly organically bound metals (e.g., methylmercury, tetraethyl lead, and methylcyclopentadienyl manganese tricarbonyl). However, toxic metals have some peculiarities not exhibited by organic xenobiotics. For example, toxic metals act as "chemical competitors" with chemically and physically similar nutritional trace metals (e.g., cadmium competes with zinc, lead competes with calcium, mercury competes with selenium).[61] This phenomenon may result in high rates of loss of the competitive nutrient metal or, alternatively, inhibition (or overactivation) of metal-dependent physiologic systems such as enzymes.

Metal-Catalyzed Oxidative Injury

In addition, non-nutrient metals may bind to molecular regions where they carry out inappropriate catalytic activities, including the generation of free radicals.[38,62] The resulting oxidative damage

to high-energy membrane pumps and other transport mechanisms required for the homeodynamic regulation of trace mineral and electrolyte balance may then exacerbate nutrient mineral loss even further. If membrane pumps are damaged, sharp concentration gradients of minerals and electrolytes can become blunted, leading to marked changes in the regulatory activity of the cell.[53] For example, cytosolic levels of calcium are normally 1/10,000th the concentration found outside the cell or inside the endoplasmic reticulum or mitochondria. Oxidative injury to membrane pumps or calcium channels can result in a loss of this steep gradient. This rise in cytosolic calcium can result in overactivation of calcium-dependent systems, such as the calmodulin family of enzymes. This may, in turn, result in various events, such as hypertonia of skeletal muscle or activation of membrane phospholipases with subsequent degradation of membrane phospholipids and increased inflammation.

Mitochondrial Disruption

Toxic metals and a wide variety of xenobiotics also target the membranes of the mitochondria and result in marked alterations of energy metabolism.[63] Toxic mitochondrial damage may lead to rapid cellular aging, cell death, or intracellular acidosis. Paradoxically, intracellular acidosis may then place the cell into a partially "hibernative" state in which it is protected from lethal injury.[64] This may help to explain the high degree of functional impairment and the minimal risk of lethality in patients with conditions such as chronic fatigue syndrome or fibromyalgia. In this model, toxic mitochondrial injury results in energy depletion, clinical exhaustion, and evidence of intracellular acidosis.

BIOCHEMICAL INDIVIDUALITY AND TOXIC RESPONSE

Detoxifying Enzymes and Genetic Polymorphism

A significant amount of cumulative data demonstrates that widespread genetic polymorphism for the expression of cytochrome P450 enzymes exists within the human species.[65] The significance of this phenomenon has not been completely described, but several studies suggested a strong correlation between genetic deficiency of certain cytochrome P450 enzymes and susceptibility to environmentally mediated disorders such as Parkinson's disease[66] and lung cancer.[67] In addition, individual variation in drug or xenobiotic metabolism due to genetic variation has been extensively investigated. Population studies showed a wide range in metabolizing ability for all detoxification pathways, including both cytochrome P450 systems and conjugating pathways.[68] The most well-described polymorphism in this category was due to the absence of cytochrome $P450_{2D6}$. Such individuals, comprising 5% to 10% of Caucasian populations, are referred to as poor metabolizers. These individuals have a severely impaired capacity to metabolize more than 25 therapeutic drugs and a wide range of xenobiotics.[69] On the other end of the spectrum are individuals described as extensive metabolizers. Such individuals require a higher dose of several drugs to achieve therapeutic effects and may have a more robust capability to handle certain environmental toxins. Heritable polymorphisms are also known for several conjugating enzymes (phase 2 detoxification) that are extensively involved in the metabolism of exogenous chemicals.[70] For example, genetic polymorphism of the glutathione-S-transferase (phase 2, glutathione conjugation) enzyme family is known to occur.[71] This is well regarded as a significant factor conferring susceptibility to environmental toxins. The significance of these genotypic variants to the incidence of functional illnesses, such as chronic fatigue syndrome or fibromyalgia, is likely but has not been studied.

Metallothioneins and Genetic Polymorphism

One of the most important detoxification systems in all species from bacteria to humans depends on the production of a family of four different proteins known as metallothioneins (MTs). MTs are highly unusual proteins composed of about 30% cysteine and are responsible for storage, transfer, and detoxification of intracellular metal ions.[72] The primary role of MTs in the absence of toxic metals is the transport and short-term storage of zinc and copper. However, the importance of MT in protection against and elimination of toxic metals has also been well described. MT is known to efficiently bind several toxic metals (particularly cadmium and mercury) and act as a transporter of the toxic metal to the liver or kidneys, where glutathione conjugation and subsequent excretion of the toxic metal may then occur. Because MT forms high affinity complexes with several metals, it may prevent toxic metals from reacting with other biomolecules or acting as free radical catalysts, thus attenuating their toxicity.[73]

There is a wide variation in the concentration of MTs among species. Humans, for example, have about 10 times the concentration of MT in their organs as do rats or mice. Additionally, genotypic polymorphism for expression of certain MTs within a species has been demonstrated. Mutant mice and rat models were identified with complete absence of the genes for one of four MT isoforms. In these MT-deficient animals, susceptibility to the toxic effects of heavy metals is increased by 60-fold to 100-fold. In contrast, it was shown in animal models that resistance to heavy metal toxicity might be conferred in mutants that possess multiple copies of MT genes in their chromosomes. These animals might be capable of more prolific upregulation of MT production.[74] Genetic polymorphism for MT expression also exists in humans.[75] Human cancer cell lines are known to be highly polymorphic in their ability to express MT genes. This is the primary reason why cancer patients vary in their resistance to metal cancer chemotherapeutic drugs.[76] Some laboratories offer test panels that assess MT function. These assays may provide clinically significant means to screen an individual's susceptibility to metal intoxication. Importantly, gene expression for MT production is highly inducible (e.g., through zinc supplementation and exercise).[77-79] Because of this, working with the factors that induce optimal production of MT may be important during a heavy metal detoxification regimen.

Nutritional and Environmental Factors That Modify Susceptibility to Environmental Toxicants

Although genetic predisposition may confer certain absolute risks in an individual's response to toxic stress, most aspects of detoxification and resistance to toxic agents involve highly modifiable nutritional, environmental, and lifestyle factors. The cytochrome P450 enzymes are located primarily in the liver. However, several other organs, including the small intestine, lungs, brain, and kidneys, contribute in a lesser way to the P450 mediated oxidation of xenobiotics, as well as endobiotics, such as hormones and neurotransmitters. Numerous factors can markedly influence phenotypic expression of these critical enzymes. Although there have been more than 30 P450s characterized in detail in humans, it appears that the majority of P450 activity is carried out by about six isoforms.[80] The impact of various physical, chemical, and

microbiological agents on P450 activity is highly complex and may invoke either upregulation, downregulation, inhibition, or stimulation of enzyme activity.

Monofunctional and Multifunctional Effects

Some agents act in a monofunctional manner, upregulating only one P450, whereas others are multifunctional, with a wide pattern of induction or inhibition, or both, of several phase 1 and phase 2 enzyme systems. The impact of any factor on detoxification status results from the sum of all effects on phase 1 and phase 2 enzyme systems. For example, moderately high-protein diets bring about upregulation of P450s in a pattern that decreases susceptibility to pesticides and other xenobiotics, whereas low-protein diets increase pesticide toxicity because of P450 downregulation. In contrast, cigarette smoking effects a monofunctional induction of P450, bringing about biotransformation of certain xenobiotics into potent carcinogens while simultaneously increasing oxidative stress.[81]

Numerous phytochemicals are known to exert potent effects on both phase 1 and phase 2 enzyme activities. With few exceptions (such as grapefruit slowing drug metabolism or St. John's wort accelerating drug metabolism), plant foods common to the human diet have been shown to have highly beneficial effects on detoxification systems. Onions and garlic, cruciferous vegetables, chlorophyll, terpenoids (e.g., citrus, ginkgo biloba, menthol, camphor), bioflavonoids (e.g., citrus, pine bark, grape seed, green tea), and others all act in a complex yet highly beneficial manner in bringing about improvements in detoxification capability.[82]

Fasting

One significant consideration for the natural medicine clinician is the impact of fasting on detoxifying enzyme function. For the most part, P450 enzymes are relatively resistant to depletion during fasting and may even be significantly induced by products of starvation, such as ketones and xenobiotics released from stored fat.[80] In contrast, the conjugating enzymes are highly dependent on dietary provision of adequate amounts of substrate and are consumed rapidly under states of high xenobiotic load or oxidative stress.[83]

Because they do not provide adequate substrate for phase 2 detoxification, complete fasting, juice fasts, or other nutritionally marginal fasting regimens may therefore result in a marked rise in highly toxic bioactive intermediates and free radicals with a concomitant decrease in phase 2 detoxification activity. This state of unbalanced detoxification can result in marked oxidative stress and may be particularly deleterious to chronically ill patients whose antioxidant reserves are already exhausted or significantly weakened. Perhaps in the past, when tissue burdens of xenobiotics and heavy metals were low, fasting regimens were of significant benefit. However, the modern human is probably ill advised to follow such traditional detoxification methods, especially for lengthy periods of time.

Phase 2

Phase 2 detoxification systems are particularly dependent on and responsive to adequacy of substrates necessary to carry out the conjugation of oxidized intermediates. Adequate amounts of protein with special attention to the adequacy of glycine, L-glutamine, methionine, L-cysteine, and *N*-acetylcysteine, along with inorganic sulfate, selenium, and additional taurine are all examples of nutrients that are highly important in the support of phase 2 activity.[84-87] Lipoic acid supplementation markedly enhances the level of intracellular glutathione in states of adequate sulfur amino acid intake.[88] Undenatured whey protein, rich in glutathione precursors, was shown in several studies to increase cellular and plasma glutathione.[89] Cruciferous vegetables significantly upregulate phase 2 enzyme activity.[90] Antioxidants also provide a highly supportive role in liver detoxification by reducing oxidative stress resulting from phase 1 activity and by preventing glutathione consumption by reactive oxygen species. Milk thistle, curcumin, and green tea extracts are particularly useful antioxidants for the liver.[91-93]

Other Nutritional Factors

Other nutritional factors affect detoxification. High carbohydrate diets bring about downregulation of P450s in a pattern that results in an undesirable reduction in the metabolism of several drugs and hormones.[54] Intestinal dysbiosis inhibits P450 activity through an increase in nitric oxide production.[94] In contrast, supplementation with probiotic bacteria can markedly reduce the adverse effects of bacterial endotoxin on the liver, as well as decreasing gut permeability.[95] Certain types of dietary fiber markedly enhance the activity of both phase 1 and phase 2 detoxification systems in the liver.[96] Fiber also decreases stool transit time, acts to sequester conjugated xenobiotics and endobiotics located in the bile, and reduces the level of bacterial deconjugating enzymes in the stool. All of these effects reduce the recycling of xenobiotics and endobiotics through enterohepatic circulation.[97,98]

Exercise

Exercise, if accompanied by adequate calories and protein, was shown to result in liver hypertrophy and a multifunctional induction of detoxification enzyme systems, as well as a marked increase in antioxidant enzymes and reduced glutathione in several organs.[99-101] Additionally, exercise results in a mobilization of extracellular fluid and lymph where xenobiotics often temporarily reside after being released from cells by exocytosis or other mechanisms. In addition, sweating augments the liver's detoxification mechanisms; it was shown to be a highly important route of elimination for both organic[102,103] and metallic[104,105] toxicants.

Nutritional and Environmental Regulation of Toxic Metals

Nutritional adequacy has a marked influence on the absorption, retention, toxicity, and excretion of toxic metals.[106] The absorption of lead, as well as cadmium, is increased in states of iron or calcium deficiency. In addition, iron deficiency is one of many factors that lead to increased intestinal permeability. This, in turn, markedly enhances the uptake of aluminum, an abundant dietary constituent that is not well absorbed through intact enteric mucosa.[107] The absorption of several other toxic metals may be enhanced by increased intestinal permeability. Inadequacy of certain minerals also leads to enhanced retention of toxic metals. For example, calcium deficiency increases both lead and cadmium body burden, and selenium deficiency increases mercury retention.

As described previously, toxic metals compete with nutritional minerals and lead to displacement of nutrient minerals from protein binding sites, as well as excessive loss of minerals from the body.[108] Therefore, the requirement for several nutrient minerals may rise significantly above the recommended daily allowance in the metal toxic patient. The clinician must also be aware that

certain nutritionally necessary metals (e.g., iron, copper) can become conditionally toxic, and perhaps should only be supplemented if a deficiency is determined. The best example of this is excessive iron stores in patients who are homozygous or heterozygous for a hemochromatosis mutation, the most common genetic disorder. Although homozygotes are relatively uncommon, heterozygotes for this disorder may be as high as one in five in certain populations; these individuals may be at risk for manifestations of iron toxicity, particularly if iron supplementation is administered.[109] Other nutrient metals (e.g., manganese) may be nontoxic unless control of absorption is bypassed through inhalation or injection.[110]

The excretion of toxic metals is governed by a complex chain of interwoven activities. If any link in this chain is broken, proper elimination of the toxic metal may not occur. Toxic metals must be released from the cell; moved from the extracellular fluid into the blood; transported from the blood to the liver or kidneys; and then transported from the kidneys to the urine or the liver into the bile. Once the metal is in the bile, it must then be transported out of the body in the stool before being reabsorbed back into the circulation.

For example, the first step in mercury excretion involves binding of the mercury to MT or glutathione within the cell. MT production, in turn, is highly inducible through exercise and supplementation with zinc, whereas zinc deficiency results in MT depletion. MT production is also induced by supplementary L-cysteine or by brief periods of oxidative stress (as occurs from aerobic exercise).[111] MT works in cooperation with glutathione in the initial mobilization of mercury from cells, and it also shares intracellular antioxidant activity with glutathione (MT is 50 times as potent as an antioxidant as glutathione).[112] Selenium may also play a role in binding to mercury within the cell and forming a transportable complex. Therefore, selenium supplementation has been recommended in the treatment of mercury toxicity.[113]

Once mercury is mobilized by MT or glutathione, it is transported through the cell membrane (probably by exocytosis). Mercury must then be carried away from the cell to limit toxicity on the cell membrane and to transport mercury to the liver. Exercise is probably helpful in accelerating the movement of mercury from the extracellular fluid, through the lymph and into the blood. As well as exercise, hyperthermic therapy, such as with a sauna, may be helpful in mobilizing mercury directly from the extracellular fluid.[104] Once the mercury reaches the liver, it usually undergoes conjugation with glutathione and is transformed into a mercapturate. The mercury mercapturate is then released into bile.[114] Both the liver and the kidneys are highly sensitive to glutathione depletion by mercury. Hepatic and renal glutathione production can be enhanced by supplementing the diet with L-cysteine, *N*-acetylcysteine, glutathione, cruciferous vegetables, dietary fiber, undenatured whey protein, lipoic acid, onions, and garlic. Lipoic acid may also assist in this process by directly binding inorganic mercury in the liver and accelerating its excretion into the bile while simultaneously inducing the formation of glutathione.[115]

Once mercury has entered the intestine through the release of bile, it must leave the body via the stool. Optimal gastrointestinal function is important to prevent recycling of mercury through enterohepatic circulation. Fiber was shown to have a significant effect in lowering total body burden of mercury through sequestration of intestinal mercury and reduction in stool transit time.[116] Other factors, including increased gut permeability, or intestinal dysbiosis resulting in deconjugating bacterial enzymes, are all key factors that determine how efficiently mercury can leave the body once it has passed from the liver into the small intestine. Because about 90% of excreted mercury leaves the body through the enteric route, colonic elimination is a vital component in maintaining an unbroken and efficient chain of excretion from the cell to the outside of the body for mercury, as well as a host of other toxicants.



ASSESSING THE TOXICOLOGICALLY IMPAIRED PATIENT

A carefully gathered toxic exposure history is a vital part of the clinical evaluation. The mnemonic C(H2) OP(D4) aids in remembering important elements of the toxic exposure history, as shown in Box 53-1.

Of course, patients may not be aware of important sources of toxic exposure. They may also have genetic, nutritional, or lifestyle factors that leave them at elevated risk for toxicologically mediated health problems. The field of toxicogenomics is in its infancy, but several laboratories offer toxicogenomic assays to help evaluate a patient's genetic risk of toxin-mediated illness. Evaluations of single nucleotide polymorphisms to assess cytochrome P450 variability, DNA, or RNA amplification techniques (primarily polymerase chain reaction) to assess adequacy of MT or glutathione S-transferase activity are examples of toxicogenomic tests that are or are becoming commercially available to the clinician.

Some laboratories developed panels that include evaluation of several factors relative to a particular toxicologic system. For example, an available MT profile consists of measurements of serum zinc, serum copper, serum ceruloplasmin, serum ceruloplasmin copper, nonceruloplasmin ("free") copper, whole blood reduced glutathione, whole blood MTs, the copper/zinc ratio, the reduced glutathione/MT ratio, and the zinc/MT ratio. Other examples include the functional liver detoxification profiles offered through several commercial laboratories. In these tests, patients are given drugs (often acetaminophen, aspirin, and caffeine) as a single oral dose. Urine is gathered after the ingestion of the test, and levels of metabolites processed through phase 1 and phase 2 detoxification are measured. Although no profile that assays the function of more than a few of the several dozen possible detoxification enzymes currently exists, these tests often do provide useful information for the clinician.

BOX 53-1 **C(H2) OP(D4)—The Toxic Exposure History**

Community: City and neighborhood air quality, noise, electromagnetic fields
Home: Home heating and ventilation, cleaning chemicals, pesticides, paints, carpets, building materials, molds, allergens, water
Hobbies: Toxic chemicals, paints, solvents, metal fumes
Occupation: Workplace air quality, toxic chemicals
Personal habits: Smoking, drinking, drug use, sun exposure, exercise, stress management
Diet: Overall quality of diet, overeating or undereating, meat eater or vegetarian, fast foods, snack foods, deep-fried foods, fish and seafood, organic or nonorganic foods, food allergies or intolerances, leaky gut syndrome, abnormal microbial ecology of the digestive tract
Drugs: Prescription and nonprescription
Dental: Amalgams placed and removed, extractions, root canals
Development: Mother's pregnancy history (e.g., smoking, drugs, drinking, toxic exposures, dental work), childhood exposures (e.g., leaded paints, pesticides, secondhand smoke)

Organic Toxicants

In some cases, an occupational history provides clues for which specific toxicants should be searched. Some toxicology laboratories offer extensive panels to quantify the level of organic toxins in blood, urine, or adipose tissue. Available panels include PCBs, organochlorine pesticides, PBDE fire retardants, furans, and dioxins. Body burdens for these agents are accurately assessed by providing a small sample of adipose tissue (often taken through a small incision under the umbilicus). For example, an electric utility worker with chronic fatigue syndrome may have a high body burden of PCBs as measured in a provided fat biopsy. In this case, PCB tissue levels can be followed in a serial fashion after detoxification efforts. Such assessment may also help a patient to support a disability or worker's compensation claim. However, unless a specific chemical or family of chemicals can be suggested by an exposure history, the range of possible organic toxicants is far too vast to be determined practically and financially in most cases. It is generally more realistic to assume that all functionally impaired patients carry a wide range of synergistically active organic toxicants at various levels and focus instead on engaging the patient in a comprehensive detoxification program using outcome-based measures and functional testing to gauge success.

Metal Toxicants

In contrast, the definitive assessment of a patient's heavy metal burden is relatively simple, and probably should be performed early on in the assessment of most patients with polysymptomatic, chronic illness. Metal toxic patients present a unique clinical challenge and, if a significant toxic metal burden is present, the outcome of clinical intervention may be disappointing unless the metal burden is effectively diminished. Once metal burdens are diminished, patients often respond far more effectively to other clinical interventions.

Only a limited number of toxic metals are commonly found in humans, and most laboratories provide panels that include most of these metals. Hair analysis is simple and inexpensive to perform, and it may provide a reasonable means to screen patients for levels of certain metals, such as lead or methylmercury (from seafood). However, the precision of this methodology in determining long-standing body burdens of most other metals is probably too low to base confident clinical decisions on, and some toxicology authorities suggest that hair analysis be limited to population screening.[117]

Conventional toxicologists generally rely on other methodologies of assessing metal burden to gauge clinical decision making. "Acceptable" blood levels of lead in children and adults, as well as blood and urine levels of several other metals in industrial settings, have been widely suggested in published literature. However, the limitation of blood or urine tests is that they largely reflect only the level of ongoing exposure to the metal and may bear little relationship to tissue levels. Because tissue biopsy for heavy metal levels is impractical, postprovocative urine testing is probably the most reliable means to assess body burden of metals acquired through long-standing, low-level exposure, especially in the assessment of low-level inorganic mercurialism.[118]

Although many variations on the challenge test have been performed with various metal chelating agents, a methodology used by the German toxicologist Daunderer is simple, relatively inexpensive, and correlates to clinical response to further treatment.[119,120] This methodology utilizes the chelating agent dimercapto-propane sulfonate (DMPS) (Box 53-2). The use of the oral chelator dimercaptosuccinic acid (DMSA or succimer) for diagnostic postprovocative challenge testing has not been established, and some data suggest that it does not reflect mercury body burden.[121] Although no challenge test for mercury has been accepted using the chelators DMSA or ethylenediaminetetraacetic acid, both agents may be useful for the assessment of lead burden (see Box 53-2).[122]

Not every clinician has the training or legal ability to safely use drug chelating agents to assess metal burdens or provide metal detoxification therapies. In the United States, DMSA is currently classified as a nutritional supplement. In several regions of the United States and Canada, naturopathic physicians can administer both oral and intravenous chelating drugs.

BOX 53-2 Dimercapto-propane Sulfonate (DMPS) Challenge Test Methodology

The patient empties his or her bladder completely, drinks a large glass of water, and then has an IV inserted. The patient is placed supine, and DMPS is administered undiluted at a dose of 3 to 4 mg/kg (more than or equal to 250 mg) over 20 minutes.

Following the DMPS injection, the patient is instructed to walk around for approximately 1-1/2 hours and then a random urine sample is gathered. The volume of urine does not need to be measured in this case. The urine metal values are reported in micrograms of metal per gram of urinary creatinine. This method of reporting normalizes the sample for level of urinary concentration. A postprovocative urinary level of mercury more than 50 mg mercury per gram of urinary creatinine is indicative of significantly elevated mercury body burden.

Because a 24-hour collection is not used, the test is much easier for patients to perform and results in much higher compliance than 24-hour sampling methods. Patients are not required to collect multiple samples and record urine volumes, so the accuracy may be improved over 24-hour methods as well. The half-life of DMPS is short, and the short sampling interval is a good reflection of quantities of toxic metals excreted with one injection.

The lack of a baseline or preinjection urine sample is a departure from usual methodologies. However, the purpose of urine collection beforehand and afterward is to compare the level of current metal exposure (presample) to the body burden (postsample). Because most patients are not industrially exposed and probably have little ongoing exposure, the level of metals found on the preinjection sample is usually extremely low, and these data do not add information to guide clinical decisions.

Modified from references 119 and 120.

DETOXIFICATION

The Detoxification Lifestyle

When working with chronically ill patients whose health is affected by toxicologic stresses, clinicians need to provide education to help these individuals develop habits of living that will reduce their exposure to toxicologic factors and improve the efficiency of their detoxification mechanisms. The mnemonic A NERD (see the following) can help the clinician remember the important elements of a detoxification lifestyle. Patients who learn to follow these habits of living create a foundation for better long-term health, and their response to more extensive clinical interventions will be more successful.

Avoid exposure to all known sources of toxicity. Chemical dependencies, smoking, excessive alcohol, unnecessary prescription drugs, toxic work environments, homes with lead paint, severe

air pollution, polluted drinking water, standard North American diets (particularly sugary drinks, junk foods, processed meats, fast foods, and deep-fried foods), and dental amalgam fillings are all examples of toxic sources that must be removed or avoided.

Nutrition must be optimized for efficient detoxification. The diet must be based on whole foods (plenty of vegetables, fruits, and fiber) and should emphasize foods with a net alkalinizing impact with lower amounts of acid-forming foods. Generous portions of cruciferous vegetables should be eaten daily with modest amounts of olive oil, as well as onions, garlic, and modest amounts of lean, unprocessed protein. Supplements should include alkalinizing minerals (calcium, magnesium, potassium, zinc) along with multivitamin and/or trace elements, essential fatty acids (docosahexaenoic acid/eicosapentaenoic acid), *N*-acetylcysteine, lipoic acid, and antioxidant support (vitamin C, vitamin E, grape seed extract, green tea extract). Undenatured whey protein supports synthesis of glutathione. Detoxification medical food products are available with a base of undenatured whey, rice, or pea protein, along with a range of nutrients to support detoxification. These can be used as a supplement to or in replacement of one meal per day to simplify the daily detoxification supplement program.

Exercise accelerates lymphatic flow, induces sweating, and increases metabolism and detoxification efficiency. Exercise should be a daily part of the detoxification lifestyle.

Rest, including proper sleep, relaxation, and stress management, is an essential element in the detoxification lifestyle.

Detoxification as a specific therapeutic activity should be considered as a periodic means to improve vitality and reduce toxic body burdens. Traditions of fasting and purification have been incorporated into the way of life and health care systems of most traditional cultures, and variations of fasting are central to the practices of natural, integrative, and functional medicine. Taking a few days to rest and rejuvenate the gastrointestinal tract and bolster the excretion of xenobiotics is a lifestyle habit that can improve a patient's vitality. Nutritionally controlled fasting for 5 to 7 days with every change of season is a reasonable recommendation for clinicians to make to their patients. Another alternative is to have patients undergo a nutritionally controlled fast 1 day per week on an ongoing basis. In addition, natural health care providers may use more intensive or lengthier detoxification programs for specific conditions responsive to these interventions.

Nutritionally Controlled Fasting

The traditional practices of fasting or purification are usually religious in nature and usually involve an abstinence from food or certain kinds of food and a focus on spiritual disciplines of prayer or meditation. Practitioners of natural medicine have also used various forms of fasting to treat various chronic maladies and to decrease toxic stress. In some countries the use of water fasting as part of an inpatient sanitarium treatment remains a popular and accepted means of treatment for pain and fatigue syndromes, as well as certain autoimmune disorders.[123] Extreme low-calorie or zero-calorie forms of fasting result in loss of adipose tissue, with glucose being liberated from hepatic and muscle glycogen stores. Within 2 days of starvation or near starvation, necessary glucose is provided from cellular apoptosis and autophagy (programmed degradation of cellular organelles and muscle protein),[124] and the brain increasingly adapts to the use of the ketone body, β-hydroxybutyrate.[125] (See Chapter 37 for a more complete discussion of fasting metabolism.)

During fasting, stored xenobiotics and heavy metals are released and may largely be redistributed to and accumulate in the liver, kidneys, and brain because the mechanisms for excretion of these toxins require complex nutritional support that is lacking in starvation.[126-129] Because of these concerns, many practitioners of natural and functional medicine prescribe a nutritionally controlled form of fasting intended to stimulate the mobilization of xenobiotics from cells while supporting and protecting detoxification and excretory mechanisms.

Rigden[130] described the "enterohepatic resuscitation program for chronic fatigue syndrome" and reported significant improvement in the majority of patients studied. In this uncontrolled study, subjects consumed a limited, low-calorie diet supplemented by a medical food product designed to provide nutritional support of hepatic detoxification, including phase 1 (antioxidants) and phase 2 detoxification (phase 2 conjugation substrates). Bland,[131] in another uncontrolled study, used a similar program with a high degree of success in 106 patients with various chronic illnesses. Using a much different approach, clinicians who prescribed exercise and saunas combined with supplementary niacin, calcium, magnesium, and polyunsaturated oil reported a significant reduction in tissue PCBs and other fat soluble xenobiotics in toxic patients.[132-134] Europeans successfully used sauna treatment to decrease mercury levels in exposed workers.[105] These approaches have not been validated with controlled clinical trials.

Recent studies reported that the sucrose polyester fat substitute olestra results in a marked loss of lipophilic xenobiotics and decreased brain levels of these agents during caloric restriction, secondary to sequestration of biliary-excreted xenobiotics and interruption of enterohepatic recycling.[135-138] Concerns relating to gastrointestinal side effects and marked loss of fat-soluble vitamins secondary to olestra, as well as the need to consume it as part of a snack food, limit olestra's use as a detoxifying agent. Another practical tool that may bring about accelerated elimination of lipophilic xenobiotics is the lipase inhibitor Orlistat (prescription, Xenical; over the counter, Alli). This agent is a derivative of the naturally occuring lipase inhibitor, lipstatin, a metabolite of a *Streptomyces* bacteria. By inducing malabsorption of fat, Orlistat enables bile excreted xenobiotics to dissolve into intestinal contents and be eliminated with fat laden feces rather than being reabsorbed. If given during weight loss or partial fasting along with modest amounts of dietary fats, Orlistat works via the same mechanism as olestra in the reduction of lipophilic xenobiotics.[139] The advantage of Orlistat is that it is readily available as an over-the-counter medicine, but patients must be cautioned to avoid high fat meals and to be aware that fatty stools will occur and can result in anal leakage of fat or fecal incontinence.

Decreasing stool transit time and increasing dietary soluble fiber may also reduce enterohepatic recycling of xenobiotics, but further research is required. Many clinicians practicing natural or functional medicine also prescribe metal-detoxifying therapies using chelating drugs such as DMSA or DMPS.[140] Clinicians should be completely familiar with the use of these agents before prescribing them, and they should be aware, as is true with all drugs, that serious side effects can occur with these agents. DMSA is classified as a nutritional supplement in the United States, but it is a drug with potential side effects. Dosing protocols for DMSA vary depending on physician preference and individual patient need, but currently two protocols are most often used. In one protocol, 10 to 20 mg/kg per day is given in three divided doses, using a 3-days-on, 11-days-off cycle, with a minimum of eight cycles. A second protocol involves giving 500 mg/day (in two or three divided doses) every other day for a minimum of 5 weeks. DMSA is best taken between meals (Box 53-3).[141]

BOX 53-3 Nutritionally Controlled Fasting

Many clinicians have been successfully prescribing a program of nutritionally controlled fasting that follows this general approach:

- Mild to moderate caloric restriction to promote fat loss
- No fast foods, junk foods, deep-fried foods
- High quantities of fresh vegetables and often fresh vegetable juice
- Simple, low-processed, oligoantigenic foods (low allergy potential); protein (e.g., chicken, fish, legumes); and whole grains (e.g., brown rice, millet, quinoa)
- Medical food products designed to support detoxification (1 to 3 times daily depending on quantities of other foods eaten)
- Light exercise daily
- Sauna 3 to 5 times weekly

The nutritionally controlled fast is continued for 5 to 21 days or more depending on the patient's condition and the clinician's experience.

Gastrointestinal Rehabilitation

Gastrointestinal rehabilitation is a concept familiar to practitioners of natural medicine. Many clinicians consider gastrointestinal rehabilitation to be an essential part of any detoxification program that should occur even before detoxification interventions begin. This involves therapeutic steps to reduce intestinal permeability, improve nutrient absorption, and increase immune response to gut pathogens while diminishing hypersensitivities. A useful approach follows the mnemonic "ANT PIE" (Abstain, Nourish, Toxins/detoxification, Probiotics, Identify, Eliminate).

Abstain from junk foods, deep-fried foods, sugary drinks, and other foods that harm or irritate the gut, as well as unnecessary drugs or excessive alcohol.

Nourish the digestive tract with nutrients that support gut healing. Medical foods that combine low allergy potential protein with a number of nutrients helpful for gastrointestinal healing are readily available.

Toxins/detoxification: Nutritionally controlled fasting as described earlier begins after evidence that gut permeability has diminished and digestive processes have improved. Detoxification efforts continue simultaneously with ongoing gastrointestinal rehabilitation. In addition, chelation therapy is often started once gastrointestinal rehabilitation has progressed and the patient has shown some improvement.

Probiotics are therapeutic bacteria (and some yeast), which may improve the gastrointestinal microecology, improve immune response toward gut pathogens, reduce immune hypersensitivities, and stimulate gut repair.

Identify allergenic or intolerant foods and gut pathogens. Food allergies (type 1 or immediate hypersensitivity food reactions) can be identified by skin prick testing, radioallergosorbent testing, or enzyme-linked immunosorbent assay testing for immunoglobulin-E antifood antibodies. Patients with evidence of type 1 hypersensitivity food allergies (e.g., postprandial swelling of the lips, urticaria, wheezing) should be referred to an allergist for definitive testing, because serious anaphylaxis could occur without proper avoidance. Delayed hypersensitivity reactions (usually type 3 mediated) are best identified with a properly conducted elimination test diet followed by carefully observed reintroductions of individual food items eliminated in the test diet. Immunoglobulin-G antifood antibodies may also be tested, but only before any dietary manipulation has occurred.

Intestinal parasites, yeast, and pathogenic bacteria may also be identified by stool testing, *C. albicans* and *Helicobacter pylori* serology, breath testing, and urinary organic acids.

Eliminate foods found to be allergic or intolerant with elimination test diet or laboratory testing. Gut pathogens, parasites, and *C. albicans* overgrowth may be treated.

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CHAPTER 54

Homocysteine Metabolism: Nutritional Modulation and Impact on Health and Disease

Alan L. Miller, ND, Gregory S. Kelly, ND, and Jessica Tran, ND

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INTRODUCTION

Homocysteine is an intermediate in the conversion of the amino acid methionine to cysteine. Elevated homocysteine levels are an independent risk factor for coronary heart disease, stroke, and other vascular conditions. Homocysteine and its relationship to cardiovascular disease emerged in the late 1960s, when Kilmer McCully, MD encountered two children with homocystinuria (a rare autosomal recessive condition) who had advanced atherosclerosis, although the coronary plaques contained no lipids. Increased homocysteine levels have been implicated in several other clinical conditions, including neural tube defects, spontaneous abortion, placental abruption, renal failure, non–insulin-dependent diabetes and complications of diabetes, rheumatoid arthritis, alcoholism, osteoporosis, and neuropsychiatric disorders.

HOMOCYSTEINE METABOLISM

Homocysteine is metabolized along two pathways: remethylation to methionine (which requires methionine synthase along with vitamin B_{12} and folic acid or betaine) or transsulfuration to cysteine (which requires vitamin B_6). A defect in either of these pathways leads to accumulation of homocysteine. Insufficient dietary intake of vitamin B_6, vitamin B_{12}, and folic acid can lead to increased homocysteine levels.

Gender and Genetics

Studies of healthy men and women indicate that certain acquired and genetic determinants may affect total plasma homocysteine. Women tend to have lower basal levels than men,[1] and neither contraceptives nor hormone replacement therapy seem to alter their levels significantly.[2] However, in postmenopausal women, hormone replacement therapy might slightly decrease elevated homocysteine concentrations. No significant lowering effect was observed in women with low homocysteine levels.[3] Generally, homocysteine concentrations are significantly higher in postmenopausal women than in premenopausal women; however, the previously mentioned sex differences in homocysteine concentrations persist even in elderly populations.[4-6] The antiestrogen drug tamoxifen, used in the long-term treatment of breast cancer patients, was reported to decrease homocysteine levels in postmenopausal women with breast cancer.[7]

A number of reports also demonstrated that elevated plasma total homocysteine in children was correlated to either cardiovascular disease or death in their parents or close relatives. This relationship was observed in both white and black children, and in white children with hypercholesterolemia. In the latter study group, the 5,10-methylenetetrahydrofolate reductase (MTHFR) *TT* genotype tended to be most frequent in children with a parental history of cardiac disease.[8] Epidemiologic evidence showed homocysteine levels to be more than 45% lower in Westernized adult black Africans than in age-matched white adults, revealing racial genetic differences in homocysteine metabolism.[9]

The *MTHFR* gene has two different alleles where the "T" allele is associated with decreased enzyme activity, hyperhomocysteinemia, and increased risk for thromboembolism in coronary heart disease. The presence of the "C" allele is correlated to lower homocysteine levels and, not surprisingly, may even provide protection against occlusion of coronary arteries. One Hungarian study concluded that the

carriers of the T allele with coronary heart disease died earlier due to myocardial infarction.[10]

Lifestyle

An association between coffee and black tea consumption and the concentration of total homocysteine in plasma has been reported.[11] A marked positive dose–response relation between coffee consumption and plasma homocysteine levels was observed. The relationship was most marked in males and females consuming more than eight cups of coffee per day. The combination of cigarette smoking and high coffee intake was associated with particularly high homocysteine concentrations.[12] Long-term ingestion of alcohol has also been associated with increased homocysteine levels.[13,14] Plasma total homocysteine is inversely related to exercise.[15]

Nutritional Relationships

Nutrition affects homocysteine concentrations in both men and women. For example, individuals in the lowest quartiles for serum folate and vitamin B_{12} have significantly higher concentrations of homocysteine, and men in the lowest quartile of serum pyridoxal 5′-phosphate (P5P; the bioactive form of vitamin B_6) also have increased homocysteine concentrations.[2]

Methionine

Metabolism of the amino acid methionine, a limiting amino acid in the synthesis of many proteins, affects several biochemical pathways involving the production of nutrients that are essential to the optimal functioning of the cardiovascular, skeletal, and nervous system.

Homocysteine is an intermediate product of methionine metabolism and is metabolized by two pathways: the remethylation pathway, which regenerates methionine, and the transsulfuration pathway, which degrades homocysteine into cysteine and then taurine. In essence, the intermediate metabolite homocysteine is located at a metabolic crossroads, so it directly and indirectly affects all methyl and sulfur group metabolism occurring in the body. Experiments demonstrated that high levels of L-homocysteine and adenosine in the cell inhibit all methylation reactions.[16]

The remethylation pathway (Figure 54-1) comprises two intersecting biochemical pathways and results in the transfer of a methyl group (CH_3) to homocysteine by either methylcobalamin or betaine (trimethylglycine). Methylcobalamin originally receives its methyl group from S-adenosylmethionine (SAMe) or 5-methyltetrahydrofolate (5-methylTHF), an active form of folic acid. After remethylation, methionine can be reused to produce SAMe, the body's "universal methyl donor," which participates in several key metabolic pathways, including methylation of DNA and myelin, synthesis of carnitine, coenzyme Q_{10} (CoQ_{10}), creatine, epinephrine, melatonin, methylcobalamin, and phosphatidylcholine (PC), as well as phase 2 methylation detoxification reactions.

The transsulfuration pathway of methionine/homocysteine degradation (see Figure 54-1) produces the amino acids cysteine and taurine, which are important nutrients for cardiac health, hepatic detoxification, cholesterol excretion, bile salts formation, and glutathione (GSH) production. This pathway depends on

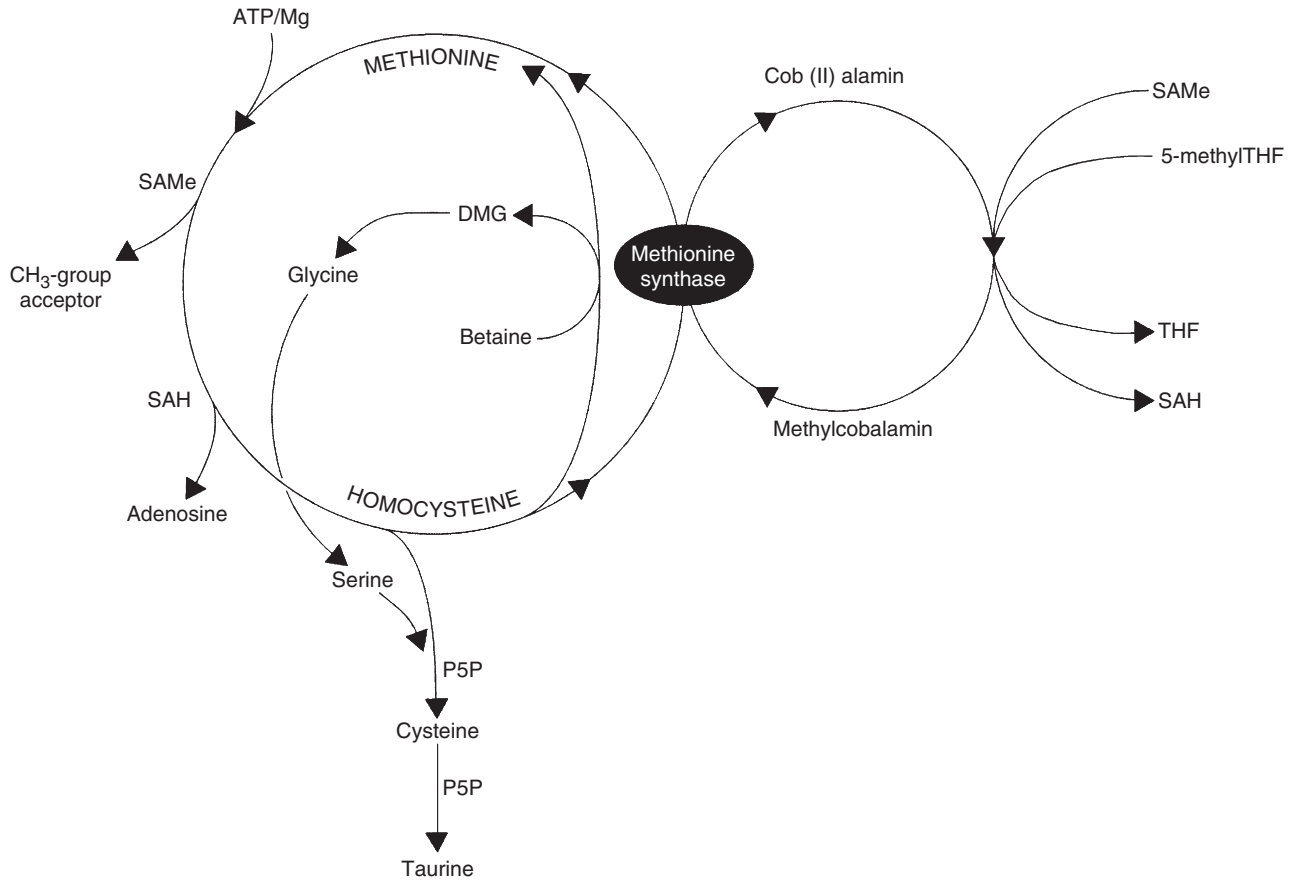


FIGURE 54-1 Homocysteine metabolism. DMG, dimethylglycine; 5-methylTHF, 5-methyltetrahydrofolate; P5P, pyridoxal 5′-phosphate (vitamin B_6); SAH, S-adenosylhomocysteine; SAMe, S-adenosylmethionine; THF, tetrahydrofolate.

adequate dietary intake and hepatic conversion of vitamin B_6 into its active form, P5P. The amino acid serine, a down-line metabolite generated from betaine via the homocysteine remethylation pathway, is also necessary.

In addition to 5-methylTHF, methylcobalamin, betaine, and P5P, *N*-acetylcysteine (NAC) has been reported to significantly lower homocysteine levels.[17]

S-Adenosylhomocysteine

The metabolic precursor of homocysteine in all tissues is S-adenosylhomocysteine, which is more difficult to measure than homocysteine, but has recently been indicated as a more sensitive marker for cardiovascular disease and Alzheimer's disease. S-adenosylhomocysteine is formed by the demethylation of SAMe (Figure 54-2). S-adenosylhomocysteine hydrolase catalyzes the hydrolysis of S-adenosylhomocysteine to adenosine and homocysteine. S-adenosylhomocysteine hydrolase deficiency is a genetic disorder of methionine metabolism that results in slow psychomotor development.

Increased levels of S-adenosylhomocysteine may occur when the intracellular concentration of homocysteine increases.[18-20]

Methyltetrahydrofolate

Folates function as carbon donors in the synthesis of serine from glycine, directly in the synthesis of purines and pyrimidine bases, and indirectly in the synthesis of transfer RNA. Folates also function as methyl donors to create methylcobalamin, which is used for remethylation of homocysteine to methionine. Dietary folic acid is a mixture of folates in the form of polyglutamates, which are readily destroyed by cooking.

Synthesis of the active forms of folic acid is a complex process requiring several enzymes, as well as adequate supplies of niacin, P5P, and serine as cofactors (Figure 54-3). In plants, folic acid is formed from a hetero-bicyclic pteridine ring, para-aminobenzoic acid, and glutamic acid. Folate is initially deconjugated in the cells of the intestinal wall to the monoglutamate form. This is then reduced to dihydrofolate and then to tetrahydrofolate (THF) via folate and dihydrofolate reductase. Both enzymes require reduced nicotinamide adenine dinucleotide phosphate (niacin dependent) as a cofactor. Serine combines with P5P to transfer a hydroxymethyl group to THF. This results in the formation of 5,10-methylenetetrahydrofolate (5,10-methyleneTHF) and glycine. This molecule is of central importance, being the precursor of the metabolically active 5-methylTHF, which is involved in homocysteine metabolism, and 10-formyltetrahydrofolate (involved in purine synthesis), as well as functioning on its own in the generation of thymine side chains for incorporation into DNA.

The following may contribute to a deficiency of folic acid:

- A deficient food supply
- A defect in utilization, as in alcoholics
- Malabsorption
- Increased needs in pregnant women and cancer patients
- Metabolic interference by drugs
- Folate losses in hemodialysis

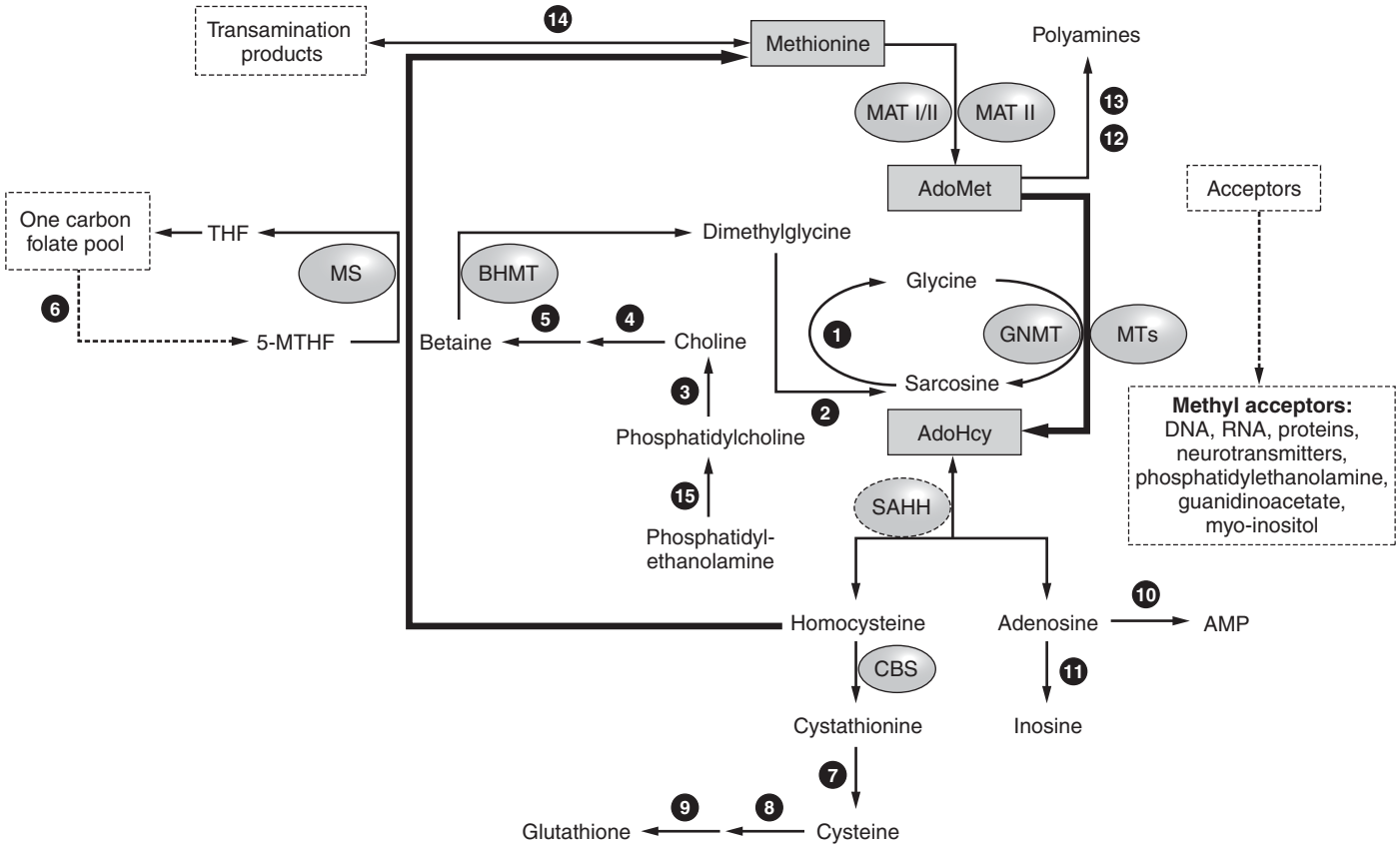


FIGURE 54-2 Methionine, AdoMet (S-adenosylmethionine), and AdoHcy metabolism. (From Baric I, Fumić K, Glenn B, et al. S-adenosylhomocysteine hydrolase deficiency in a human: a genetic disorder of methionine metabolism. Proc Natl Acad Sci , 2004:101:4234-4239.)

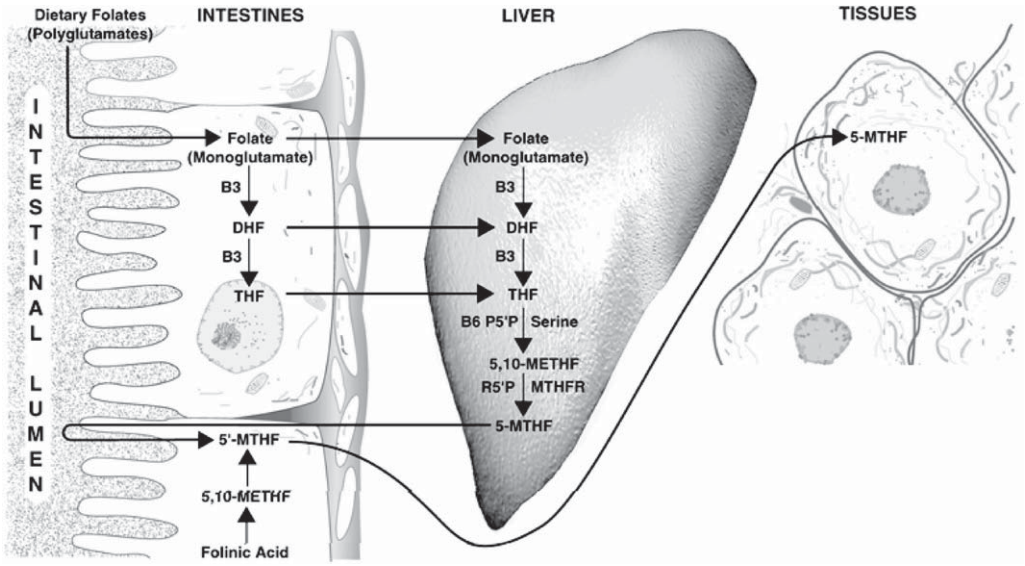


FIGURE 54-3 Absorption and activation of folic acid. DHF, dihydrofolate; 5,10-METHF, 5,10-methylenetetrahydrofolate; 5-MTHF, 5-methyltetrahydrofolate; MTHFR, methylenetetrahydrofolate reductase; P5′-P, pyridoxal 5′-phosphate; R5′-P, riboflavin 5′-phosphate; THF, tetrahydrofolate.

- Enzyme or cofactor deficiency necessary for generation of active folic acid

Individuals using supplements or consuming either breakfast cereals or green leafy vegetables have significantly greater plasma folate and lower homocysteine levels than those who do not.[1]

Folinic acid (5-formylTHF), available supplementally as calcium folinate (also known as leucovorin calcium), is an immediate precursor to 5,10-methyleneTHF and 5-methylTHF. Folinic acid can correct deficiencies of the active forms of folic acid, is more stable than folic acid, and has a longer half-life in the body. Folinic acid also readily crosses the blood–brain barrier and is slowly cleared, compared with folic acid, which is poorly transported into the brain and, once in the central nervous system (CNS), is rapidly cleared.[21]

Methylcobalamin

The coenzyme form of vitamin B_{12} is a complex molecule containing cobalt bound to five nitrogens and one carbon. The metal–carbon bond found on this coenzyme is the only known biological example of this type of linkage. The use of cobalt in the two biologically active forms of cobalamin, adenosylcobalamin and methylcobalamin, is the only known function of this metal in biological systems.

In humans, the cobalt in cobalamin exists in a univalent oxidation state, designated as cob(I)alamin. The compound commonly referred to as vitamin B_{12} has a cyanide molecule at the metal–carbon position, and the oxidation state of the cobalt is +3 instead of the biologically active +1. To be used in the body, the cyanide molecule must be removed. It is thought that the compound GSH may perform this function. Other available forms of vitamin B_{12} include hydroxocobalamin and the two active forms, adenosylcobalamin (cobamamide) and methylcobalamin.

The absorption of dietary cobalamin requires the formation of a complex between dietary vitamin B_{12} and R-proteins and the secretion, by the stomach mucosa, of intrinsic factor. The vitamin B_{12} complex is split by pancreatic proteases, and the released vitamin B_{12} attaches to intrinsic factor and is absorbed in the distal ileum. The amount of cobalamin required in the diet is low, and even people with pernicious anemia can generally absorb sufficient amounts if the coenzyme is supplemented at a high enough dosage.

Although the basic cobalamin molecule is only synthesized by microorganisms, all mammalian cells can convert this into the coenzymes adenosylcobalamin and methylcobalamin. Adenosylcobalamin is the major form in cellular tissues, where it is retained in the mitochondria. Methylcobalamin predominates in blood plasma and certain other body fluids, and in cells found in the cytosol.

Adenosylcobalamin functions in reactions in which hydrogen groups and organic groups exchange places. In humans, adenosylcobalamin is required in only two reactions: the catabolic isomerization of methylmalonyl coenzyme A (CoA) to succinyl CoA and interconversion of α- and β-leucine. After its formation from methylmalonyl CoA, succinyl CoA is either involved in the synthesis of porphyrin molecules (along with glycine) or it transfers its CoA to form acetyl CoA. The latter reaction is magnesium dependent, and the remaining succinate is fed into the citric acid cycle. Deficiencies in this coenzyme form of vitamin B_{12} result in increased amounts of methylmalonyl CoA and generally an increase in glycine levels.

Methylcobalamin's only known biological function in humans is in the remethylation of homocysteine to methionine via the enzyme methionine synthase, also known as 5-methyltetrahydrofolate-homocysteine methyltransferase. To originally form methylcobalamin from cyanocobalamin or other Cob(III)alamin or Cob(II)alamin precursors, SAMe must be available to supply a methyl group. Once methylcobalamin is formed, it functions in the regeneration of methionine by transferring its methyl group to homocysteine. Methyl-cobalamin can then be regenerated by 5-methylTHF (Figure 54-4). The cell's ability to methylate important compounds such as proteins, lipids, and myelin is compromised by a deficiency of either folate or vitamin B_{12}.[22] Shortages of active folic acid, SAMe, or a dietary deficiency of cobalamin lead to a decrease in the generation of methylcobalamin and a subsequent impairment of homocysteine metabolism. Because lack of methylcobalamin leads to depressed DNA synthesis, rapidly dividing cells in the brain and elsewhere are affected.

At least 12 different inherited inborn errors of metabolism related to cobalamin are known. Abnormalities are detectable by urine and plasma assays of methylmalonic acid and homocysteine; and plasma

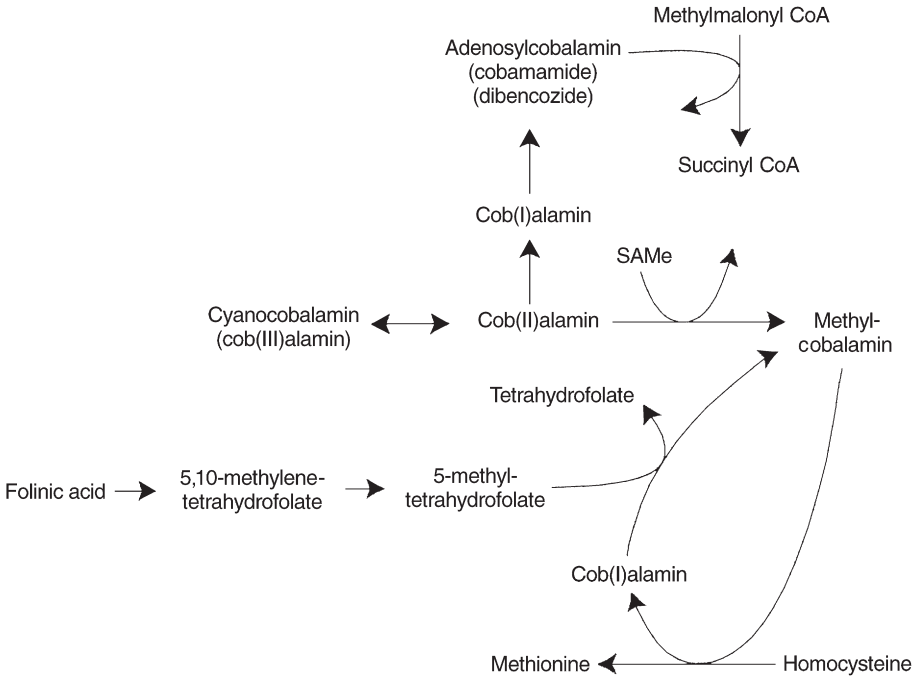


FIGURE 54-4 Cobalamin metabolism.

and erythrocyte analysis of cobalamin coenzymes, which can reveal deficiencies of methylcobalamin or adenosylcobalamin.[23]

Betaine

The metabolic pathways of betaine, methionine, methylcobalamin, and methylTHF are interrelated, intersecting at the regeneration of methionine from homocysteine. This regeneration is accomplished in one of two ways. One involves the generation in the cytosol of 5-methylTHF from methylene THF and the transfer of its methyl group to regenerate methylcobalamin, which then acts as a coenzyme in the regeneration of methionine. Because THF and its derivatives can only cross the mitochondrial membrane slowly, inside, the mitochondria regeneration of methionine relies on recovery of a methyl group from betaine.

Betaine donates one of its three methyl groups via the enzyme betaine-homocysteine methyltransferase to homocysteine, resulting in the regeneration of methionine. After the donation of the methyl group, one molecule of dimethylglycine remains. This molecule is oxidized to glycine and to two molecules of formaldehyde by riboflavin-dependent enzymes. The formaldehyde can combine with THF within the mitochondria to generate one of the active forms of folic acid, methylenetetrahydrofolate, which can be converted to 5-methylTHF and subsequently used as a methyl donor (Figure 54-5).

In animal studies, a disturbance in the metabolism of either of the two methyl-donor pathways, due to limited availability of either betaine or folates and vitamin B_{12}, affects levels of nutrients in the coexisting pathway, because more of a drain is placed on the other pathway as a source of methyl groups. Rats fed diets deficient in choline and methionine had hepatic folate concentrations half that of controls after 5 weeks.[24] During choline deficiency, hepatic SAMe concentrations were also shown to decrease by as much as 50%.[25] Similarly, THF deficiency resulted in decreased hepatic total choline levels.[26]

Patients with a congenital deficiency of the enzyme MTHFR, which is needed for the formation of 5-methylTHF, have reduced levels of both methionine and SAMe in the cerebrospinal fluid

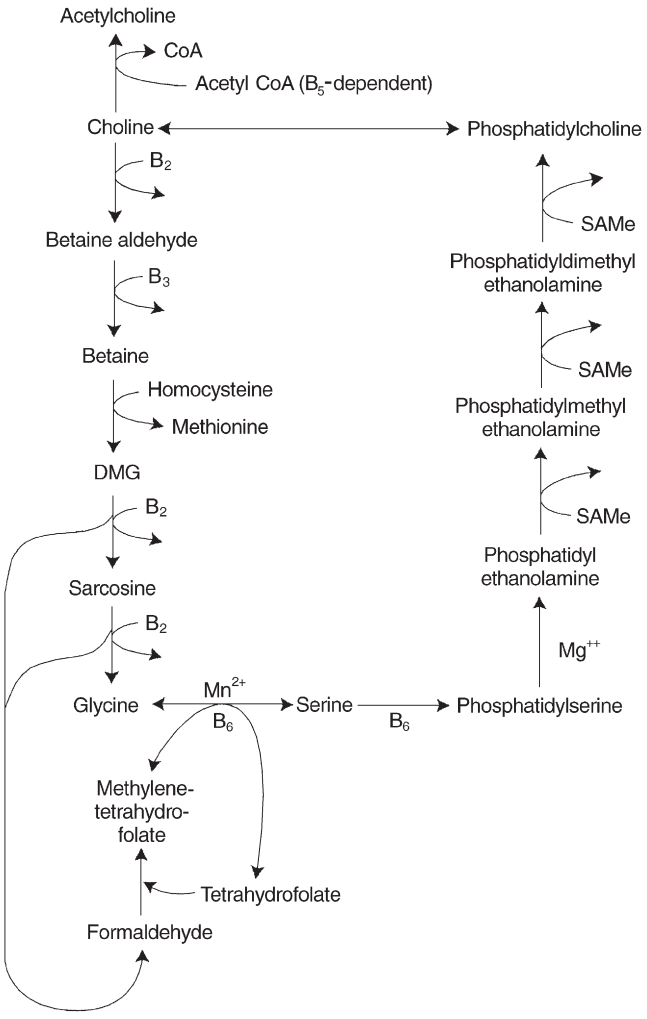


FIGURE 54-5 Phosphatidylcholine metabolism.

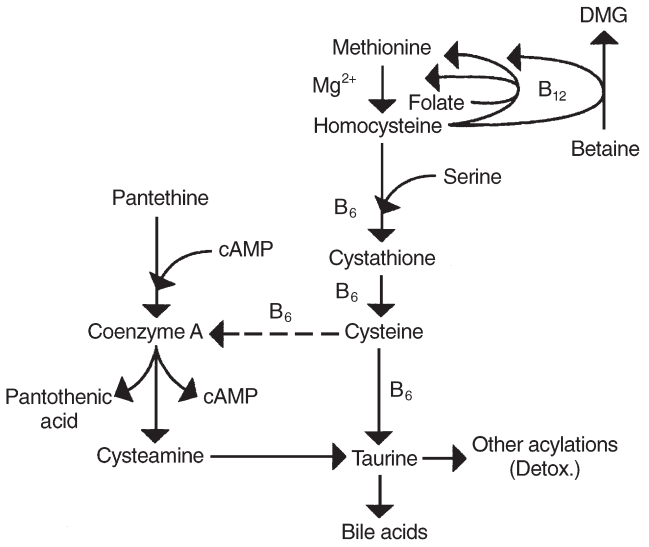


FIGURE 54-6 Synthesis of taurine.

and show demyelination in the brain and degeneration of the spinal cord. Methionine is effective in the treatment of some of these patients; however, betaine was shown to restore cerebrospinal fluid SAMe levels to normal and to prevent the progress of neurologic symptoms in all patients in whom it was tried.[27]

Betaine supplementation has been shown to reduce homocysteine levels[28] while resulting in modest increases of plasma serine and cysteine levels.[29] Stimulation of betaine-dependent homocysteine remethylation causes a commensurate decrease in plasma homocysteine that can be maintained as long as supplemental betaine is taken.[30]

Serine levels are depressed in some individuals with excess homocysteine who are treated with folic acid, cobalamin, and vitamin B_6.[31] Because serine is required (1) for the conversion of folic acid to its active form, (2) as a shuttle for methyl groups between the cytosol and the mitochondria, and (3) as a cofactor in the transsulfuration pathway of methionine/homocysteine metabolism, supplementation with betaine should be included with folic acid, cobalamin, and P5P to optimize the interrelated pathways of homocysteine metabolism.

Pyridoxal 5′-Phosphate

P5P is the active coenzyme form of vitamin B_6. This cofactor is involved in myriad biological processes, including the transsulfuration pathway of homocysteine. This degradation pathway involves a two-step process, resulting in the formation of cystathionine and its subsequent cleavage to cysteine. Cystathionine synthase and cystathioninase require P5P as a cofactor, and the committed first step in the degradation of homocysteine, cystathionine synthase, also requires serine, a downstream metabolite of betaine (Figure 54-6). Some studies suggest that cystathionine could be a useful marker to assess the effect of vitamin B_6 and should be monitored with homocysteine to better elucidate clinical outcomes.[32]

Once cysteine is generated, it can be directed into several different pathways, including synthesis of GSH, acetyl CoA, and taurine. Three pathways from cysteine to taurine are known; all require P5P.

RENAL FUNCTION

Impaired kidney function appears to be a factor in raised homocysteine concentrations.[33] It has been shown that a decreased glomerular filtration rate may be a contributing factor, and some researchers suggest that hyperhomocysteinemia may actually reflect early nephrosclerosis,[8] although other studies demonstrate only a minor renal influence.[34] Fenofibrate treatment, known to increase homocysteine levels, is also known to promote elevations in serum creatinine (see "Pharmaceutic Drug Effects on Homocysteine").[35] Cystatin C, a creatinine-independent indicator of glomerular filtration rate, has also been shown to be well associated with homocysteine levels in kidney transplantation patients, as well as those with coronary disease.[35,36]

PHARMACEUTIC DRUG EFFECTS ON HOMOCYSTEINE

Fibrates such as gemfibrozil are a class of drugs used to lower triglycerides and raise high-density lipoprotein levels. In a paradoxic effect working against a safer cardiac risk profile, these drugs have been observed to raise homocysteine levels up to 40%.[35,37,38] The mechanism of this observation is unknown, although it seems that renal mechanisms may be involved (see "Renal Function").

Thiazides and angiotensin-converting enzyme inhibitors are often a first-line conventional treatment to lower elevated blood pressure. One preliminary, randomized, prospective treatment study investigated 40 hypertensive patients after treatment with hydrochlorothiazide or captopril. In this study vitamins B_6, B_{12}, folic acid, creatinine, and cystatin C were used as parameters of renal function. For 31 and 29 days, respectively, 21 patients were prescribed hydrochlorothiazide and 19 were prescribed captopril. It was found that hydrochlorothiazide, but not captopril, significantly raised homocysteine by 16%, as well creatinine and cystatin C.[39]

IMPACT OF HOMOCYSTEINE ON KEY NUTRIENTS

Because of its central role in sulfur and methyl group metabolism, elevated levels of homocysteine would be expected to negatively affect the biosynthesis of all of the following: SAMe, carnitine, chondroitin sulfates, CoA, CoQ_{10}, creatine, cysteine, dimethylglycine, epinephrine, glucosamine sulfate, GSH, glycine, melatonin, pantethine, phosphatidylcholine, phosphatidylserine, serine, and taurine.

S-Adenosylmethionine

SAMe is formed by the transfer of an adenosyl group from adenosine triphosphate to the sulfur atom of methionine. This reaction requires magnesium as a cofactor. When methyl groups are transferred from SAMe, S-adenosylhomocysteine is formed. This is then hydrolyzed to release the adenosine and results in the formation of homocysteine.

SAMe is known to be used in the synthesis of the following compounds: carnitine, CoQ_{10}, creatine, methylcobalamin from cob(III)alamin, 1-methylnicotinamide, *N*-methyltryptamine, PC, and polyamines. It is also used in methylation reactions as part of hepatic phase 2 detoxification.

Carnitine

A trimethylated amino acid roughly similar in structure to choline, carnitine is a cofactor for transformation of free long-chain fatty acids into acyl-carnitines and their transport into a mitochondrial matrix, where they undergo β-oxidation for cellular energy production. Synthesis of carnitine begins with the methylation of the

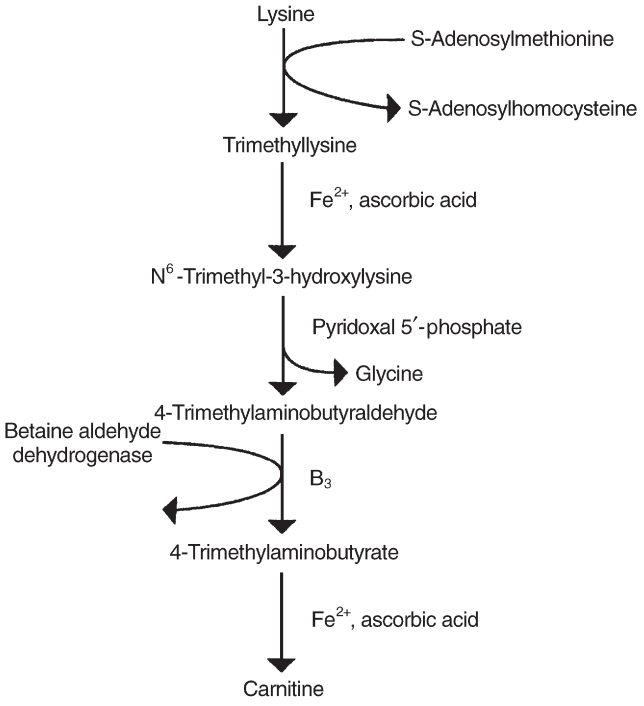


FIGURE 54-7 Synthesis of carnitine.

amino acid L-lysine by SAMe. Methionine, magnesium, vitamin C, iron, P5P, and niacin, along with the cofactors responsible for regenerating SAMe from homocysteine (5-methylTHF, methylcobalamin, and betaine), are required for optimal carnitine synthesis (Figure 54-7).

A pivotal enzyme in carnitine synthesis, betaine aldehyde dehydrogenase, is the same enzyme responsible for synthesis of betaine from choline. Studies suggest this enzyme has a preference for the choline–betaine conversion, and that choline supplementation may decrease carnitine synthesis; therefore, it may be of greater benefit to supplement with betaine rather than its precursor, choline.[40,41]

Chondroitin Sulfates, Glucosamine Sulfate, and Other Sulfated Proteoglycans

Proteoglycans are amino sugars found in all tissues, the highest being in cartilage, tendons, ligaments, synovial fluid, skin, fingers, toenails, heart valves, and the basement membrane of all blood vessels. Perhaps the most widely known of the amino sugars are the chondroitin sulfates and glucosamine sulfate (see Chapter 94 for further discussion).

Chondroitin sulfates are primarily composed of alternating residues of *N*-acetyl-D-galactosamine and D-glucuronate. Sulfate residues are present on C-4 of the galactosamine residues in one type of chondroitin and on C-6 in another. Glucosamine sulfate is a simple molecule composed of glucose, the amino acid glutamine, and a sulfate group. Other sulfated proteoglycans include dermatan sulfates, keratan sulfates, and heparan sulfates.

High levels of homocysteine are likely to negatively affect the formation of the sulfated amino sugars, because although some sulfates are present in the diet, the sulfoxidation of cysteine is an important source of sulfate molecules. The sulfoxidation pathway proceeds through the toxic intermediate sulfite and requires molybdenum as a cofactor.

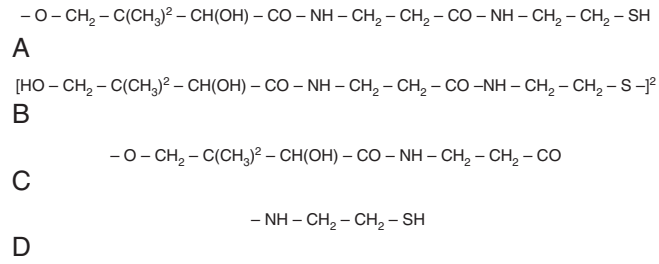


FIGURE 54-8 **A,** Pantotheine. **B,** Pantothine. **C,** Pantothenic acid. **D,** Cysteamine.

Coenzyme A

CoA consists of an adenine nucleotide and phosphopantetheine. Contained within the structure of this coenzyme is pantothenic acid; however, the reactive component of the molecule is a sulfhydryl group that is not contained within the vitamin. To form the sulfhydryl-containing molecule (pantotheine), pantothenic acid must combine with cysteamine. Cysteamine is formed through conjugation and decarboxylation reactions of cysteine. The disulfate form of pantetheine, known as pantethine, as opposed to pantothenic acid, bypasses cysteine conjugation and decarboxylation. This might account for some of the clinical benefits seen with pantethine supplementation that have not been reproduced with the supplementation of pantothenic acid (Figure 54-8, *A to D,* for the chemical structures of pantotheine, pantothine, pantothenic acid, and cysteamine).

Coenzyme Q_{10}

CoQ_{10} is a fat-soluble quinone occurring in the mitochondria of each cell (see Chapter 79 for a full discussion). The primary biochemical action of CoQ_{10} is as a cofactor in the electron transport chain, the biochemical pathway that generates adenosine triphosphate. Because most cellular functions depend on an adequate supply of adenosine triphosphate, CoQ_{10} is essential for the health of virtually all human tissues and organs. CoQ_{10} also functions as an antioxidant, assisting in the recycling of vitamin E.[42,43]

Biosynthesis of CoQ_{10} begins with the amino acid tyrosine. Pantothenic acid, P5P, and vitamin C are all required for the initial steps in its synthesis. An isoprenyl side chain from farnesyl diphosphate, an intermediate in cholesterol synthesis between 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) and squalene, is then added. An inadequate supply of this intermediate, which can be caused by HMG-CoA reductase inhibitors (cholesterol-lowering drugs of the statin family), results in decreased levels of CoQ_{10}.[44]

In two of the final steps in the synthesis of CoQ_{10}, methyl groups are provided by SAMe (Figure 54-9). Adequate dietary methionine and a sufficient supply of the nutrients required for the remethylation of homocysteine to methionine (5-methylTHF, methylcobalamin, and betaine) are required to generate sufficient SAMe. Suboptimal amounts of SAMe may negatively affect the body's ability to synthesize sufficient CoQ_{10}. This relationship between SAMe and CoQ_{10} has been suggested in various animal studies.[45,46]

Creatine

In humans, more than 95% of the total creatine content is located in skeletal muscle, of which approximately one third is in its free form as creatine, also known as methyl-guanidinoacetic acid,

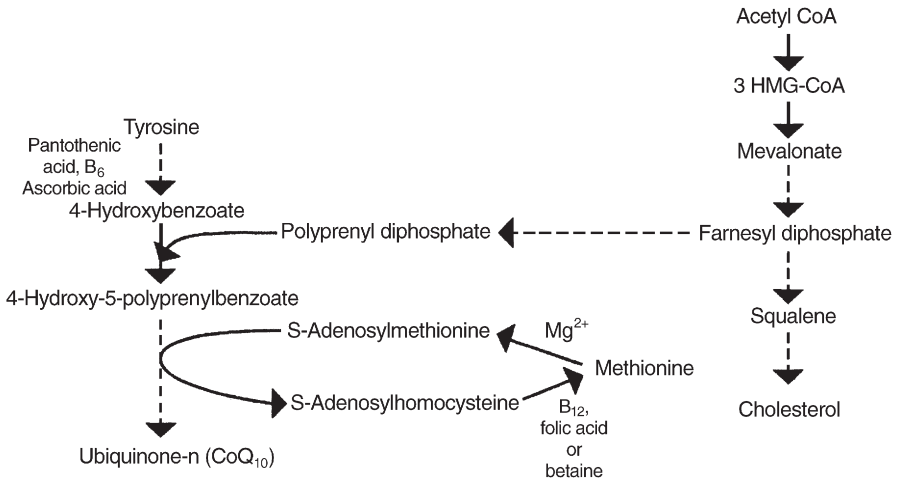


FIGURE 54-9 Synthesis of coenzyme Q_{10}.

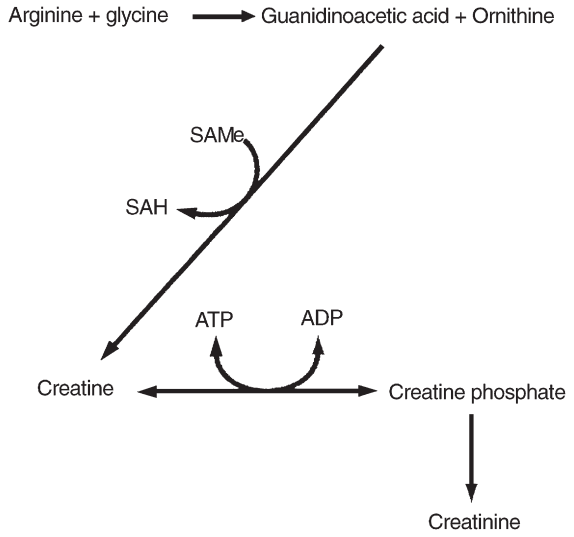


FIGURE 54-10 Synthesis of creatine, creatine phosphate, and creatinine.

whereas the remainder is present in a phosphorylated form as creatine phosphate (also called phosphocreatine). Creatine phosphate is used within skeletal muscle as a means of storing high-energy phosphate bonds.

Creatine is formed in the liver, kidney, and pancreas, beginning with the combination of arginine and glycine to produce guanidinoacetate. A methyl group from SAMe is then transferred, resulting in the formation of creatine. The by-product of this reaction, S-adenosylhomocysteine, is subsequently hydrolyzed into homocysteine and adenosine. To optimize endogenous production of creatine, the amino acids arginine, glycine, and methionine must be available as substrates. Additionally, cofactors needed to optimize remethylation of homocysteine to form methionine are required to recycle the homocysteine to methionine for reuse as SAMe (Figure 54-10). Serum creatine levels have been positively correlated with plasma homocysteine levels (i.e., as creatine levels rise, so do homocysteine levels).[47]

Epinephrine and Melatonin

Derivatives of the aromatic amino acids, L-tyrosine and L-tryptophan, require methylation for the biosynthesis of their down-line metabolites.

The biosynthesis of catecholamines begins with the amino acid L-tyrosine and proceeds through dopa and dopamine, resulting in the formation of norepinephrine, the neurotransmitter substance found in most sympathetic nerve terminals, as well as in some synapses of the CNS. In the chromaffin cells of the adrenal medulla, a methyl group is provided by SAMe, resulting in the formation of epinephrine from norepinephrine. A number of metabolites are formed from the degradation of both norepinephrine and epinephrine. Catecholamine degradation proceeds independently, and in conjunction with monoamine oxidase, by catechol-*O*-methyltransferase. This enzyme catalyzes the transfer of a methyl group donated by SAMe and, depending on the substrate, results in the formation of homovanillic acid, normetanephrine, and metanephrine.

The formation of melatonin from L-tryptophan proceeds through 5-hydroxytryptophan, serotonin, and *N*-acetylserotonin. Melatonin is then formed in the pineal gland by the donation of a methyl group. 5-Methoxytryptamine, an alternate metabolite of serotonin, also requires the addition of a methyl group.

Phosphatidylcholine

Phosphatidylcholine (PC) is a primary component of lecithin. It is the most frequently encountered phospholipid in animals and is structurally related to phosphatidylserine and phosphatidylethanolamine. PC consists of a glycerol backbone that is esterified with fatty acids on carbon atoms 1 and 2, and with a phosphoric acid/choline complex in position 3. Although PC is usually referred to as if it were a single compound, it is actually a group of related compounds that vary depending on the fatty acid composition at positions C-1 and C-2.

Dietary choline is derived primarily from PC, which, after absorption by the intestinal mucosa, is metabolized to choline in the liver by the enzyme phospholipase D. Most choline is rephosphorylated to PC; however, a small amount is carried to the brain via the bloodstream, where it is converted to the neurotransmitter acetylcholine. If PC or choline is lacking in the diet, it can be synthesized from phosphatidylserine and phosphatidylethanolamine (see Figure 54-5). Synthesis of PC depends on the availability of SAMe as a methyl donor, because synthesis involves the transfer of methyl groups from three SAMe molecules to phosphatidylethanolamine to generate one molecule of PC.

The metabolic pathways of PC, methionine, methylcobalamin, and 5-methylTHF are interrelated, intersecting at the regeneration

of methionine from homocysteine by betaine (see Figure 54-1). The use of choline molecules as methyl donors in this process is probably the main factor that determines how rapidly a diet deficient in choline induces pathologic changes.[25]

Taurine

Taurine is a unique amino acid because it carries a sulfonic acid group ($-SO_3H$) instead of a carboxyl group ($-CO_2H$). Taurine is biosynthesized from methionine or from cysteine via the transsulfuration pathway (see Figure 54-6). Once cysteine is generated, it can be directed into several different pathways, including synthesis of GSH, acetyl CoA, 3′-phosphate 5′-phosphosulfate (PAPS), and taurine. The committed first step in the degradation of homocysteine requires cystathionine synthase, P5P, and serine. P5P is also required as a cofactor in the cleavage of cystathionine to cysteine. Homocystinuria, resulting from an absence of cystathionine synthase, can lead to mental retardation. Low levels of cystathionine synthase can also lead to abnormally high levels of homocysteine, especially when remethylation cofactors are also deficient.

CLINICAL APPLICATIONS

Phase 2 Detoxification

Because homocysteine is a critical intermediate in both methyl and sulfur group metabolism, elevated levels could indicate nutrient deficiencies that might compromise function in virtually all of the hepatic phase 2 detoxification reactions.

Amino acid conjugation reactions require either glycine, glutamine, or taurine. Glycine functions in the conjugation of aromatic acids (e.g., benzoic acid to hippuric acid). Elevated levels of homocysteine might indicate reduced nutritional levels of betaine and subsequently its down-line metabolite, glycine. Taurine functions in acylations (e.g., bile conjugation).

Sulfur conjugation requires NAC, GSH, PAPS, or methionine/cysteine. NAC is used for mercapturic acid synthesis and is involved in detoxification of a wide variety of compounds, including aromatic hydrocarbons, some phenols, halides, esters, epoxides, and caffeine. GSH is involved in dismutation reactions of organic nitrates (e.g., nitroglycerin). PAPS is used in sulfate ester synthesis, mostly with phenols, and some aliphatic alcohols (e.g., ethanol) and aromatic amines. Methionine and cysteine are used in cyanide-thiocyanate detoxification. A portion of the inorganic sulfur needed for the formation of all of these compounds passes through the homocysteine cycle.

Alkylation reactions require SAMe, methylcobalamin, or 5-methylTHF. These compounds provide methyl groups to detoxify compounds containing hydroxide, SH, or NH_2 groups. Examples of these reactions include norepinephrine to epinephrine, epinephrine to metanephrine, guanidoacetic acid to creatine, and *N*-acetylserotonin to melatonin.

Other phase 2 detoxification reactions that might be affected by elevated homocysteine as a biological marker of reduced nutrient formation include acetylation by acetyl CoA, which requires cysteine as a source of its cysteamine component, and the use of carnitine for the conversion of valproic acid to valpropylcarnitine.

Heart Disease

Increased blood levels of homocysteine are correlated with significantly increased risk of coronary artery disease (CAD),[48-54] myocardial infarction,[55,56] peripheral occlusive disease,[57-60] cerebral occlusive disease,[57,60] and retinal vascular occlusion (Box 54-1).[61]

BOX 54-1 What Homocysteine and Homocysteine Thiolactone Do to Arteries

- Generate superoxide and hydrogen peroxide, which have been linked to damage to arterial endothelium
- Change coagulation factor levels so as to encourage clot formation
- Prevent small arteries from dilating, so they are more vulnerable to obstruction
- Cause smooth muscle cells in the arterial wall to multiply
- Interact with low-density lipoproteins, causing them to precipitate and damage endothelial tissue
- Cause platelets to aggregate

Inborn errors of homocysteine metabolism result in high levels of homocysteine in the blood and severe atherosclerotic disease; even within the range considered normal (4 to 16 µmol/L), there is a graded increase in risk for CAD. In a study of 304 patients with CAD versus controls, the odds ratio for CAD increased as plasma homocysteine increased, even within the normal range. A 5 µmol/L increase in plasma homocysteine was correlated with an increase in the odds ratio of 2.4 (P <0.001), with no "threshold effect."[51]

A review of numerous studies found that mild hyperhomocysteinemia after a methionine load test occurred in 21%, 24%, and 32% of patients with CAD, cerebrovascular disease, and peripheral vascular disease, respectively.[46] Another group of researchers found a 29.3% incidence of hyperhomocysteinemia (>14 µmol/L by their definition) in a group of 1160 elderly (ages 67 to 96 years) individuals in the Framingham Heart Study. The study also indicated that plasma homocysteine levels increased with age.[57]

A number of interrelated atherogenic mechanisms are thought to be involved with hyperhomocysteinemia. These include advanced thickening and smooth muscle cell proliferation of endothelial vessel wall intima, enhanced lipid deposition in the vessel wall, forced detachment of endothelial cells, activation of leukocytes and thrombocytes, increased low-density lipoprotein oxidation, initiation of platelet thromboxane synthesis, enhanced oxidative stress induced by peroxide formation during homocysteine oxidation, and prothrombotic coagulation interference.[62,63] One way homocysteine assists this process is by the generation of hydrogen peroxide.[64] By creating oxidative damage to low-density lipoprotein cholesterol and endothelial cell membranes, hydrogen peroxide can then catalyze injury to vascular endothelium.[64,65]

Nitric oxide and other oxides of nitrogen released by endothelial cells (also known as endothelium-derived relaxing factor) protect endothelial cells from damage by reacting with homocysteine, forming S-nitrosohomocysteine, which inhibits hydrogen peroxide formation. However, as homocysteine levels increase, this protective mechanism can become overloaded, allowing damage to endothelial cells to occur.[65-67] Because of the role of sulfate compounds in the formation of amino sugars needed to form the basement membrane of blood vessels, high levels of homocysteine are likely to contribute to the formation of blood vessels that are more susceptible to oxidative stress.[67] The end result of the combination of oxidative damage and endothelial collagen instability can be the formation of atherosclerotic plaques.

Decreased plasma folate levels are correlated with increased levels of homocysteine, as well as a subsequent increased incidence of CAD. In a 15-year Canadian study of CAD mortality in 5056 men

and women ages 35 to 79 years, lower serum folate levels were correlated with a significantly increased risk of fatal CAD.[68] In a cohort from the Framingham Heart Study, concentrations of folate and P5P were inversely correlated with homocysteine levels and the risk of extracranial carotid artery stenosis.[57] Low P5P and low vitamin B_{12} have also been linked with hyperhomocysteinemia and a significantly increased risk of CAD.[51] Another study of 160 cardiac transplantation patients followed for an average of 28 days found that the high homocysteine levels seen in 99 of these patients surprisingly demonstrated no causal role in the atherothrombotic vascular complications of transplantation. Vitamin B_6 deficiency was seen in 21% of recipients with, and in 9% without, cardiovascular complications or death, or both. Compared with patients with normal B_6 levels, there was a 2.7-fold increase in untoward cardiac events for those patients with B_6 levels less than or equal to 20 nmol/L.[69]

Remethylation of homocysteine and the subsequent formation of SAMe are critical for biosynthesis of L-carnitine, CoQ_{10}, and creatine. Similarly, the transsulfuration pathway must be functioning properly for optimal biosynthesis of cysteine, GSH, pantethine, and taurine. All of these nutrients are used clinically to reduce oxidative stress, improve risk factor markers, or treat heart disease.

Plasma S-adenosylhomocysteine is a more sensitive indicator of cardiovascular disease than plasma homocysteine.[18]

Peripheral Vascular Disease

Elevated homocysteine levels have been established as an independent risk factor for intermittent claudication and deep vein thrombosis. Elevated homocysteine levels corresponded with an increased incidence of intermittent claudication and decreased serum folate levels in a study of 78 patients with intermittent claudication.[70] A four-fold increase in risk of peripheral vascular disease was noted in individuals with hyperhomocysteinemia compared to those with normal homocysteine levels.[71] A group of researchers in the Netherlands found high homocysteine levels to be a significant risk factor for deep vein thrombosis, with a stronger relationship among women than men.[72]

An increased risk of peripheral vascular occlusion was noted in women taking oral contraceptives, which might be linked to the significantly increased homocysteine levels in women so affected. It is already known that oral contraceptives can cause declines or deficiencies in vitamins B_6, B_{12}, and folate, nutrients integral to the processing of homocysteine. Laboratory assessment of plasma homocysteine levels may be helpful to detect women who may be predisposed to peripheral vascular occlusion while on oral contraceptives.[73]

Stroke

Stroke patients have significantly elevated homocysteine levels compared to age-matched controls,[74] with a linear relationship between risk of stroke and homocysteine levels[75] and a significant decrease in blood folate concentrations in those with elevated homocysteine.[76] One investigation revealed that people with a dietary intake of at least 300 mcg/day of folic acid reduced their risk of stroke and heart disease by 20% and 13%, respectively, compared with those who consumed less than 136 mcg of folic acid per day.[77]

Pregnancy

Biochemical enzyme defects and nutritional deficiencies are receiving increasing attention for their role in causing neural tube defects (NTDs), as well as other negative pregnancy outcomes, including spontaneous abortion, placental abruption (infarct), preterm delivery, and low infant birth weight. Evidence has suggested that derangement of methionine-homocysteine metabolism could be the underlying mechanism of pathogenesis of NTDs and might be the mechanism of prevention observed with supplementation of folic acid.[78,79] It has been firmly established that a low dietary intake of folic acid increases the risk for delivery of a child with an NTD and that periconceptional folic acid supplementation reduces the occurrence of NTDs.[80-86] Research also indicates that supplemental folic acid intake results in increased infant birth weight and improved Apgar scores, along with a concomitant decreased incidence of fetal growth retardation and maternal infections.[87-90]A derangement in methionine-homocysteine metabolism has also been correlated with recurrent miscarriage and placental infarcts (abruption).[91]

The amino acid homocysteine, when elevated, might be a teratogenic agent contributing to congenital defects of the heart and neural tube. Evidence from experimental animals lends support to this belief. When avian embryos were fed homocysteine to raise serum homocysteine to over 150 nmol/mL, dysmorphogenesis of the heart and neural tube, as well as of the ventral wall, was observed.[92]

Because homocysteine metabolism, through the remethylation and transsulfuration pathways, affects several biochemical pathways involving the production of nutrients that are essential to the optimal functioning of the cardiovascular, skeletal, and nervous systems, it is not surprising that these other nutrients have been linked to complications of pregnancy in animal models and humans. Low plasma vitamin B_{12} levels have been shown to be an independent risk factor for NTD.[93,94] Methionine has been shown to reduce the incidence of NTD by 41% in an animal model when administered on days 8 and 9 of pregnancy.[95,96] This evidence indicates that a disturbance in the remethylation pathway with a subsequent decrease in SAMe may be a contributing factor to these complications of pregnancy.

PC, due to its role as a precursor to acetylcholine and choline, is acknowledged as a critical nutrient for brain and nerve development and function.[97-99] Because the metabolic pathways of choline (via betaine), methionine, methylcobalamin, and 5-methylTHF are interrelated, intersecting at the regeneration of methionine from homocysteine, a disturbance in the metabolism of either of these two methyl-donor pathways, due to limited availability of key nutrients or decreased enzyme activity, directly affects the body's ability to optimize levels of SAMe.

Evidence suggests that women with a history of NTD-affected pregnancies have altered folic acid metabolism.[100-103] Patients with a severe congenital deficiency of the enzyme MTHFR, which is needed for the formation of 5-methylTHF, have reduced levels of both methionine and adenosylmethionine in their cerebrospinal fluid and show demyelination in the brain and degeneration of the spinal cord.[2,104] Because of its direct impact in the activation of folic acid to its methyl derivative, a milder version of this enzyme defect is also strongly suspected to increase the incidence of NTDs.[105]

It is established that high vitamin A intake during the first 2 months of pregnancy is associated with a several-fold higher incidence of birth defects.[106,107] Although the mechanism of action remains to be elicited, in an animal model, the activity of hepatic MTHFR was suppressed with high vitamin A levels, suggesting that its teratogenic effect during early pregnancy might be associated with a subsequent derangement in the remethylation of homocysteine.[108]

Because a more significant correlation has been found between high homocysteine levels in women experiencing placental abruption, infarction, and spontaneous abortion than in control women, and homocysteine and CoQ_{10} synthesis depend on the methionine-SAMe-homocysteine pathway, it is possible that low CoQ_{10} and elevated homocysteine independently found in complicated pregnancy may also be found in related conditions.[109,110]

Nutritional intervention with the cofactors required for optimal metabolism of the methionine-homocysteine pathways offers a new integrated possibility for primary prevention of NTD and several other complications of pregnancy. Supplementation with betaine and the active forms of cobalamin and folic acid, such as methylcobalamin and folinic acid, along with riboflavin-5′-phosphate (because of its role as a cofactor for the MTHFR enzyme), may play a significant role in reducing or preventing these emotionally devastating outcomes.

Neurologic and Mental Disorders

In addition to the known impact of homocysteine on the cardiovascular system and micronutrient biochemical pathways, numerous diseases of the nervous system are correlated with high homocysteine levels and alterations in vitamin B_{12}, folate, or vitamin B_6 metabolism, including depression, schizophrenia, multiple sclerosis, Parkinson's disease, Alzheimer's disease (AD), and cognitive decline in the elderly.

Methylation reactions via SAMe, including methylation of DNA and myelin, are vitally important in the CNS. The neurologic complications of vitamin B_{12} deficiency are likely due to a reduction of activity of the vitamin B_{12}-dependent enzyme methionine synthase and the subsequent reduction of SAMe production. The CNS lacks the alternate betaine pathway of homocysteine remethylation; therefore, if methionine synthase is inactivated, the CNS has a greatly reduced methylation capacity.[111] Other causes of reduced methionine synthase activity include folic acid deficiency and nitrous oxide anesthesia exposure.[112]

Homocysteine has also been found to be a neurotoxin, especially in conditions in which glycine levels are elevated, including head trauma, stroke, and vitamin B_{12} deficiency.[113] Homocysteine interacts with the *N*-methyl-D-aspartate receptor, causing excessive calcium influx and free radical production, resulting in neurotoxicity.[94] The neurotoxic effects of homocysteine or reduced methylation reactions, or both, in the CNS contribute to the mental symptomatology seen in vitamin B_{12} and folate deficiency. Increased homocysteine levels can also be seen in schizophrenics.[114]

Significant deficiencies in vitamin B_{12} and folate are common in the elderly population and can contribute to a decline in cognitive function.[115-117] An investigation of cognitive ability in older men (54 to 81 years old) found poorer spatial copying skills in those with higher homocysteine levels. Better memory performance was correlated with higher vitamin B_6 levels.[118]

Vitamin B_{12} deficiency and increasing severity of cognitive impairment have been seen in AD patients compared with controls and patients with other dementias.[119] In a study of 52 AD patients, 50 hospitalized nondemented controls, and 49 elderly subjects living at home, patients with AD were found to have the highest homocysteine levels and the highest methylmalonic acid (an indicator of vitamin B_{12} deficiency) levels.[120]

In another Framingham study cohort with an average of 8 years' follow-up, dementia developed in 111 of 1092 nondementia subjects, including 83 who were diagnosed with AD. The adjusted relative risk of dementia was 1.4 for each increase of 1 standard deviation in the logarithmically adjusted homocysteine value. The relative risk of AD was 1.8 per increase of 1 standard deviation at baseline and 1.6 per increase of 1 standard deviation 8 years before baseline. Additionally, in those with a plasma homocysteine level that was greater than 14 μmol/L, the risk of AD nearly doubled.[121]

In a study of 741 psychogeriatric patients, high plasma homocysteine levels were found in demented and nondemented patients; however, only demented patients also had lower blood folate concentrations compared with controls. Patients with concomitant vascular disease had significantly higher plasma homocysteine than those without diagnosed vascular disease. Significantly higher homocysteine levels, compared with controls, have also been found in Parkinson's disease patients.[122]

Homocysteine's effects on neurotransmitter metabolism, along with its potential reduction of methylation reactions, could be a contributing factor to the etiology of depression. Folate and vitamin B_{12} deficiency can cause neuropsychiatric symptoms, including dementia and depression. SAMe is used therapeutically as an antidepressant in Europe and was the third most popular antidepressant treatment in Italy in 1995.[123,124] Long-term treatment of post-stroke survivors with folic acid (2 mg), vitamin B_6 (25 mg), and vitamin B_{12} (0.5 mg) was associated with a reduction in major depression in a 563-patient population, randomized, double-blind, placebo-controlled trial.[125]

Methylation of myelin basic protein is vital to the maintenance of the myelin sheath. The worst case scenario of folate and vitamin B_{12} deficiency includes demyelination of the posterior and lateral columns of the spinal cord, a disease process called subacute combined degeneration of the spinal cord (SCD).[111] SCD can also be precipitated by nitrous oxide anesthesia, which causes an irreversible oxidation of the cobalt moiety of the vitamin B_{12} molecule and the subsequent inhibition of methionine synthase activity, a decrease in homocysteine remethylation, and decreased SAMe production.[112] This has been treated using supplemental methionine, which further supports the theory of a nitrous oxide–induced biochemical block at methionine synthase.[126] Particularly at risk for this condition are vitamin B_{12}-deficient individuals who visit their dentist and receive nitrous oxide.[112,127]

Abnormal methylcobalamin metabolism is one of the proposed mechanisms for the pathophysiology of the demyelinating disease multiple sclerosis (MS). Deficiency of vitamin B_{12} has been linked to some cases of MS, and it has been suggested that dietary deficiency, or more likely, a defect in R-protein–mediated absorption or methylation of vitamin B_{12}, might be a significant contributor to the pathogenesis of MS.[128]

Individuals with genetic variation in the 5,10-MTHFR gene are more susceptible to having a psychiatric disorder. The genetic variation MTHFR C677T was significantly associated with schizophrenia, bipolar disorder, and unipolar depressive disorder.[129]

Diabetes Mellitus

Homocysteine levels appear to be lower in individuals with type 1 diabetes mellitus. Forty-one type 1 diabetic subjects (age 34.8 ± 12 years; duration of illness: 10.7 ± 11.1 years) were compared with 40 age-matched control subjects (age 34.2 ± 9.1 years). After an overnight fast, homocysteine was significantly lower ($P = 0.0001$) in the diabetic group (6.8 ± 2.2) than in the controls (9.5 ± 2.9). This difference was apparent in male and female subgroups.[130] However, increased levels of homocysteine have been reported in type 1 diabetics with proliferative retinopathy[131] and nephropathy.[131,132]

Evidence to date suggests that metabolism of homocysteine is impaired in patients with non–insulin-dependent diabetes

mellitus (NIDDM). After a methionine load, hyperhomocysteinemia occurred with significantly greater frequency in patients with NIDDM (39%) compared with age-matched controls (7%). The area under the curve over 24 hours, reflecting the total period of exposure to increased homocysteine, was also elevated with greater frequency in patients with NIDDM and macrovascular disease (33%) compared with controls (0%). The authors concluded that hyperhomocysteinemia was associated with macrovascular disease in a significant proportion of patients with NIDDM.[133] Other researchers reported a correlation between increased homocysteine levels and the occurrence of macroangiopathy in patients with NIDDM. Intramuscular injection of 1000 µg methylcobalamin daily for 3 weeks reduced the elevated plasma levels of homocysteine in these individuals.[134]

Elevated homocysteine levels appear to be a risk factor for diabetic retinopathy in individuals with NIDDM. This might be due to a point mutation on the gene for the enzyme MTHFR.[135,136] A significantly higher percentage of diabetics with retinopathy exhibit this mutation.[137] Elevated homocysteine levels cause cell injury to the small vessels, which may contribute to the development of retinopathy, as well as macroangiopathy in the cardiovascular system.[135]

Rheumatoid Arthritis

Elevated total homocysteine levels have been reported in patients with rheumatoid arthritis (RA) and psoriasis. Twenty-eight patients with RA and 20 healthy age-matched control subjects were assessed for homocysteine levels while fasting and in response to a methionine challenge. Fasting levels were 33% higher in RA patients than in controls. Four hours after the methionine challenge, the increase in plasma homocysteine concentration was also higher in patients with RA.[137] Another study found statistically significant increases in homocysteine in RA patients ($P = 0.003$), with 20% of the patients having homocysteine levels above the reference range.[138] A mechanism for this increased homocysteine in RA patients has not been elucidated. Penicillamine, a common sulfhydryl-containing arthritis treatment, has been found to lower elevated homocysteine levels in vivo.[139]

Psoriasis

One study of 30 psoriasis patients and their matched controls were evaluated for blood concentrations of lipids, lipoproteins, acute phase reactants, homocysteine, and atherothrombotic markers. This study observed that more than 50% of the psoriasis patients had homocysteine levels that were higher than 15 mmol/L, whereas only 20% of the control individuals were above this cutoff point. It was concluded that the mean levels of serum homocysteine, fibrinogen, fibronectin, intercellular adhesion molecules, plasminogen activator inhibitor, and autoantibodies against oxidized low-density lipoprotein were increased in psoriatic patients, whereas tissue plasminogen factor, vitamin B_{12}, and folate levels were decreased significantly.[62]

Further investigation into both the prevalence of hyperhomocysteinemia and the mechanism of action affecting RA and psoriasis is necessary.

Kidney Failure

Because homocysteine is cleared by the kidneys, chronic renal failure, as well as absolute or relative deficiencies of 5-methylTHF, methylcobalamin, P5P, or betaine results in increased homocysteine levels. In 176 patients with end-stage renal disease on peritoneal or hemodialysis, homocysteine concentrations averaged 26.6 ± 1.5 µmol/L in patients with renal failure compared with 10.1 ± 1.7 µmol/L in normal subjects. Abnormal values exceeded the 95th percentile for normal controls in 149 of the patients with renal failure.[140] Data also indicated that plasma homocysteine values represented an independent risk factor for vascular events in patients on peritoneal and hemodialysis. Patients with a homocysteine concentration in the upper two quintiles (>27.8 µmol/L) had an independent odds ratio of 2.9 (confidence interval, 1.4 to 5.8; $P = 0.007$) of vascular complications. Vitamin B levels were also lower in patients with vascular complications than in those without such complications.[141]

Alcoholism and Ethanol Ingestion

Chronic alcoholism is known to interfere with one-carbon metabolism. Because of this, it is not surprising to find that mean serum homocysteine levels are two times higher in chronic alcoholics than in nondrinkers ($P < 0.001$). Beer consumers have lower concentrations of homocysteine compared with drinkers of wine or spirits ($P = 0.05$). In chronic alcoholics, serum P5P and red blood cell folate concentrations have been shown to be significantly lower than in control subjects.[13] Plasma homocysteine was significantly higher, compared with controls, in 42 active alcoholics hospitalized for detoxification. In another group of 16 alcoholics who abstained from ethanol ingestion, plasma homocysteine did not deviate from that of controls.[14]

Feeding ethanol to rats produces prompt inhibition of methionine synthase, as well as a subsequent increase in activity of betaine homocysteine methyltransferase. Despite the inhibition of methionine synthase, the enhanced betaine homocysteine methyltransferase pathway uses hepatic betaine pools to maintain levels of SAMe.[142] Results indicate that ethanol feeding produces a significant loss in SAMe in the first week, with a return to normal SAMe levels in the second week. Betaine feeding enhances hepatic betaine pools in control animals, as well as ethanol-fed animals; attenuates the early loss of SAMe in ethanol-fed animals; produces an early increase in betaine homocysteine methyltransferase activity; and generates increased levels of SAMe in both control and ethanol-fed groups.[143] It has been shown that minimal supplemental dietary betaine at the 0.5% level increases SAMe two-fold in control animals and five-fold in ethanol-fed rats. Concomitant with the betaine-generated SAMe, ethanol-induced hepatic fatty infiltration was ameliorated.[142] Betaine supplementation also reduces the accumulation of hepatic triglyceride produced after ethanol ingestion.[143]

Gout

Although homocysteine levels have been positively correlated with increased uric acid levels,[2,144,145] no studies have investigated homocysteine levels in gout patients. It is possible the increased uric acid levels in gout are due to decreased SAMe production because of the reduction in homocysteine recycling. The excess adenosine, which reacts with methionine to form SAMe, is degraded to form uric acid as its end product.

Niacin is contraindicated in gout, since it competes with uric acid for excretion.[146] Animal studies have shown that increased levels of S-adenosylhomocysteine and, thus homocysteine, cause significant reductions in SAMe-dependent methylation reactions.[16] Therefore, because degradation of the niacin-containing coenzyme nicotinamide adenine dinucleotide is dependent on

methylation by SAMe, and SAMe activity is severely reduced in hyperhomocysteinemia, niacin levels might be higher in these people, resulting in less uric acid excretion, higher uric acid levels, and increased gout symptoms in susceptible individuals. This possibility and its mechanism need further investigation.

Osteoporosis

Osteoporosis is a common presenting symptom in children with homocystinuria due to cystathionine synthase deficiency, as a result of an autosomal recessive error of sulfur amino metabolism.[147,148] Individuals with cystathionine synthase deficiency have decreased concentrations of cysteine and its disulfide form, cystine. Because of the role of sulfur compounds in the formation of sulfated amino sugars, disturbed cross-linking of collagen has been proposed as a possible mechanism of action. One group of researchers studying 10 patients with homocystinuria found normal synthesis of collagen but a significant reduction of cross links.[149]

Because of the correlation between homocystinuria and osteoporosis in children with this amino acidopathy and the increase in homocysteine concentrations in postmenopausal women, several authors have implied that elevated homocysteine levels contribute to postmenopausal osteoporosis. The Framingham study of 825 men and 1174 women, ranging from 59 to 91 years old, affirmed this suspicion by evaluating plasma homocysteine levels and relative incident of hip fracture over a period of 16 to 19 years. The mean plasma total homocysteine concentration was 13.4 ± 9.1 μmol/L with 41 hip fractures among men and 12.1 ± 5.3 μmol/L and 146 hip fractures among women. It was shown that both men and women in the highest quartile of plasma homocysteine had a greater risk of hip fracture than those in the lowest quartile, where the risk was almost 4 times as high for men and 1.9 times as high for women.[150] Because physical activity is well known to lower homocysteine, as well as prevent falls, it may therefore influence the association between homocysteine levels and the risk of fracture.[15] Therefore, it seems prudent to prescribe exercise, as well as appropriate supplemental therapies for women and men with high homocysteine and osteopenia/osteoporosis.

Autism

Children with autism have higher levels of urinary homocysteine than children without autism, which may reflect nutritional deficiencies of folic acid, vitamin B_6, and vitamin B_{12}.[151]

In addition, autistic children have elevated levels of S-adenosylhomocysteine (SAH) and adenosine, whereas levels of methionine, S-adenosylmethionine (SAM), and the SAM/SAH ratio are significantly decreased compared with age-matched controls.[152]

Drug-Induced Hyperhomocysteinemia

Because fibrate drugs are known to increase homocysteine levels (see "Pharmaceutic Drug Effects on Homocysteine"), one randomized, double-blind crossover study investigated the effect of using fenofibrate adjunctively with 650 mcg of folic acid, 5 mg of vitamin B_6, and 50 mcg of vitamin B_{12}, or just fenofibrate in hyperlipidemic men. Subjects who received the fenofibrate plus placebo had an average increase in homocysteine concentration of 44%. Subsequent to the fenofibrate plus vitamin treatment, it was 13%. In this study, vitamins significantly prevented most of the homocysteine increase seen after fenofibrate plus placebo. The authors of this study suggested that routine use of these nutrients might be beneficial with this pharmaceutic therapy.[35]

DIAGNOSTIC CONSIDERATIONS

Many studies cited herein have used a reference range, with 12 to 16 μmol/L being the upper limit of normal for homocysteine. Researchers found a highly significant increase in relative risk of atherosclerotic cardiovascular disease and other disease processes as homocysteine levels increased, even within the "normal" range. Optimal levels of homocysteine and vitamin B_{12} are needed to maintain the methylation cycle, along with adequate levels of vitamin B_6 to convert to cysteine, which is a precursor to form GSH. A number of clinical laboratories currently perform plasma homocysteine determinations, by themselves or within a cardiovascular panel.

THERAPEUTIC CONSIDERATIONS

Although folic acid supplementation (400 mcg/day) alone can reduce homocysteine levels in many subjects, given the importance of vitamins B_{12} and B_6 to proper homocysteine metabolism, all three should be used together. In one study, the prevalence of suboptimal levels of these nutrients in men with elevated homocysteine levels was 56.8%, 59.1%, and 25% for folic acid, vitamin B_{12}, and vitamin B_6, respectively, indicating that folic acid supplementation alone would not lower homocysteine levels in many cases.[153] In other words, folic acid supplementation will only lower homocysteine levels if there are adequate levels of vitamin B_{12} and B_6. This fact could reduce the effect of folic acid fortification of food. In 1998, the Food and Drug Administration mandated the fortification of food products with folic acid. Although homocysteine levels have decreased modestly after the fortification of food with folic acid, the effect on mortality has been minor at best.[22] This indicates the importance of more aggressive supplementary measures to reduce homocysteine-associated cardiovascular risk. In one study of 100 men with hyperhomocysteinemia, oral therapy with 650 mcg folic acid, 400 mcg vitamin B_{12}, 10 mg vitamin B_6, or a combination of the three nutrients was given daily for 6 weeks. Plasma homocysteine was reduced 41.7% during folate therapy and 14.8% during vitamin B_{12} therapy, whereas 10 mg of vitamin B_6 did not reduce plasma homocysteine significantly. The combination worked synergistically to reduce homocysteine levels by 49.8%.[154]

Several studies using folic acid, vitamin B_6, vitamin B_{12}, and betaine, either alone or in combination, demonstrated the ability of these nutrients to normalize homocysteine levels.* Other studies confirmed that oral folate supplementation alone would almost always lower high homocysteine, whereas B_6 and B_{12} would lower homocysteine only in those with a genetic metabolic defect or dietary deficiency in those nutrients, or both.[155,156] Some studies used high-dosage oral folate therapy (2.5 to 5 mg) to effectively reduce hyperhomocysteinemia in patients with peripheral atherosclerotic vascular disease, 50% of whom had abnormally high fasting plasma homocysteine levels, whereas 100% had abnormal plasma homocysteine after a methionine load.

Despite the demonstrated efficacy of individual studies lowering homocysteine levels with folic acid and B vitamins, a meta-analysis of eight randomized trials of folic acid and vitamin B supplementation to lower homocysteine levels was found to have

*References 29, 32, 58, 60, 155, 158.

no significant effects within 5 years on cardiovascular events, cancer, or mortality.[157]

If a dietary deficiency or an increased demand resulting from genetic biochemical individuality exists for 5-methyl-THF, methylcobalamin, P5P, or betaine, treatment with these active forms of micronutrients should reduce homocysteine levels better than the nonactive forms (e.g., folic acid, cyanocobalamin, pyridoxine, betaine hydrochloride). In addition, betaine is important when there is a deficiency of the P5P-dependent enzyme cystathionine synthase—the most common genetic abnormality affecting the transsulfuration pathway of homocysteine breakdown. Betaine supplementation in combination with vitamin B_6 corrects the hyperhomocysteinemia in these individuals.[28,155]

Therapeutic Approach

Supplements

- Folic acid: 800 mcg/day
- Vitamin B_{12}: 800 mcg/day
- Pyridoxine: 25 to 50 mg/day

If unresponsive to the previous dosages, patients may take the following:

- Folinic acid: 800 mcg/day
- Methylcobalamin: 800 mcg/day
- P5P: 20 mg/day
- Betaine (trimethylglycine): 1200 mg/day
- NAC: 500 mg/day
- 5-MethylTHF: 1 to 5 mg/day

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CHAPTER 55

Hyperventilation Syndrome/Breathing Pattern Disorders

Angela Sadlon, ND, and Leon Chaitow, ND, DO

INTRODUCTION

Hyperventilation Syndrome/Breathing Pattern Disorders Defined

Hyperventilation syndrome/breathing pattern disorders (HVS/BPDs) are described as follows:

- Hyperventilation is a pattern of overbreathing in which the depth and rate exceed the metabolic needs of the body at that time. This is usually seen at 30 breaths/min or more.
- Breathlessness usually occurs at rest or with only mild exercise.
- Physical, environmental, or psychological stimuli override the automatic activity of the respiratory centers, which are tuned to maintain arterial carbon dioxide ($PaCO_2$) levels within a narrow range.
- Although at any given time, the body's carbon dioxide (CO_2) production is set at a certain level, the exaggerated breathing depth and rate associated with HVS/BPDs eliminates CO_2 at a faster pace, resulting in arterial hypocapnia (low CO_2 in blood).
- The arterial hydrogen ion (pH) (acid/alkaline balance) rises into the alkaline region, thus inducing respiratory alkalosis.[1]

As a direct result of HVS/BPDs, many patients present with multiple symptoms, some of which mimic serious disease. However, blood tests, electrocardiograms (ECGs), and thorough physical examinations may reveal nothing out of the ordinary. Up to 10% of patients in general internal medicine practice reportedly experience HVS/BPDs as their primary diagnosis.[2] Many individuals with HVS/BPDs experience severe and genuinely distressing symptoms, and considerable medical expenses are incurred in excluding more serious pathology.

Gender

More females than males have HVS/BPDs, ranging from a ratio of 2:1 to 7:1. The peak age of incidence is 15 to 55 years, although other ages can be affected.[2] Women may be more at risk because of hormonal influences, because progesterone stimulates respiratory rate, and in the luteal (postovulation/premenstrual) phase, CO_2 levels drop on average 25%. Additional stress can then "increase ventilation at a time when CO_2 levels are already low."[3] A case report linked progesterone (medroxyprogesterone) therapy as a cause of hyperventilation in a 52-year-old menopausal woman.[4]

Normal Breathing Pattern

To recognize HVS/BPDs, one must be aware of the characteristics of a normal breathing pattern.

- The breathing rate should be 10 to 14 breaths/min, moving 3 to 5 L of air per minute through the airways of the chest.
- During the active inhalation phase, air flows in through the nose where it is warmed, filtered, and humidified before being drawn into the lungs by the downward movement of the diaphragm and the outward movement of the abdominal wall and lower thoracic structures.
- The upper chest and accessory breathing muscles should remain relaxed.

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- The expiratory phase is ideally effortless as the abdominal wall and lower intercostals relax downward and the diaphragm ascends back to its original domed position, aided by the elastic recoil of the lung.
- A relaxed pause at the end of exhalation releases the diaphragm briefly from the negative and positive pressures exerted across it during breathing.
- Under normal circumstances individuals are quite unaware of their breathing.
- Breathing rates and volumes increase or fluctuate in response to physical or emotional demands, but in normal subjects they return to relaxed low chest patterns after the stimuli ceases.

Patients, especially those whose symptom presentation includes chronic fatigue or anxiety, or both, and who display or report a number of the following signs or symptoms, might be considered suitable candidates for respiratory treatment (see also Diagnostic Considerations).

Benefits of Normal Respiratory Function

The exchange of gases involving acquisition of oxygen (O_2) and elimination of CO_2 leads to enhanced cellular function and facilitates the following:

- Normal performance of the brain, organs, and tissues of the body
- Normal speech and human nonverbal expression (e.g., sighing)
- Fluid movement (lymph, blood)
- Spinal mobility through regular, mobilizing, thoracic cage movement
- Digestive function via rhythmic positive and negative pressure fluctuations, via normal diaphragmatic function

Any chronic alteration in breathing function automatically modifies these functions negatively.

The impact of habitual BPDs, such as hyperventilation, on an individual's physiology can be profound, potentially resulting in or exacerbating a wide range of health problems, sometimes severely, ranging from anxiety and panic attacks to fatigue and chronic pain.

The Carbon Dioxide–Oxygen Balancing Act

Chaitow et al[10] addressed the misconception that oxygen is "good" and carbon dioxide is "bad" by stating:

> *"Yet if one considers that life-giving oxygen can also be corrosive and toxic, and that a deficiency of the waste gas carbon dioxide (CO_2) can cause fainting, seizures, or death, then the "good/bad" distinction must be restated as "good within certain limits" and "bad within certain limits." Maintaining these two gases within those limits is a complex task for the body, even more so because the supply of each gas fluctuates with each breath."*

Respiratory Homeostasis

Jennett[5] described the delicate homeostatic balancing act in which pH and CO_2 are key features:

> *When there are not other overriding drives affecting breathing, the neural control system acts to maintain a constant arterial PCO_2. This must mean that the volume of CO_2 expired continually balances the volume produced by tissue metabolism. Measurements show that alveolar and arterial concentrations of CO_2 stay constant, which means that the volume of gas breathed out from the functional (alveolar) volume of the lungs must vary precisely with the rate of metabolic CO_2 production. In rest and activity, when the system is left to itself, it is so efficient that the matching occurs virtually breath-by-breath, even when metabolic activity is continually changing.*

Pathophysiology

Physiologic and Pathophysiologic Causes of Altered Patterns of Breathing

Hyperventilation can be an appropriate physiologic response to the body's metabolic needs; for example, tachypnea (rapid breathing) or hyperpnea (increase in respiratory rate proportional to increase in metabolism) may result as the respiratory centers respond automatically and appropriately to rising CO_2 production due to exercise or organic disease that may be creating acidosis. It is therefore important to exclude organic causes that diminish PaO_2 or elevate $PaCO_2$ levels.[6]

Organic causes of HVS/BPDs that should be excluded and/or identified before breathing rehabilitation is initiated include the following:

- Respiratory: asthma, chronic obstructive respiratory disease, pneumonia, pulmonary embolus, pneumothorax, and pleural effusion. A case of carbon monoxide poisoning presenting as HVS has been reported.[7]
- Cardiovascular: acute and chronic left heart failure, right heart failure, tachyarrhythmias
- Hematopoietic: anemia
- Renal: nephrotic syndrome, acute and chronic kidney failure
- Endocrine: Diabetes with ketoacidosis, pregnancy
- Metabolic: liver failure
- Pharmaceutic: aspirin, caffeine, amphetamine, nicotine, progesterone therapy

BPDs may also emerge from a background of established pathology (e.g., asthma, cardiovascular disease, kidney failure, chronic pain). Even tumor infiltrates into brain respiratory centers and central chemoreceptors have caused hyperventilation.[8] Where this is the case, the aim of this chapter is not to explore these states, since they are discussed elsewhere in this textbook.

Fluctuating blood glucose levels may trigger HVS/BPD symptoms in patients with high carbohydrate diets, which produce rapid rises followed by sharp falls to fasting levels or below.[6,9]

Chaitow et al[10] noted that the following factors could lead to altered breathing patterns through pH shifts:

- Ketoacidosis promotes deeper, faster breathing because the breathing centers respond to the higher CO_2 content.
- Diarrhea results in the loss of alkaline plasma bicarbonate ions, which if prolonged, leads to acidosis. This stimulates corrective overbreathing to remove CO_2 (as carbonic acid [H_2CO_3]) and normalizes the pH.
- Excessive vomiting causes loss of hydrochloric acid, shifting the body toward alkalosis, slowing breathing to allow CO_2 to build up and restore pH. Hypoventilation is the result.
- Use of steroids and diuretics can lead to alkalosis.

Categorization of Causes

It is possible to place the common etiologic features of HVS/BPD into biomechanical, biochemical, psychological, environmental, pathologic, and habitual categories.

The reasons for an individual breathing inappropriately can derive directly from structural, biomechanical causes, such as a restricted thoracic spine, rib immobility, or shortness of key primary and accessory respiratory muscles.

Causes of breathing dysfunction can also have a more biochemical etiology, possibly involving allergy or infection, which triggers narrowing of breathing passages and subsequent asthmatic-type responses. Acidosis, resulting from conditions such as kidney failure, also directly alters breathing function as the body attempts to reduce acid levels via elimination of CO_2 through hyperventilation.

The link between psychological distress and breathing makes this another primary cause of many manifestations of dysfunctional respiration. Examining a person with anxiety or depression without breathing dysfunction being noted is difficult to imagine.

Other catalysts that may affect breathing function include environmental factors (e.g., altitude, humidity).[11]

The etiology of HVS/BPD may involve combinations of the factors listed previously; however, in most instances, altered breathing patterns, whatever their origins, seem to be maintained by nothing more sinister than pure habit.[6,12]

The Hydrogen Ion Factor

Chaitow et al[10] stated the following:

> *The story [of HVS/BPD] might best begin with pH, because this factor influences every organ of the body. The variable of relative acidity facilitates many metabolic exchanges and it must be kept in careful balance. Since pH describes proportion of hydrogen ions available for combination, and the pH is on a log scale, a small change in pH, such as 7.4 to 7.2, means roughly a doubling of the number of hydrogen ions present. The binding of hydrogen to negative sites helps to regulate enzymatic action, endocrine secretion, integrity of protein molecules, and cellular metabolism, including oxygen absorption and release. A pH of 7.2 would seriously compromise many physiologic functions. The physiologic normal pH in the arterial blood is around 7.4, with an acceptable range from 7.35 to 7.45. Outside these limits lie ill effects of many kinds. The body will sacrifice many other things in order to maintain proper pH.*

The Carbon Dioxide–Hydrogen Ion Connection

- The acidity of the blood is determined mainly by CO_2.
- CO_2 is the end-product of aerobic metabolism, deriving mainly from the mitochondria. CO_2 is odorless, heavier than air and, if inhaled in its pure form, causes suffocation.
- CO_2 is present in the atmosphere at a concentration of around two-hundredths of 1%, and is harmless to humans but adequate to sustain plant life.
- Transportation of CO_2 occurs from the tissues into the blood and then to the lungs for exhalation. The body converts CO_2 to H_2CO_3, of which there is a perpetual surplus.
- The lungs exhale around 12,000 mEq of H_2CO_3 per day, compared with less than 100 mEq of fixed acids excreted by the kidneys. Normal range of end-tidal CO_2 pressure is 35 to 45 mm Hg.[13]
- Any increase in bodily activity produces CO_2, acidifying the blood, unless more CO_2 is excreted and/or exhaled.
- It is therefore obvious that changes in breathing volume relative to CO_2 production regulate the moment-to-moment concentration of pH of the bloodstream (longer term regulation of pH is shared with the kidneys).
- It is the concentration of CO_2 in the blood, not oxygen, that is the major regulator of breathing drive.
- Higher CO_2 levels immediately stimulate more breathing, apparently on the assumption that abundance of CO_2 means oxygen-poor air is being breathed, breathing has stopped, or something else is happening that is an antecedent to suffocation.

The Bicarbonate Buffer

Chaitow et al[10] explained the following:

> *There exists a further balancing mechanism, the bicarbonate buffer. The bicarbonate ion (HCO_3–) is derived from CO_2 during its ride in the bloodstream; CO_2 dissociates into hydrogen ions (H+) and (HCO_3–). This bicarbonate reserve is adjustable as needed, up to a point, and constitutes a major alkaline buffer system which opposes rises in acidity. The kidneys regulate the regulators by adjusting the amount of bicarbonate returned to the bloodstream. If the kidneys detect excess acidity (a surplus of positively-charged hydrogen ions) they will try to retain more bicarbonate to balance the acid, but this is not a fast process; adjusting their filtration characteristics takes hours to days. In the short run, meanwhile, if bicarbonate buffering of excess acid is not sufficient, or if the bicarbonate is depleted, a faster back-up buffering system is available: hyperventilation. Excessive breathing exhales more CO_2 (acid), thereby bringing pH closer to normal.*

Oxygen Delivery and Smooth Muscle Constriction

The blood carries oxygen mainly in molecules of hemoglobin, which are contained in red blood cells. In an appropriate environment, hemoglobin combines readily with oxygen (to form oxyhemoglobin). This process varies according to local pH, as well as PO_2. This ability to combine is important for both absorbing oxygen through the alveoli and also for releasing oxygen through the capillary walls, where oxygen diffuses into the tissues.

These two properties are largely determined by local conditions, so that when pH is low (i.e., the blood is more acidic), hemoglobin in that area is stimulated to release additional oxygen. This is true of metabolically active tissues in general but especially of muscles. An exercising muscle needs all the oxygen it can get, and this is assisted by its chemical nature, explained by West as follows:

An exercising muscle is acid, hypercarbic, and hot, and it benefits from increased unloading of oxygen from its capillaries.[11]

The effect of pH on oxyhemoglobin dissociation is called the Bohr effect.

In the lungs the need is to bind oxygen to hemoglobin, not release it. Not surprisingly, the lungs have a more alkaline environment.

The fact that a shift of the blood toward acidity promotes dissociation and release of oxygen from the hemoglobin is particularly important when considering hyperventilation, because the resulting alkalinity causes the hemoglobin molecule to retain more oxygen than usual. With increased alkalinity encouraging smooth muscle contraction and therefore diminished diameter of blood vessels, as well as the reluctance of hemoglobin to release its oxygen, a relative oxygen deficit is likely in tissues and the brain, leading to symptoms such as fatigue, aching, cramping, and cognitive problems.

Psychology and Hyperventilation Syndrome/Breathing Pattern Disorders

On a psychological level, Bradley[14] described a "cascade of symptoms" (see Figure 55-1) in which an original cause (emotional or physical) leads to tension and anxiety that results in hyperventilation, possibly an acute hyperventilation attack, which (with repetition) over time, results in anticipation, anxiety, and avoidance behaviors or phobias, or both.

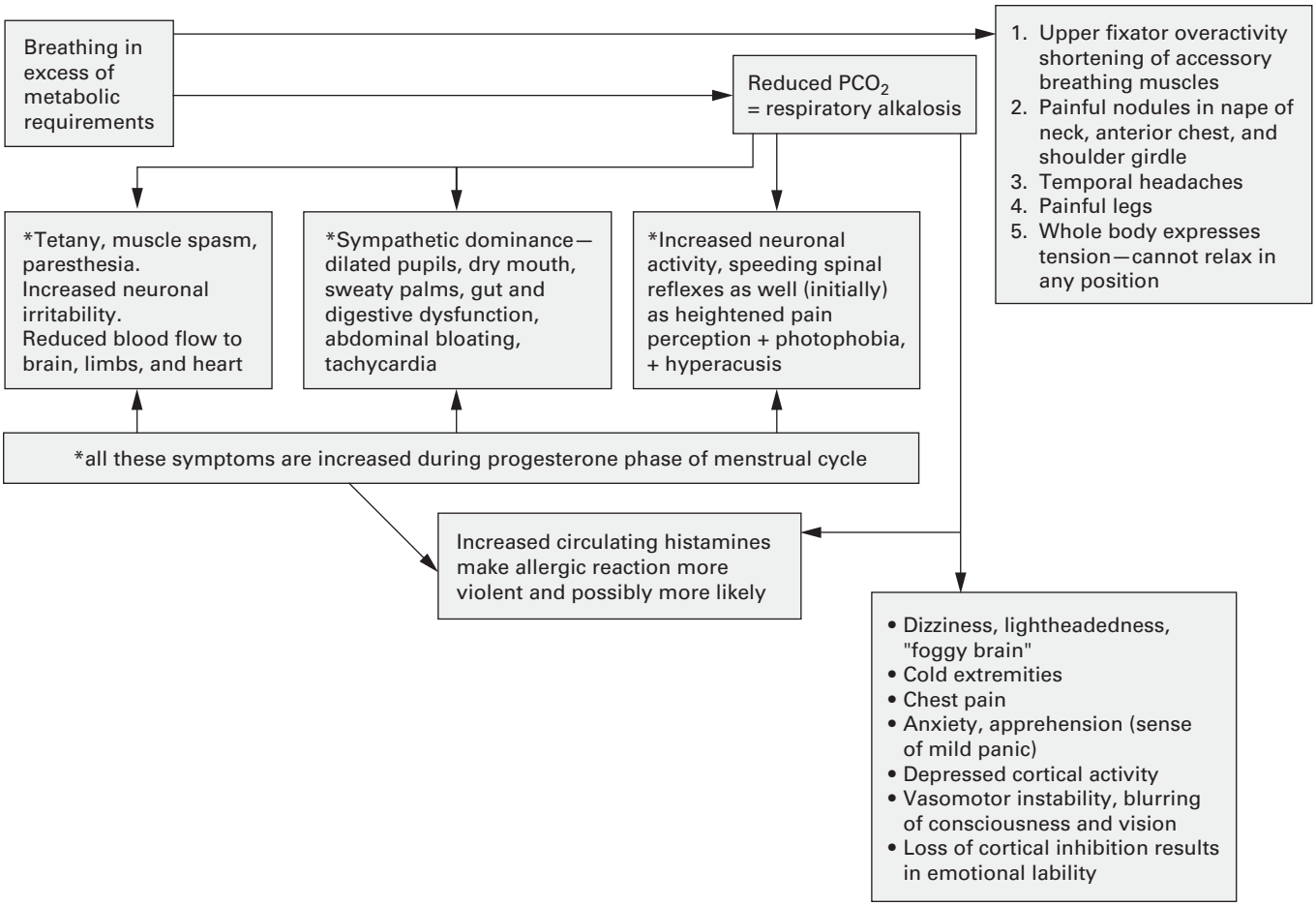


FIGURE 55-1 Negative health influences of a dysfunctional breathing pattern such as hyperventilation. (From Chaitow L, Bradley D, Gilbert C. Multidisciplinary approaches to breathing pattern disorders. London: Churchill Livingstone, 2002:90.)

Chaitow et al[10] described aspects of the influence of emotion on breathing[15-17]:

> *Increased variability from breath to breath is known to correlate with anxiety states. Low PCO_2 and increased frequency of sighing are typical of those with panic disorder even when not panicking. These generalizations miss individuals who do not have a chronic BPD, but who do experience disrupted breathing under particular conditions. These "conditions" can provoke either an amygdala "alarm" discharge or some specific, learned breathing response, as well as occasional panic.*

Conway et al[18] used hypnosis to investigate the sources of hyperventilation episodes and found emotional events such as loss, separation, and impotent anger were common precipitating factors that began the hyperventilation trend. They concluded that hypnosis might be helpful in discovering the underlying cause of hyperventilation.

Freeman et al[19] also showed that individuals who reported several symptoms indicating hyperventilation (including chest pain/palpitations and dizziness—not exclusively respiratory symptoms) displayed rather strong hyperventilation in response to recalling emotionally disturbing events, whereas the control subjects did not. Bereavement, loss of control, grief, and anger were common topics associated with the symptoms.

Chaitow et al[10] concluded (Figure 55-2):

> *"Aside from medical problems, there are still many factors in the psychological and behavioral realms competing for control of breathing. Successful regulation must take all factors into account, with special consideration for priorities of survival. The human brain adds a layer of complication with its power to imagine, project, and recall, often stimulating breathing reflexes without apparent reason."*

DIAGNOSTIC CONSIDERATIONS

Symptoms

Acute hyperventilation represents approximately 1% of all cases of hyperventilation, which is well outnumbered by chronic hyperventilation.[20] The symptoms and signs of HVS are extremely variable, and none are absolutely diagnostic. The following symptoms are indications of possible breathing pattern dysfunction:

- A feeling of constriction in the chest
- Shortness of breath
- Accelerated or deepened breathing
- Inability to breathe deeply
- Feeling tense (the Nijmegen questionnaire avoids the use of the word anxiety)
- Tightness around the mouth
- Stiffness in the fingers or arms
- Cold hands or feet

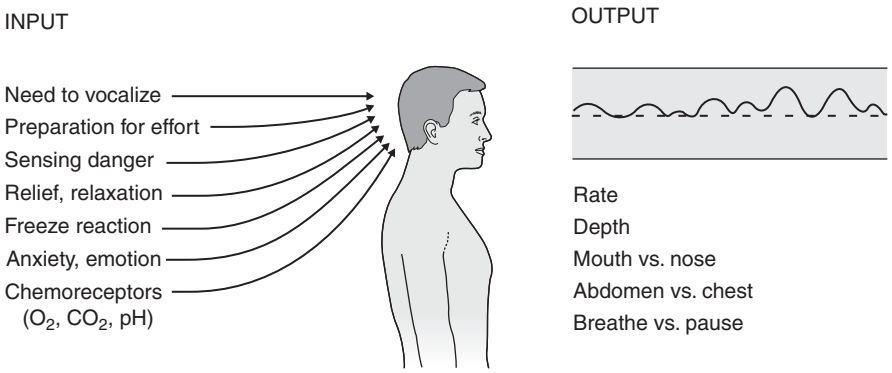


FIGURE 55-2 Final modulation of the breathing act includes input from many possible sources: the need for vocalization (a cry for help, a shouted warning, perhaps a growl); preparation for exertion; the need to freeze and become less noticeable; the need to maximize sensory acuity by keeping the body still; and the need to either remain calm or return to a baseline state of calmness. These inputs often conflict with each other, but if there is a hint of a threat to survival, they seem to have priority over all other considerations. (From Chaitow L, Bradley D, Gilbert C. Multidisciplinary approaches to breathing pattern disorders. London: Churchill Livingstone, 2002:122.)

TABLE 55-1 **Most Common Symptoms and Signs of Hyperventilation Syndrome/Breathing Pattern Disorders**

SYSTEM	SYMPTOMS	SUGGESTED CAUSES
Cardiovascular	Chest pain and angina, palpitation and arrhythmias, tachycardia, lightheadedness and syncope, altered ECG features	Reduced coronary blood flow, altered excitability of SA and AV nodes of cardiac muscle, reduced cardiac output, peripheral vasodilatation
Gastrointestinal	Discomfort in lower chest and epigastric area, esophageal reflux and heartburn, bloating/distension, exacerbation of hiatal hernia symptoms, dry mouth, air swallowing and belching	Aerophagia, increased swallowing rate, mouth breathing
Neurologic	Headache; numbness and tingling (mainly involving extremities and perioral); positive Trousseau's and Chvostek's signs; dizziness/giddiness; ataxia and tremor; blurred and tunnel vision; anxiety and panic; phobias; irritability; depersonalization; detachment from reality; impaired concentration, cognition, performance; easy fatigue; insomnia; hallucinations	Cerebrovascular constriction (see notes on smooth muscle contraction below); vasoconstriction of vertebral or carotid arteries, or both; reduced oxygen delivery, neuronal excitability resulting from alkalosis; hypocalcemia
Respiratory	Breathlessness; restricted sensation around thorax; sighing/yawning; obvious use of upper chest, accessory breathing muscles (e.g., scalenes) on inhalation; chest tenderness	Overuse of accessory breathing muscles and fatigue of primary respiratory muscles
Muscular	Stiffness and aching, weakness in limbs, cramping, carpopedal spasm, tetany	Hyperexcitability of motor nerves, muscle fatigue, calcium/magnesium imbalance

AV, atrioventricular; ECG, electrocardiogram; SA, sinoatrial.

- Tingling fingers
- Bloated abdominal sensation
- Dizzy spells
- Blurred vision
- Feeling of confusion or losing touch with environment

Table 55-1 is not fully comprehensive, but does represent the most common symptoms and signs of HVS/BPD. For greater depth, see Timmons and Ley,[6] Gardner,[21] Nixon,[22] and Chaitow et al.[10]

Metabolic Disturbances and Hyperventilation Syndrome

- Two tests of nerve hyperexcitability produced by hypocapnia-induced hypocalcemia are Trousseau's and Chvostek's signs.
- Chest pain associated with HVS/BPDs requires that heart disease is excluded as a diagnosis. Adrenaline-induced electrocardiographic changes can occur in hyperventilation, uncomplicated by coronary heart disease. One study suggested that up to 90% of noncardiac chest pain is thought to be induced by HVS/BPDs.[23]

In older patients, established coronary artery disease can be exacerbated by vasoconstriction arising from hypocapnia, which puts them at risk of coronary occlusion and myocardial damage.

Alternatively, hyperventilation can trigger spasms of normal caliber coronary arteries.

- Rapid breathing or mouth breathing instigates aerophagia from air gulping, causing bloating, burping, and extreme epigastric discomfort. Irritable bowel syndrome is listed as a common symptom of chronic overbreathing. Fear and anxiety may induce abdominal cramps and diarrhea.[1] The median swallowing rate in healthy, nondyspeptic controls is 3 or 4 swallows per 15 minutes. In the absence of food, up to 5 mL of air accompanies saliva into the gastrointestinal tract with each swallow.[24]
- Hyperventilation leading to hypocapnia causes cerebral arterioles to constrict, increasing vascular resistance and reducing cerebral blood flow. This is a natural response to changes in CO_2 to regulate oxygen delivery to the brain.[25]

Acute Hyperventilation Progression

- The patient presenting with an acute hyperventilation episode appears distressed.
- The pattern of respiration is of deep, rapid breaths, using the accessory muscles visible in the neck and the upper chest.
- Wheezing may be heard as a result of bronchospasm triggered by hypocapnia.
- A stressful precipitating event is usually reported.
- Hypocapnia reduces blood flow to the brain (2% decrease in flow per 1 mm Hg reduction in arterial CO_2), causing frightening central nervous system symptoms. The reduced oxygenation of brain and tissues of the body results from contraction of smooth muscle surrounding blood vessels and a reluctance of the hemoglobin carrier molecule to release oxygen in the increasingly alkaline environment caused by excessive loss of CO_2.
- Poor concentration and memory lapses may occur as a result, with tunnel vision and onset in those susceptible to migraine-type headaches or tinnitus.
- Sympathetic dominance brings on tremors, sweating, clammy hands, palpitations, and autonomic instability of blood vessels causing labile blood pressures.[26]
- Bilateral perioral and upper extremity paresthesia and numbness may be reported. Unilateral tingling is most often confined to the left side.
- Dizziness, weakness, visual disturbances, tremor, and confusion—sometimes fainting or even seizures—are typical symptoms.
- Spinal reflexes become exaggerated through increased neuronal activity caused by loss of CO_2 ions from the neurons.
- Tetany and cramping may occur in severe bouts.[27]

Chronic Hyperventilation

The diagnosis of chronic and intermittent hyperventilation is more difficult than acute hyperventilation. A careful history and systemic inquiry, checking all other symptoms in the other body systems, usually highlights a suspicious pattern, particularly to the experienced clinician who can think beyond his or her own specialist area. Examination must exclude organic diseases of the brain and nervous system; the heart, particularly angina and heart failure; respiratory disease; and gastrointestinal conditions, especially if there are suspicious symptoms in these systems.

Careful inquiries as to the precipitating causes of attacks helps both with the diagnosis and focusing on choice of treatment. Nixon[22] suggested that there are often attacks where there is no preceding stressful event. For example, in chronic hyperventilators, the respiratory center may have been reset to tolerate a lower than normal partial pressure of $PaCO_2$ levels in the blood. In such patients, a single sigh or one deep breath may reduce the $PaCO_2$ enough to trigger symptoms.

Laboratory and Office Tests for Hyperventilation Syndrome/Breathing Pattern Disorders

Many possible tests for respiratory function exist. Some are difficult to perform (e.g., airway resistance), and some are invasive (e.g., blood gases).[14] A selection of tests are listed as follows:

- Preliminary tests to exclude respiratory and cardiac disease including peak expiratory flow rate, chest radiograph, ECG, and an exercise ECG if chest pain is present.
- Palpation and observation can demonstrate a paradoxic breathing pattern in which the abdomen retracts and the upper chest expands on inhalation (as opposed to normal abdominal protrusion and lower thorax expansion).
- The breath-holding time test does not require additional measurements or equipment. The time a hyperventilating patient can hold his or her breath is usually greatly reduced, often not beyond 10 to 12 seconds. Thirty seconds has been used as the approximate dividing line between hyperventilators and normals by some clinicians. It is worth noting that breathless patients without hyperventilation may have equal difficulty in breath holding.[21]
- A peak expiratory flow rate measurement, compared with age, sex, and height tables, provides a simply done, quick exclusion of significant respiratory restriction in the clinic room.
- If a hyperventilation provocation test (HVPT) is performed (during which the patient is asked to voluntarily overbreathe to bring on symptoms), ECG should be monitored (see "Caution" later).
- Elevated erythrocyte carbonic anhydrase (ECA) was recently (2009) suggested as a clinical marker for hyperventilation. The values of ECA were significantly elevated (~31 U/g hemoglobin) in patients who hyperventilated compared with controls (24.7 U/g hemoglobin). However, hyperventilation sensitivity and specificity were only 52.1% and 76.7%, respectively. There are other conditions that might elevate ECA, such as glucose-6-phosphate dehydrogenase deficiency and different anemias (aplastic, iron deficiency, autoimmune hemolytic, β-thalassemia).[28]
- Arterial blood gas determination is invasive and painful (arterial puncture) but appropriate in the emergency department, where the diagnosis of acute hyperventilation is required. For patients in whom chronic hyperventilation is suspected, the pressure of end-tidal carbon dioxide (PET CO_2) can be measured noninvasively from a continuous sampling through nasal prongs or cannula with the mouth occluded, or the tube can be sited in an oral airway for those with nasal obstruction to monitor CO_2 deficits. The PET CO_2 is the level of CO_2 released at the end of expiration.
- Capnography: PET CO_2 can be evaluated after a 4-minute quiet breathing rest period, followed by exercise and recovery, or a HVPT can be conducted in the recovery period. Most patients with chronic hyperventilation have a PET CO_2 at or below 30 mm Hg and a markedly delayed recovery from hypocapnia after overbreathing, sometimes lasting 30 minutes after testing.[29,30] By measuring PET CO_2 or transcutaneous CO_2 levels while a hyperventilation provoking activity is performed, a potential link can be made between symptoms and CO_2 levels.[31]
- The think test[32] may be initiated 3 to 4 minutes into the recovery period. The patient is asked to recall a painful emotional experience during which symptoms developed. If the PET CO_2 drops 10 mm Hg, the test supports hyperventilation. Bradley[14] noted: "In some patients with hyperventilation the $PaCO_2$ and the PET CO_2 may be in the normal range. In those who are asymptomatic at the time of testing, this finding could be accepted. However, a normal level while experiencing symptoms negates hypocapnia as the cause of symptoms. It prompts a search for an alternative explanation."
- Buteyko performed comparative studies with a simple breath-holding technique to test CO_2 levels and found that a simple technique of breath holding after expiration could predict the percent of alveolar CO_2 and therefore the degree of hyperventilation to a high degree of accuracy. According to his calculations,

	Never 0	Rare 1	Sometimes 2	Often 3	Very often 4
Chest pain					
Feeling tense					
Blurred vision					
Dizzy spells					
Feeling confused					
Faster or deeper breathing					
Short of breath					
Tight feelings in chest					
Bloated feeling in stomach					
Tingling fingers					
Unable to breathe deeply					
Stiff fingers or arms					
Tight feelings round mouth					
Cold hands or feet					
Palpitations					
Feelings of anxiety					
		Total:	/64*		

*Nijmegen. Patients mark with a tick how often they suffer from the symptoms listed. A score above 23/64 is diagnostic of hyperventilation syndrome.

FIGURE 55-3 Nijmegen questionnaire. (From Chaitow L, Bradley D, Gilbert C. Multidisciplinary approaches to breathing pattern disorders. London: Churchill Livingstone; 2002:176.)

optimal levels of alveolar PCO_2 correlated with postexpiratory breath-holding time of 40 to 60 seconds. Many asthmatics and hyperventilators are found to be able to hold the breath out for less than 10 seconds.[33-35]

Caution

Bradley[14] cautioned the following:

> *"The hyperventilation provocation test is best done before explanations of symptoms, to prevent suggestion and bias. Patients need to be warned only of a dry mouth. The patient is asked to concentrate on how they feel during the 1-2 minute period when they are over breathing at the rate of 30-40 per minute. The rate is set by the examiner's hand movements. The operator must stress the importance of the test and the need to continue for as long as they can. An arterial blood gas determination at the end of the test can be of use to establish the depth of hypocapnia. Some clinicians rely on as little as 12 deep breaths which the patient can recover from easily, and subjective symptoms produced are recorded. In both the breath holding and voluntary over-breathing tests, the skills of the clinician are important for maintaining the trust and co-operation of patients."*

The Nijmegen Questionnaire

Bradley[14] pointed out that no "gold standard" exists for chronic HVS, but the Nijmegen Questionnaire is noninvasive with a high level of sensitivity (up to 91%)[36] and specificity (up to 95%).[37] It is also a way to monitor the progress of treatment by re-evaluating symptoms. Bradley noted that the results of this simple test also helped indicate whether the initiating trigger causing the HVS/BPDs resolved, suggesting that the patient had to deal with only the "bad breathing" habit and musculoskeletal and motor pattern changes, or whether the initiating triggers were ongoing or unresolved and might need further cognitive help (Figure 55-3).

Warburton and Jack[30] stated the Nijmegen Questionnaire was neither sensitive nor specific for chronic idiopathic hyperventilation without physiologic testing because many of the symptoms on the questionnaire were common to an organic respiratory disease.



BIOMECHANICAL (STRUCTURAL) CONSIDERATIONS

The Structure–Function Continuum

Nowhere in the body is the axiom of structure governing function more apparent than in its relation to respiration. Just as prolonged changes in patterns of use, such as an inappropriate (hyperventilation) breathing pattern, induce structural changes involving the muscles and joints (e.g., rib) of respiration, so do these changes ultimately prevent normal function.

Ultimately, the self-perpetuating cycle of functional change creating structural modification, leading to reinforced functional tendencies, can become complete, from whichever direction dysfunction derives. Examples follow:

- Structural adaptations can prevent normal breathing function.
- Abnormal breathing function ensures continued structural adaptational stresses.[38]

Restoration of normal function demands restoration of adequate structural mobility, whereas maintenance of restored biomechanical flexibility requires that function (how the individual breathes) should be normalized through reeducation and training.

Individually, neither approach is as useful as a combination of restoration of structural integrity, combined with functional improvement. It should be obvious that other underlying etiologic features, whether these relate to psychosocial, biochemical, or biomechanical factors, should be addressed as far as possible as a prerequisite of rehabilitation.

The Muscles of Breathing

The muscles associated with breathing function can be grouped as either inspiratory or expiratory. They are either primary in that capacity or provide accessory support.

Because expiration is primarily an elastic response of the lungs, pleura, and "torsion rod" elements of the ribs, all muscles of expiration could be considered accessory muscles, since they are recruited only during increased demand. They include internal intercostals, abdominal muscles, transverse thoracis, and subcostales. With increased demand, iliocostalis lumborum, quadratus lumborum, serratus posterior inferior, and latissimus dorsi may support expiration, including during the high demands of speech, coughing, sneezing, singing, and other special functions associated with breathing.

Space does not permit in-depth discussion of the muscles of respiration, further details of which can be found in Chaitow et al.[10]

Neural Regulation of Breathing

Respiratory centers in the brainstem unconsciously influence and adjust alveolar ventilation to maintain arterial blood oxygen and CO_2 pressures at relatively constant levels, to sustain life under varying conditions and requirements.[10]

The three main groups are as follows:

- The dorsal respiratory group, located in the distal portion of the medulla, receives input from peripheral chemoreceptors and other types of receptors via the vagus and glossopharyngeal nerves. These impulses generate inspiratory movements and are responsible for the basic rhythm of breathing.
- The pneumotaxic center in the superior part of the pons transmits inhibitory signals to the dorsal respiratory center, controlling the filling phase of breathing.
- The ventral respiratory group, located in the medulla, causes either inspiration or expiration. It is inactive in quiet breathing but is important in stimulating abdominal expiratory muscles during levels of high respiratory demand.

The Hering-Breuer reflex prevents overinflation of the lungs and is initiated by nerve receptors in the walls of the bronchi and bronchioles, sending messages to the dorsal respiratory centre, via the vagus nerve. The reflex "switches off" excessive inflation during inspiration, as well as excessive deflation during exhalation.

The autonomic nervous system enables the automatic unconscious maintenance of the internal environment of the body in ideal efficiency and adjusts to the various demands of the external environment, be it sleep with repair and growth, quiet or extreme physical activity, or stress (Figure 55-4).

A "third" nervous system regulating the airways has been recognized, called the nonadrenergic noncholinergic (NANC) system. Containing inhibitory and stimulatory fibers, nitric oxide has been identified as the NANC neurotransmitter.[39]

- NANC inhibitory nerves cause calcium ions to enter the neuron, mediating smooth muscle relaxation and bronchodilation.
- NANC stimulatory fibers—also called C-fibers—are found in the lung supporting tissue, airways, and pulmonary blood vessels, and appear to be involved in bronchoconstriction after exercise-induced asthma.[40]

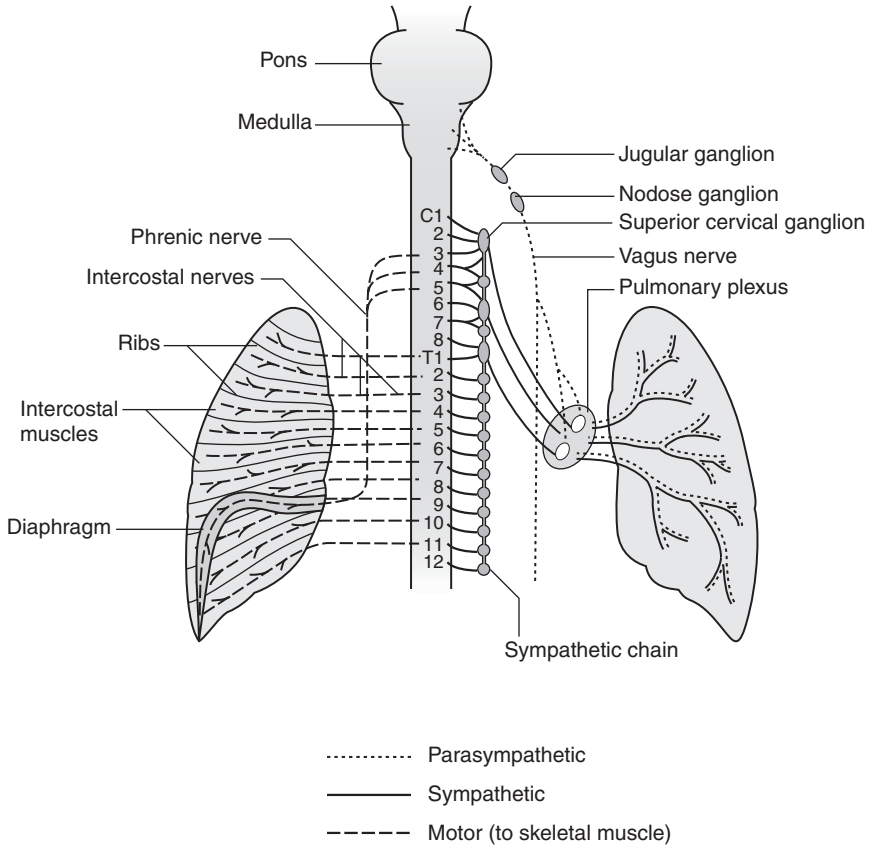


FIGURE 55-4 Schema of the autonomic innervation (motor and sensory) of the lung and the somatic (motor) nerve supply to the intercostal muscles and diaphragm. (From Scanlan C, Wilkins R, Stoller J. Egan's fundamentals of respiratory care, ed 7. St. Louis: Mosby; 1999.)

Chemical Control of Breathing

The central role of respiration is to maintain balanced concentrations of oxygen and CO_2 in the tissues. Increased levels of CO_2 act on the central chemosensitive areas of the respiratory centers themselves, increasing inspiratory and expiratory signals to the respiratory muscles. In contrast, oxygen acts on peripheral chemoreceptors located in the carotid body (in the bifurcation of the common carotid arteries) via the glossopharyngeal nerves and the aortic body (on the aortic arch), which sends the appropriate messages via the vagus nerves to the dorsal respiratory center.

Voluntary Control of Breathing

Automatic breathing can be overridden by higher cortical conscious input (directly via the spinal neurons, which drive the respiratory muscles) in response to, for instance, fear or sudden surprise. Speaking requires voluntary control to interrupt the normal rhythmicity of breathing, as do singing and wind instrument playing. Evidence indicates that the cerebral cortex and thalamus also supply part of the drive for normal respiratory rhythm during wakefulness. (Cerebral influences on the medullary centers are withdrawn during sleep.) Habitual BPDs and HVS probably originate from some of these higher centers.[6]

THERAPEUTIC CONSIDERATIONS AND THERAPEUTIC APPROACH

Treatment and Rehabilitation of Hyperventilation Syndrome/Breathing Pattern Disorders

Different models of care in managing HVS/BPDs are available.

It is assumed that all organic causes of breathing pattern changes have been excluded and that coexisting problems such as asthma, chronic obstructive airway disease, chronic pain, and hormonal imbalances receive appropriate specialized attention. It is also assumed that manual therapy approaches would be incorporated as an essential element of rehabilitation.

Bradley's[14,41] physical therapy rehabilitation follows stages that are summarized in the acronym BETTER: Breathing retraining, Esteem/self-image, Total body relaxation, Talk/breath control, Exercise prescription, Rest/sleep.

Breathing retraining incorporates a number of elements:

- Awareness of faulty breathing patterns
- Relaxation of the upper chest, shoulders, and accessory muscles
- Abdominal/low chest breathing pattern retraining
- Awareness of normal breathing rates and rhythms both at rest and during activity

The elements of the physical therapy protocol involving relaxation, exercise, talk/breath control, and sleep are all individualized and are not described here.

An Osteopathic/Naturopathic Protocol for Care of Hyperventilation Syndrome/Breathing Pattern Disorders

- Initial (and continual or periodic) assessment of breathing function based on functional evidence and palpation determines what needs to be done to improve breathing function.
- Education and information are vital for creating motivation and awareness as to why homework is essential in normalizing BPDs.
- The patient must understand clearly that the practitioner or therapist can do no more than create an environment, a possibility, for restoration of more normal function, but the breathing work itself is up to the patient.
- Treatment of muscles and joints alone, no matter how appropriate, can never restore normal breathing patterns without cooperative effort.
- Conversely, breathing retraining without the freeing of restricted structures is far more difficult to achieve.
- Psychotherapy and counseling are also unlikely to be successful unless retraining is introduced, and structural factors are dealt with.
- Manual attention to the upper fixators and/or accessory breathing muscles (upper trapezii, levator scapulae, scalenes, sternocleidomastoid, pectorals, and latissimus dorsi) is usually required.
- The diaphragm area also requires direct attention as a rule (lower anterior intercostals, sternum, costal margin, beneath costal margin, abdominal attachments, quadratus lumborum, and psoas).
- Active trigger points in these muscles may need deactivating manually or via acupuncture.
- Acupuncture being administered for 30 minutes, twice weekly, for 4 weeks showed reduction in Nijmegen score from 31 to 24. The focus was on reducing anxiety, thereby reducing hyperventilation. The points used were colon 4, liver 3, and stomach 36 bilaterally.[42]
- The thoracic spine and ribs may require mobilization (osteopathic or chiropractic adjustments).
- Osteopathic lymphatic pump methods may be required if there is evidence of stasis.
- Retraining: various breathing exercises should be introduced, individualized to the specific needs of the patient, commonly on the basis of pursed lip breathing and pranayama yoga methods (see Box 55-1).[43-47]
- Relaxation methods, including autogenic training or progressive muscular relaxation, or both, might usefully be introduced.
- Sleep pattern disturbances might require attention.
- Exercise of aerobic nature should be carefully introduced.
- Dietary advice and counseling should be introduced as appropriate.

Breathing Rehabilitation Exercises

Box 55-1 describes three breathing rehabilitation exercises.

Chronic HVS/BPDs are commonly successfully treated; however, a time frame of 12 to 26 weeks may be required, with active patient participation throughout to break well-established habits.

Lum[1] reported that more than 1000 anxious and phobic patients were treated using breathing retraining, physical therapy, and relaxation. Results indicated the following:

- Symptoms were usually abolished in 1 to 6 months, with some younger patients requiring only a few weeks.
- At 12 months, 75% were free of all symptoms, 20% had only mild symptoms, and about 1 in 20 patients had intractable symptoms.

Breathing rehabilitation therapy was evaluated in patients with HVS; the diagnosis was based on the presence of several stress-related complaints and reproduced by voluntary hyperventilation.[48] Patients with organic diseases were excluded, and most patients met the criteria for an anxiety disorder.

Therapy was conducted in the following sequence:

- Brief, voluntary hyperventilation to reproduce the reported complaints
- Reattribution of the cause of the symptoms to hyperventilation

BOX 55-1 **Breathing Rehabilitation Exercises**

1. Pursed lip breathing[44-45]

Pursed lip breathing, combined with diaphragmatic breathing, enhances pulmonary efficiency.

- The patient is seated or supine with the dominant hand on the abdomen and the other hand on the chest.
- The patient is asked to breathe in through the nose and out through the mouth, with pursed lips, ensuring diaphragmatic involvement by means of movement of the abdomen against the hand on inhalation.
- Exhalation through the pursed lips is performed slowly and has been shown to relieve dyspnea, slow the respiratory rate, increase tidal volume, and help restore diaphragmatic function.

Author's Note: Essentially blowing firmly and slowly, through a narrow aperture such as pursed lips, effectively tones the diaphragm via eccentric isotonic activity.

2. Antiarousal breathing[43,46]

The patient is asked to sit or recline comfortably and exhale slowly and fully through pursed lips, and the following guidance is given:

- Imagine a candle flame about 6 inches from your mouth, and blow a thin stream of air at it (pursed lip breathing).
- As you exhale, count silently to establish the length of the "out breath."
- When you have exhaled fully, without strain, pause for a count of "1," then inhale through the nose.
- Full exhalation creates a "coiled spring," making inhalation easier.
- Count to yourself to establish how long your "in breath" lasts.
- Without pausing to hold the breath, exhale slowly and fully, through pursed lips, blowing the air in a thin stream, and then pause for a count of 1.
- Repeat the inhalation and exhalation for at least 30 cycles twice daily.
- After some weeks of daily practice you should achieve an inhalation phase that lasts 2 to 3 seconds and an exhalation phase of 6 to 7 seconds, without strain.
- Exhalation should always be slow and continuous; there is little value in breathing the air out in 2 seconds and then simply waiting until the count reaches 8 before inhaling again!
- Feelings of anxiety should reduce with this exercise.
- Practice twice daily, and repeat the exercise for a few minutes (6 cycles takes about 1 minute) every hour if anxious or when stress increases.
- Practice on waking; before bedtime; and, if possible, before meals.

3. Recitation of mantra or prayer

- The respiratory (and cardiovascular) effects of rosary prayer ("Ave Maria" in Latin) and recitation of a yoga mantra were assessed.[47]
- Results were similar, showing a slowing of respiration to approximately 6 counts per minute and synchronization of all cardiovascular rhythms (Traube-Hering-Mayer oscillations), representing blood pressure, heart rate, cardiac contractility, pulmonary blood flow, cerebral blood flow, and movement of cerebrospinal fluid.
- This influence on autonomic activity, represented by the Traube-Hering-Mayer oscillations, is clearly health enhancing, because it slows respiratory rate to the level considered optimal in breathing rehabilitation.[1,6,12]

- Explaining the rationale of therapy involving reduction of hyperventilation by acquiring an abdominal breathing pattern, with slowing down of expiration
- Breathing retraining for 2 to 3 months working with a physiotherapist

After breathing therapy, the sum scores of the Nijmegen Questionnaire were markedly reduced. A canonical correlation analysis relating the changes of the various complaints to the modifications of breathing variables showed that the improvement of the complaints was correlated mainly with the slowing down of breathing frequency.



SUMMARY

HVS/BPDs are a common disorder affecting up to 10% of patients in a general internal medicine practice. However, it is rarely recognized or appropriately treated. Breathing retraining is effective clinically and economically, as long as enough patience is exercised to actively engage the patient in a program requiring weeks to months of behavioral change. Acupuncture was also shown to improve symptoms of HVS, especially with anxiety as the etiology.

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CHAPTER 56

Immune Support

Michael T. Murray, ND

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INTRODUCTION

The immune system is a complex integration of synergistic segments that are continuously barraged by stimuli from both internal and external sources. Immunology continues to be a rapidly developing field in which mechanisms are constantly being conceptualized and revised. For the physician interested in assessing and maintaining a patient's health, the development of a thorough understanding of the clinical aspects of the immune system and the many factors that enhance and/or inhibit normal function is essential. The immune system is truly "holistic," as evidenced by the close association of psychological, neurologic, nutritional, environmental, and hormonal factors with immune function.

Supporting the immune system is critical to good health. Conversely, good health is critical to supporting the immune system. The best approach to supporting immune function is a comprehensive plan involving lifestyle, stress management, exercise, diet, nutritional supplementation, and the use of plant-based medicines.

THE IMMUNE SYSTEM: AN OVERVIEW

The immune system has two fundamental and complementary components: the innate and adaptive immune systems, with the division largely defined by the speed and specificity of the response. The innate branch of the immune system is generally defined by a consistent response; however, when an antigen is encountered, the immune response includes phagocytic cells such as neutrophils, monocytes, and macrophages, as well as the various physical and chemical barriers to infection. The adaptive immune system, however, improves upon repeated exposure to a given infection, because these cells develop a memory of past encounters. The adaptive immune system is comprised of B (humoral) and T (cell-mediated) cells that work together to create antibodies specific to an invading organism.

PSYCHONEUROIMMUNOLOGY

The first step in supporting immune function is employing the healing power of the mind and attitude. Psychoneuroimmunology is the term used to describe the interactions between the emotional state, nervous system function, and the immune system.[1] What investigations into these interactions have documented is that the mind and attitude play a significant role in the functioning of the immune system. However, a complete and detailed account of the many facets of psychoneuroimmunology, or behavioral immunology, is beyond the scope of this chapter. An overview on the role of attitude and emotions in immune function is discussed in Chapter 7 and the importance of stress management to a healthy immune system is discussed in Chapter 60. We focus here on the effects of stress on the immune response.

Stress

Many clinical and experimental studies have clearly demonstrated that stress, personality, attitude, and emotion are etiologic or contributory in suppressing the immune system as well as leading to the development of many diverse diseases.[1] Reaction to stressful stimuli is entirely individual, reinforcing the fact that people

differ significantly in their perceptions and responses to various life events. The variations in response help account for the wide diversity of stress-induced illnesses. Stress-induced increases in corticosteroid and catecholamine levels lead to an immunosuppressed state, leaving the host susceptible to infectious and carcinogenic illnesses. This immunosuppression is proportional to the level of stress, and although the effects are numerous, they appear to involve a common mechanism: an increase in glucocorticoids, proinflammatory cytokines, and catecholamines resulting in significant alterations in hypothalamic-pituitary-adrenal and the sympathetic-adrenal medullary axes, leukocyte function, thymic involution, and suppressed lymphopoiesis. More than 150 clinical studies have now shown that stress can alter immune function and contribute to the development of significant disease and poor health.[1-3]

Lymphocytes, monocytes or macrophages, and granulocytes have receptor sites for the many regulating hormones and neurotransmitters of the hypothalamic-pituitary-adrenal and sympathetic-adrenal medullary axes. Alterations in these compounds lead to disruption of cellular trafficking, proliferation, cytokine secretion, antibody production, and cytolytic activity. For example, glucocorticoids inhibit the production of interleukin-12 (IL-12), interferon-γ (IFN-γ), IFN-α, and tumor necrosis factor-α (TNF-α) by antigen-presenting cells and type 1 helper T (Th1) cells, but upregulate the production of IL-4, IL-10, and IL-13 by Th2 cells. This mechanism systemically causes a selective suppression of the Th1-cellular immunity axis and a shift toward Th2-mediated humoral immunity, rather than generalized immunosuppression. During an immune response and inflammation, the activation of the stress system, and thus increased levels of systemic glucocorticoids through induction of a Th2 shift, may actually protect the organism from systemic "overshooting" with Th1 proinflammatory cytokines and other products of activated macrophages with tissue-damaging potential. However, conditions associated with significant changes of glucocorticoids, such as acute or chronic stress or cessation of chronic stress, severe exercise, pregnancy, and the postpartum state, through modulation of the Th1–Th2 balance may affect the susceptibility to or the course of infections as well as autoimmune and atopic and/or allergic diseases.[4,5] A study in medical students taking examinations found that psychological stress produced a shift in the cytokine balance toward a Th2 profile.[6] The data showed decreased synthesis of Th1 cytokines, including IFN-γ, and increased production of Th2 cytokines, including IL-10. This study and others indicated that stress-induced decrease of Th1 cytokines resulted in dysregulation of cell-mediated immune responses.

To help demonstrate causal relations between psychosocial stressors and the development of infectious illness, investigators inoculated subjects with several different types of vaccines to demonstrate clinically relevant alterations in an immunologic response to challenge under well-controlled conditions. For example, the chronic stress associated with caring for a spouse with Alzheimer's disease or, for younger people, experiencing stressful life events was associated with a poorer antibody response to an influenza virus vaccine than in well-matched control subjects.[7,8] The premise was that the production of a delayed, weaker, and shorter-lived immune response to a vaccine would be analogous to impaired immune responses to other pathogens. Consistent with this concept, subjects who showed poorer responses to vaccines also experienced higher rates of clinical illness as well as longer lasting infectious episodes.

Fortunately, the effects of stress on the immune system can be attenuated or even overcome with positive mood, effective stress reduction techniques, humor, laughter, and guided imagery.[1,9]

LIFESTYLE

A healthy lifestyle goes a long way in establishing a healthy immune system. This benefit is perhaps most obvious when one looks at the effects of lifestyle on natural killer cell activity.[10-12] Box 56-1 lists the lifestyle practices associated with higher natural killer cell activity. One particular lifestyle factor that is absolutely critical to healthy immune function is adequate sleep. In healthy humans, sleep deprivation has consistently been demonstrated to impair different parameters of immune function and mood. Interestingly, the deterioration of immune function precedes the plummeting of subjective well-being and psychosocial performance in sleep-deprived subjects.[13]

NUTRITIONAL FACTORS

The health of the immune system is greatly affected by a person's nutritional status. Dietary factors that depress immune function include nutrient deficiency, excess consumption of sugar, consumption of allergenic foods, and high cholesterol levels in the blood. Dietary factors that enhance immune function include all essential nutrients, antioxidants, carotenes, and flavonoids.

Consistent with good health, optimal immune function requires a healthy diet that:

- Is rich in whole, natural foods, such as fruits, vegetables, grains, beans, seeds, and nuts.
- Is low in fats and refined sugars.
- Contains adequate, but not excessive, amounts of protein.

In addition, individuals are encouraged to drink five or six 8-ounce glasses of water (preferably pure) per day. These dietary recommendations along with a positive mental attitude, a good high-potency multivitamin and mineral supplement, a regular exercise program, daily deep breathing and relaxation exercises (meditation, prayer, etc.), and at least 7 hours of sleep daily will go a long way in helping the immune system function at an optimum level.

Nutrient Deficiency

Nutrient deficiency is the most common cause of a depressed immune system. Although research relating nutritional status to immune function has historically concerned itself with severe malnutrition states (i.e., kwashiorkor and marasmus), attention is now shifting toward marginal deficiencies of single or multiple nutrients and the effects of overnutrition. The plethora of clinical and experimental data has made inevitable the conclusion that a single nutrient deficiency can impair the immune system profoundly.

BOX 56-1 Lifestyle Practices Associated with Higher Natural Killer Cell Activity

- Not smoking
- Increased intake of green vegetables
- Regular meals
- Proper body weight
- More than 7 hours of sleep per night
- Regular exercise
- A vegetarian diet

Given the widespread problem of subclinical nutrient deficiency in Americans, it can be concluded that many have impaired immunity amenable to nutritional supplementation. This statement is particularly true in the elderly. Numerous studies have shown that most elderly Americans are deficient in at least one nutrient. Likewise, numerous studies show that taking a multivitamin and mineral supplement enhances immune function in elderly subjects (whether they have overt nutritional deficiency or not).[14-16] These findings have considerable fundamental, clinical, and public health significance.

Protein

The importance of adequate protein intake to proper immune function has been extensively studied.[9] The most severe effects of protein–calorie malnutrition (PCM) are on cell-mediated immunity, although all facets of immune function are ultimately affected. PCM is not, however, usually due to a single-nutrient deficiency. It is normally associated with multiple nutrient deficiencies, and some immune dysfunctions attributed to PCM are most likely due to these other factors. Partial deficiencies of dietary vitamins produce a comparatively greater depression in the natural and inducible levels of cytotoxic activities than do partial protein deficiencies. Nonetheless, adequate protein is essential for optimal immune function.

Sugar

The oral administration of 100-g portions of carbohydrate as glucose, fructose, sucrose, honey, or orange juice significantly reduces neutrophil phagocytosis, but starch has no effect. As can be seen in Figure 56-1, effects start within 30 minutes, last for more than 5 hours, and typically show a 50% reduction in phagocytic activity at the peak of inhibition (usually 2 hours after ingestion).[17,18] Because polymorphonuclear leukocytes (PMNs) constitute 60% to 70% of the total white blood cells (WBCs) and are a major portion of the defense mechanism, impairment of phagocytic activity leads to an immune-compromised state. Oral administration of increasing amounts of glucose progressively lowers neutrophil phagocytosis, with maximal inhibition corresponding to maximal blood glucose levels.

In addition, oral ingestion of 75 g of glucose has been shown to depress lymphocyte response to mitogens, apparently through the elevation of insulin levels.[19] Other parameters of immune function are also undoubtedly affected by sugar consumption.

It has been hypothesized that the ill effects of high glucose levels are a result of elevation of insulin values and competition with vitamin C for membrane transport sites.[20,21] This hypothesis is based on evidence that vitamin C and glucose appear to have opposite effects on immunologic function and the fact that both substances require insulin for membrane transport into many tissues.

Considering that the average American consumes 125 g of sucrose, plus 50 g of other refined simple sugars each day, the conclusion that most Americans have chronically depressed immune systems is inescapable. It is clear, particularly during an infection, that the consumption of simple sugars, even in the form of fruit juice, is deleterious to the host's immune status.

Short-term fasting could be encouraged, particularly during the first 24 to 48 hours of an acute infectious illness, because it results in a significant (up to 50%) increase in phagocytic index.[17] The fast should not be continued for a long period, because eventually the leukocytes' energy sources will become depleted.

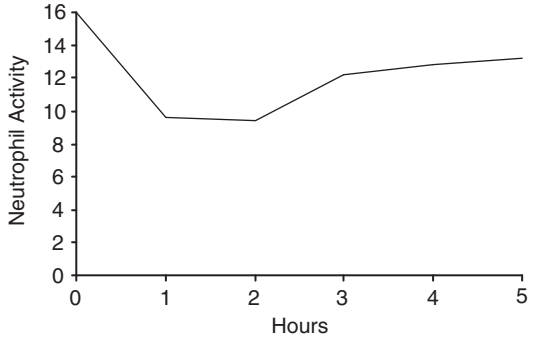


FIGURE 56-1 The effects of sugar on white cell phagocytic activity.

Obesity

Obesity is associated with decreased immune status, as evidenced by reduced bactericidal activity of leukocytes and the higher morbidity and mortality from infections as well as from certain cancers in obese individuals.[22] Obesity also increases the risk of asthma, atopic, and autoimmune diseases by inducing decreased immunologic tolerance as a consequence of immunologic changes induced by adipokines (e.g., leptin and adiponectin) and cytokines (e.g., IL-6 and TNF-α) secreted by white adipose tissue.[23] In addition, cholesterol and lipid values are usually elevated in obese individuals, which may explain their impaired immune function.

Blood Lipids

Increased blood levels of cholesterol, free fatty acids, triglycerides, and bile acids inhibit various immune functions, including[24,25]:

- Lymphoproliferation
- Response to mitogens
- Antibody response
- PMN chemotaxis
- Phagocytosis

Optimal immune function therefore depends on control of these serum components. Interestingly, L-carnitine, even at minimal concentrations, has been shown to neutralize lipid-induced immunosuppression.[26] This effect is probably due to carnitine's role as a rate-limiting factor in the removal of fat emulsion from the blood.[27]

Alcohol

Alcohol increases the susceptibility to experimental infections in animals, and alcoholics are known to be more susceptible to infections, especially pneumonia. Studies of immune function in alcoholism showed a profound depression in most parameters of immunity.[28]

Vitamins

Vitamin A and Carotenes

Vitamin A plays an essential role in maintaining the integrity of the epithelial and mucosal surfaces and their secretions. These systems constitute a primary nonspecific host defense mechanism. Vitamin A has been shown to stimulate and/or enhance numerous immune processes, including the following:

- Induction of cell-mediated cytotoxicity against tumors
- Natural killer cell activity

- Lymphocyte blastogenesis
- Mononuclear phagocytosis
- Antibody response

These effects are not due simply to reversal of vitamin A deficiency, because many of them are further enhanced by the administration of (supposedly) excessive levels of vitamin A.[16,29] In addition, vitamin A prevents and reverses stress-induced thymic involution, and additional vitamin A can actually promote thymus growth.[30]

Carotenes have also demonstrated a number of immune-enhancing effects. In addition to being converted into vitamin A, carotenes function as antioxidants. Because the thymus gland is so susceptible to damage by free radicals, β-carotene may be more advantageous in enhancing the immune system than retinol. For more information, see Chapter 135.

Vitamin C

Vitamin C (ascorbic acid) plays an important role in the natural approach to immune enhancement. Although vitamin C has been shown to be antiviral and antibacterial, its main effect is via improvement in host resistance. Many different immunostimulatory effects have been demonstrated, including enhancing lymphoproliferative response to mitogens and lymphotrophic activity and increasing INF levels, antibody responses, immunoglobulin levels, secretion of thymic hormones, and integrity of ground substance.[16,31] Vitamin C also has direct biochemical effects similar to those of INF.[32]

Numerous clinical studies support the use of vitamin C in the treatment of infectious conditions. In addition to its effects on the common cold, vitamin C has also been shown to be useful in other infectious conditions.[33] Vitamin C levels are quickly depleted during the stress of an infection as well as in chronic disease.[34]

It is useful to supplement vitamin C concurrently with flavonoids, which raise the concentration of vitamin C in some tissues and potentiate its effects as well as exert their own effects.[35]

Vitamin D

The importance of vitamin D on the regulation of cells of the immune system has gained increased appreciation over the past decade with the discovery of the vitamin D receptor and key vitamin D metabolizing enzymes expressed by cells of the immune system. Effective in supporting both innate and adaptive immunity,[36-40] vitamin D has been shown to:

- Upregulate antimicrobial peptides, namely cathelicidin, to enhance clearance of bacteria at various barrier sites and in immune cells.
- Modulate the adaptive immune system by direct effects on T-cell activation and on the phenotype and function of antigen-presenting cells.
- Protect against the development of autoimmune diseases (e.g., Crohn's disease, juvenile diabetes mellitus, multiple sclerosis, asthma, and rheumatoid arthritis).
- Reduce the frequency of viral upper respiratory infections.

Vitamin D appears to be especially important in protection against viral or bacterial upper respiratory infection.[41]

Vitamin E

Vitamin E enhances both humoral immunity and cell-mediated immunity. A vitamin E deficiency results in lymphoid atrophy and decreases of lymphoproliferative response to mitogens, splenic plaque-forming colonies, antibody response, and monocyte function. Vitamin E supplementation (30 to 150 international units [IU]) has been shown to[42]:

- Increase lymphoproliferative response to mitogens.
- Prevent free radical-induced thymus atrophy.
- Enhance helper T-cell activity.
- Increase splenic plaque-forming colonies, serum immunoglobulins, antibody response, PMN phagocytosis, and reticuloendothelial system activity.

Elderly subjects may benefit from even higher dosages of vitamin E. A recent study sought to determine the effect of vitamin E supplementation at different dosages on immune function in 88 patients older than 65 years.[16,43] To determine the effect of vitamin E on immune function, the researchers measured T-cell function by assessing delayed-type hypersensitivity skin response; antibody response to hepatitis B, tetanus, diphtheria, and pneumococcal vaccines; and autoantibodies to DNA and thyroglobulin. Vitamin E was given at 60, 200, or 800 IU for 235 days. Although the placebo group experienced only an 8% increase in delayed-type hypersensitivity, the 60-IU group had a 20% increase, the 200-IU group a 58% increase, and the 800-IU group a 65% increase. With regard to antibody production, the best results were observed in the patients who received 200 IU daily. No effect on autoimmune antibodies was noticed. No adverse effects were observed at any of the three dosage schedules of vitamin E.

In another double-blind study in 451 elderly participants in a nursing home, vitamin E supplementation (200 IU/day) demonstrated a protective effect against upper respiratory tract infections, particularly the common cold.[44]

Pyridoxine

A pyridoxine deficiency results in depression of cellular and humoral immunity, lymphoid tissue atrophy, leukopenia, reduction in quantity and quality of antibody production, diminished lymphoproliferative response to mitogens, and decreased thymic hormone activity.[16] Factors predisposing to deficiency are low dietary pyridoxine intake, excess protein intake, consumption of hydralazine (yellow) dyes, and use of alcohol and oral contraception.

Folic Acid and Vitamin B_{12}

The megaloblastic state induced by a deficiency of vitamin B_{12} and/or folate results in improper WBC production and abnormal lymphocyte responses. Folic acid deficiency (the most common vitamin deficiency in the United States) has been shown to result in lymphoid atrophy and decreased lymphoproliferative response to mitogens, splenic plaque-forming colonies, and antibody production. A B_{12} deficiency, besides producing a deficiency in folate conversion to its active tetrahydrofolate form, leads to impairment of PMN phagocytosis and bactericidal action.[16]

Other B Vitamins

Deficiencies of thiamin, riboflavin, and pantothenic acid lead to reduced antibody response, decreased splenic plaque-forming colonies, and lymphoid atrophy.

Minerals

Iron

Iron deficiency is a commonly encountered isolated nutritional deficiency that causes immune dysfunction in large numbers of patients. Marginal iron deficiency, even at levels that do not lower hemoglobin values, can influence the immune system. Lymphoid tissue atrophy, decreased lymphoproliferative response to mitogens, defective macrophage and neutrophil function, and decreased T-cell/B-cell ratios are common experimental and clinical findings.[16]

Iron is an important nutrient for bacteria as well as for humans. During infection, one of the body's nonspecific defense mechanisms to limit bacterial growth is to reduce plasma iron, and in vitro studies have shown that the bacteriostatic effects and some of the bactericidal effects of serum are eliminated by the addition of iron to the serum.[45] As temperature rises, plasma iron levels drop, and when temperature is raised to fever levels, the growth of bacteria is inhibited, but not at high iron concentrations.

These observations led us to conclude that iron supplementation is probably contraindicated during acute infection, especially in patients with low transferrin levels. However, in patients with impaired immune function, chronic infections, and subnormal iron levels, adequate supplementation is essential.

Trace Minerals

Trace minerals function primarily as activators of enzyme-metal-substrate complexes in which they are loosely bound cofactors. The role of these elements in these metalloenzymes is either structural, in which they influence the reactivity of the protein by stabilizing strained configurations of binding ligands about the metal atom, or catalytic, in which they act as centers of positive charge.

Zinc

The hereditary zinc deficiency disease acrodermatitis enteropathica offers an excellent model for understanding the role of zinc in immunity. In acrodermatitis enteropathica, the number of T cells is reduced, lymphoproliferative response to mitogens is diminished, thymic hormone levels are lower, delayed cutaneous hypersensitivity is decreased, and PMN phagocytosis, chemotaxis, and cytotoxic activities are impaired. All of these effects are reversible upon adequate administration and absorption of zinc.[46]

Zinc serves a vital role in many immune system reactions; for example, it promotes the binding of complement (C1q) to immune complex, acts as a protectant against iron-catalyzed damage by free radicals, acts synergistically with vitamin A, is required for lymphocyte transformation, acts independently on lymphocytes as a mitogen, and is a necessary cofactor in activating serum thymic factor. In vitro, zinc inhibits the growth of several viruses, including rhinoviruses, picornaviruses, togaviruses, herpes simplex virus, and vaccinia virus.[47]

Adequate zinc nutrition is particularly important in the elderly, and zinc supplementation in elderly subjects results in increased numbers of T cells and enhanced cell-mediated immune responses.[47]

Throat lozenges containing zinc became popular in the treatment of the common cold as a result of a double-blind clinical trial in 1984 demonstrating that zinc-containing lozenges significantly reduced the average duration of common colds by 7 days.[48] The lozenges used in this study contained 23 mg of elemental zinc, which the patients were instructed to dissolve in their mouths every 2 waking hours after an initial double dose. After 7 days, 86% of the 37 zinc-treated subjects were symptom free compared with 46% of the 28 placebo-treated subjects. Additional studies confirmed these results.[49] Because high doses of zinc can actually impair immune function, a daily intake higher than 150 mg of zinc for longer than 1 week cannot be recommended.

Selenium

Selenium, in its vital role in glutathione peroxidase, affects all components of the immune system, including the development and expression of all WBCs. Selenium deficiency results in depression of immune function, whereas selenium supplementation results in augmentation and/or restoration of immune functions. Selenium deficiency has been found to inhibit resistance to infection through impairment of WBC and thymus function, whereas selenium supplementation (100 to 200 mcg/day) has been shown to stimulate WBCs and thymus function.[50-53]

The ability of selenium supplementation to enhance immune function goes well beyond simply restoring selenium levels in selenium-deficient individuals. For example, in one study, selenium supplementation (200 mcg/day) to individuals with normal blood selenium concentrations resulted in a 118% improvement in the ability of lymphocytes to kill tumor cells and an 82.3% rise in the activity of natural killer cells.[51] These effects were apparently related to the ability of selenium to enhance the expression of the immune-enhancing compound IL-2 and, consequently, the rate of WBC proliferation and differentiation into forms capable of killing tumor cells and microorganisms. The supplementation regimen did not produce significant changes in the blood selenium levels of the participants. The results indicated that the immune-enhancing effects of selenium in humans require supplementation above the normal dietary intake.

ENHANCING THYMUS FUNCTION

Perhaps the most effective method of reestablishing a healthy immune system is employing measures to improve thymus function. Promoting optimal thymus gland activity involves the following:

- Prevention of thymic involution or shrinkage by ensuring adequate dietary intake of antioxidant nutrients
- Use of nutrients that are required in the manufacture or action of thymic hormones

Antioxidants

The thymus gland shows maximum development immediately after birth. During the aging process, the thymus gland undergoes a process of shrinkage, or involution. The reason for this involution is that the thymus gland is extremely susceptible to free radical and oxidative damage caused by stress, radiation, infection, and chronic illness.

Many patients with impaired immune function as well as conditions associated with impaired immunity (e.g., chronic fatigue syndrome, cancer, acquired immunodeficiency syndrome) experience a state of oxidative imbalance characterized by a greater number of prooxidants than antioxidants in their systems. This situation is quite detrimental to thymus function. One of the primary ways in which antioxidants affect the immune system, particularly cell-mediated immunity, may be by protecting the thymus gland from damage. The antioxidant nutrients most important for protecting the thymus include the carotenes, vitamin C, vitamin E, zinc, and selenium.

Nutrients

Many nutrients function as important cofactors in the manufacture, secretion, and function of thymic hormones. A deficiency of any one of these nutrients results in decreased thymic hormone action and impaired immune function. Zinc, vitamin B_6, and vitamin C are perhaps the most critical. Supplementation with these nutrients has been shown to improve thymic hormone function and cell-mediated immunity.

Zinc is perhaps the critical mineral involved in thymus gland function and thymus hormone action. Zinc is involved in virtually every aspect of immunity. When zinc levels are low, the number of

T cells is reduced, thymic hormone levels are lower, and many WBC functions critical to the immune response are severely lacking. All of these effects are reversible with adequate administration and absorption of zinc.[54,55]

BOTANICALS

Many herbs have been shown to have antibacterial, antiviral, and immunostimulatory effects. A complete discussion is outside the scope of this chapter, but fortunately several immune-enhancing botanicals (e.g., *Echinacea*, *Hydrastis canadensis*, and Panax ginseng), are discussed in depth in Section 5. One herb that will be described in this section is the root of *Astragalus membranaceus*, a traditional Chinese medicine used for viral infections. Clinical studies in China have shown it to be effective when used prophylactically against the common cold.[56] It has also been shown to reduce the duration and severity of symptoms in acute treatment of the common cold as well as to raise WBC counts in persons with chronic leukopenia.

Research in animals showed that *Astragalus* apparently works by stimulating several factors of the immune system, including enhancing phagocytic activity of monocytes and macrophages, increasing INF production and natural killer cell activity, improving T-cell activity, and potentiating other antiviral mechanisms.[56,57] *Astragalus* appears particularly useful in cases in which the immune system has been damaged by chemicals or radiation. In immunodepressed mice, *Astragalus* was found to reverse the T-cell abnormalities caused by cyclophosphamide, radiation, and aging.[58] As with Echinacea, the polysaccharides contained in the root of *Astragalus membranaceus* contribute to the immune-enhancing effects.

Yeast Beta-Glucans and Medicinal Mushrooms

Extracts and preparations of Baker's yeast and medicinal mushrooms like maitake (*Grifola frondosa*), shiitake (*Lentinus edodes*), reishi (*Ganoderma lucidum*), and *Cordyceps sinensis* possess significant immune enhancing effects. Much of this activity is due to the presence of β-glucans. Numerous in vitro, in vivo, and clinical studies showed that yeast and fungal β-glucans activate WBCs by binding to receptors like dectin-1 on the outer membranes of neutrophils, macrophages, natural killer cells, and cytotoxic T cells.[59,60] Just like a key in a lock, the binding of the β-glucan to cellular receptors literally flips WBCs on and triggers a chain reaction leading to increased immune activity. In addition to increasing the ability of the neutrophils and macrophages to engulf and destroy microbes, cancer cells, and other foreign cells, the binding stimulates the production of important signaling proteins of the immune system, such as IL-1, IL-2, and lymphokines. These immune activators ramp up defenses by activating immune cells.

One of the best researched β-glucan sources is Wellmune WGP, a whole glucan particle composed of 1,3-1,6-β-glucan derived from the cell walls of a highly purified, proprietary baker's yeast *(Saccharomyces cerevisiae).* Once absorbed, Wellmune is taken up by macrophages and digested into smaller fragments and slowly released over a number of days. The fragments bind to neutrophils, via complement receptor 3, and enhance their activity. As of 2011, six double-blind clinical studies have been conducted with Wellmune WGP, demonstrating positive results in reducing the signs, symptoms, frequency, and duration of upper respiratory infections. In a study in marathon runners, Wellmune WGP significantly reduced symptoms of upper respiratory tract infection (e.g., sore throat, stuffy nose, etc.) in the test subjects. Furthermore, the Wellmune group reported 22% higher scores in vigor, 48% reduction in fatigue, 38% reduction in tension, and a 38% reduction in confusion over the control groups.[61]

In a double-blind study during the cold and flu season, compared with the placebo group, the Wellmune WGP group reported: (1) no incidence of fever compared with 3.5 incidences over a 90-day period; (2) no need to take a "sick day" from work or school, compared with 1.38 days of work/school missed for the placebo group; and (3) an increase in general health, including physical energy and emotional well-being.[62]

In the latest study of 122 healthy volunteers, participants taking 250 mg of Wellmune WGP daily for 12 weeks reported a 58% reduction in upper respiratory tract infection symptoms, compared with individuals taking a placebo. These subjects also experienced improvement in energy levels compared with the placebo group.[63]

THERAPEUTIC APPROACH

A major challenge to the discerning clinician is to determine which of the preceding factors is the key to reactivating or supporting a patient's immune system. The regimen given here is meant as a general approach and must be tailored to the patient's specific needs to maximize the desired effects and limit unnecessary treatment.

General Measures

- Rest (bed rest better).
- Drink large amount of fluids (preferably diluted vegetable juices, soups, and herb teas).
- Limit simple sugar consumption (including fruit sugars) to less than 50 g/day.

Supplements

- High-potency multivitamin and mineral formula
- Vitamin C, 500 to 1000 mg every 2 hours
- Bioflavonoids, 1000 mg/day
- Vitamin A, 2500 IU/day, or β-carotene 25,000 IU/day
- Vitamin D, 2000 IU/day
- Zinc, 30 mg/day

Botanicals

All doses of botanicals should be given three times per day.

Echinacea spp.

- Dried root (or as tea), 0.5 to 1 g
- Freeze-dried plant, 325 to 650 mg
- Juice of aerial portion of *Echinacea purpurea* stabilized in 22% ethanol, 2 to 3 mL
- Tincture (1:5), 2 to 4 mL
- Fluid extract (1:1), 2 to 4 mL
- Solid (dry powdered) extract (6.5:1 or 3.5% echinacoside), 150 to 300 mg

Astragalus membranaceus

- Dried root (or as decoction), 1 to 2 g
- Tincture (1:5), 2 to 4 mL
- Fluid extract (1:1), 2 to 4 mL
- Solid (dry powdered) extract (0.5% 4-hydroxy-3-methoxy isoflavone), 100 to 150 mg

Yeast and Medicinal Mushrooms

The dosage for Wellmune WGP used in clinical trials was 250 mg of 1,3-1,6-β-glucan daily. For maitake, the dosage is based upon body weight and β-glucan content stated as MD- or D-fraction (typically 0.5 to 1.0 mg for every kilogram of body weight per day). The dosage for shiitake and reishi is based upon historical dosage levels of the dried mushrooms of 6 to 9 g/day.

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CHAPTER 57

Intestinal Protozoan Infestation and Systemic Illness

Leo Galland, MD, FACP, FACN

CHAPTER CONTENTS

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INTRODUCTION

The gastrointestinal tract is the largest organ of immune surveillance in the body, home to two thirds of the total lymphocyte population.[1] Regulatory T cells play a crucial role among the lymphocytes responding to protozoan infestation, so parasitic infestation may alter the immune response environment, exerting a major impact on systemic responses, including allergy and autoimmunity.[2] Systemic immunologic reactivity may occur in the absence of digestive complaints.[3-7]

PROTOZOA

Giardia spp.

Human giardiasis may provoke asthma,[8,9] urticaria,[10-14] arthritis,[5,14-17] and uveitis,[18] presumably by inducing immunologic hypersensitivity. Urticaria induced by *Giardia* has been associated with specific anti-*Giardia* immunoglobulin-E (IgE), which is not found in patients with intestinal symptoms only. IgE production is associated with increased activity of vascular and intercellular adhesion molecules.[19] *Giardia* may also provoke systemic illness through malabsorption or protein loss, which can occur without diarrhea.[20] Iron deficiency,[21,22] low levels of carotene and folate,[23] and abnormal absorption of vitamin A,[24-26] folic acid, and vitamin B_{12}[20] can result from chronic giardiasis and add to the burden of illness, even in patients who appear well-nourished.[25] Giardiasis may also induce small intestinal bacterial overgrowth[20,27] and jejunal candidosis,[28] each of which may independently cause systemic symptoms. *G. lamblia* may also act as a vector for double-stranded RNA viruses.[29]

Giardiasis was identified in 61 of 218 consecutive patients presenting to the author's medical clinic with a chief complaint of chronic fatigue.[30] The symptoms of patients with and without giardiasis are shown in Table 57-1. Giardiasis was strongly associated with myalgia, muscle weakness, flu-like feelings, sweats, adenopathy, and a previous diagnosis of chronic fatigue immune dysfunction syndrome (CFIDS). Cure of giardiasis resulted in clearing of fatigue and related "viral" symptoms (myalgia, sweats, flu-like feelings) in 70% of cases and in some palliation of fatigue in 18%. The association between intestinal protozoa and chronic fatigue in patients without prominent digestive complaints may not be limited to giardiasis. In an unpublished presentation, the author reported that 80% of patients with a diagnosis of CFIDS who were infected with the protozoan *Blastocystis hominis* showed significant improvement of fatigue associated with treatment that cleared the protozoa from stool specimens.[31]As in giardiasis, infestation with *B. hominis* has also been associated with several patterns of urticaria: acute, chronic, and pressure-induced.[32-34]

Entamoeba histolytica

Chronic infestation with *Entamoeba histolytica* has been associated with autoimmune phenomena, including the appearance of antibodies to colonic epithelial cells[35] and the development of ulcerative colitis after cure of amebic colitis.[36] Extraintestinal autoimmune reactions to intestinal amebiasis include a case of antiphospholipid antibody syndrome with deep vein thrombosis and pulmonary embolism[37] and development of symmetrical polyarthritis mimicking rheumatoid

TABLE 57-1 **Systemic Symptoms of Patients with Chronic Fatigue Immune Dysfunction Syndrome**

SYMPTOM	WITH GIARDIASIS (%) (N = 63)	WITHOUT GIARDIASIS (%) (N = 157)
Depression	61	41
Muscle weakness	46	19
Headache	41	36
Sore throat	41	11
Lymphadenopathy	36	8
Arthralgia	36	27
Myalgia	34	18
Flu-like symptoms	34	6
Poor exercise tolerance	30	10

Modified from Galland L, Lee M, Bueno H, et al. Giardia lamblia infection as a cause of chronic fatigue. J Nutr Med 1990;2:27-32.

arthritis.[5,38-41] Diarrhea, polyarthritis, and circulating antinuclear antibodies developed in a United States serviceman heavily infested with *Endolimax nana*, an allegedly nonpathogenic ameba.[42] Metronidazole rapidly reversed all abnormalities. Amebic arthritis may be an example of parasitic rheumatism, an inflammatory polyarthropathy produced by circulating antigen–antibody complexes.[43,44] Reiter syndrome (arthritis, uveitis, and urethritis) has been reported as a complication of infection with two other intestinal protozoa, *Cryptosporidium*[45-47] and *Cyclospora.*[48] *Cyclospora cayetanensis* has also provoked Guillain-Barré syndrome, a severe autoimmune neuropathy.[49]

E. histolytica contains a soluble lectin that is mitogenic for T lymphocytes.[50,51] Activation of helper T cells by this lectin may induce replication of human immunodeficiency virus (HIV) in vivo. In one report, soluble *E. histolytica* protein, although not mitogenic itself, induced HIV replication in tissue culture of lymphocytes obtained from three of seven men with chronic HIV infection.[52] Infection with *E. histolytica* and other parasites may promote the development of acquired immunodeficiency syndrome in HIV-infected individuals.[53,54] Epidemiologic evidence associated preexisting intestinal protozoan infection with the appearance of Kaposi's sarcoma among homosexual men in the United States.[55] Although the influence of treating intestinal protozoan infection on the course of HIV infection has not been systematically studied, treatment of intestinal helminth infestation decreased the HIV viral load among African patients with AIDS.[56] Synergism between intestinal parasites and other lymphotrophic retroviruses was considered an explanation for the pathogenesis of Burkitt lymphoma[57] and adult T-cell leukemia and/or lymphoma.[58]

DIAGNOSTIC CONSIDERATIONS

Protozoan infection is usually diagnosed with stool examination; however, comparison of results of stool microscopy and duodenal aspiration has consistently shown that stool may fail to contain identifiable parasites even at the height of acute giardiasis.[59,60] Some authorities have suggested empirical treatment for intestinal parasites in high-risk groups, such as immigrants to the United States from Asia, the Middle East, sub-Saharan Africa, Eastern Europe, Latin America, and the Caribbean, and have justified this approach on a cost-effective basis, given the safety of current medical therapies.[61] A similar case might be made for treating chronically ill patients at high risk for parasitic infection because of residence, travel, sexual practices, or the context in which illness occurred.

THERAPEUTIC CONSIDERATIONS

Artemisia annua

Numerous naturally occurring substances have antiprotozoan activity. The most extensively studied is *Artemisia annua* (sweet Annie or qinghao), a plant that yields the lactone artemisinin (qinghaosu), which is the basis for a new class of antimalarial compounds widely used in Asia and Africa.[62] Artemisinin is thought to owe its antiprotozoan effects to its content of endoperoxides and killing of parasites through oxidation. Its activity, at least in the treatment of Simian malaria, is enhanced by coadministration of cod liver oil and diminished by coadministration of vitamin E. Artemisinin has low toxicity. In addition to its antibiotic activity, it stimulates macrophages, an important component of the immune response to protozoan infestation.[63] Artemisinin may induce abortion if given during pregnancy.

Berberine

The alkaloid berberine can be extracted from the roots of several plant species, notably *Berberis aquifolium* (Oregon grape), *Hydrastis canadensis* (goldenseal) root, and *Coptis chinensis* (goldthread). Berberine has protostatic and protocidal activity against *E. histolytica, G. lamblia,* and *B. hominis.*[64-66] It has shown benefit in the treatment of giardiasis in children.[67]

Allium sativum and *Juglans nigra*

Allium sativum (garlic) and *Juglans nigra* (black walnut) have a long history of use as antimicrobials. Allicin inhibits growth of *E. histolytica* in culture[68] and may be responsible for the antimicrobial activity of garlic.[69] Human studies on the efficacy of garlic and black walnut in treatment of protozoan infections are lacking.

Intestinal Bacterial Milieu

The intestinal bacterial milieu may be important in the treatment of protozoan infestation, especially for colonic organisms like *E. histolytica*. Pathogenic strains of *E. histolytica* are able to evade lysis by both classic and alternative pathways of complement. Intestinal bacteria, *Escherichia coli* in particular, are necessary for complement resistance and for amebic virulence.[70] Gitler and Mirelman[71] suggested that ingested bacteria lowered the redox potential within the parasite and allowed the amebae to escape destruction by oxidative enzymes.[71] Mirelman et al[72] reported that one can reversibly change the zymodeme patterns of *E. histolytica* isolates from nonpathogenic to invasive by culturing amebae with the gut flora of patients who have either invasive disease or no symptoms. Optimal treatment of protozoan infection requires not only the administration of antimicrobial substances but also strategies aimed at enhancing the function of intestinal resistance factors such as secretory IgA and phagocyte function and creating a bacterial milieu that is not parasite friendly.

CONCLUSION

Intestinal protozoan infestation is a significantly underrecognized cause of systemic illness. Undiagnosed infestations with *Giardia* spp., *E. histolytica*, and other organisms have been associated with

diverse diseases such as arthritis, asthma, Reiter syndrome, urticaria and uveitis, CFIDS, increased rate of progression of HIV infection, and a wide range of systemic dysfunction, such as fatigue, malabsorption, muscle weakness, and myalgia. Effective eradication of protozoa can result in surprisingly quick and complete clinical response.

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CHAPTER 58

Maldigestion

Michael T. Murray, ND

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INTRODUCTION

Proper digestion, absorption, and elimination are necessary to gain the nutritional benefits from foods. Any disruption of these processes causes substantial, and usually progressive, health problems throughout the body. This chapter provides some overview of digestive dysfunction and ways to improve digestion. For specific digestive tract disorders (e.g., irritable bowel syndrome, peptic ulcers, inflammatory bowel disease, celiac disease), see Section 6. For information on the various laboratory procedures for evaluation of digestive function (e.g., comprehensive digestive stool analysis, intestinal permeability assessment, small intestinal bacterial overgrowth breath test), see Section 2.

THERAPEUTIC CONSIDERATIONS

Indigestion

The term indigestion is often used by patients to describe a feeling of gaseousness or fullness in the abdomen. It can also be used to describe "heartburn." In a survey of over 20,000 adults in the United States, the overall prevalence of at least 1 upper gastrointestinal symptom was reported in 45% of those surveyed (based on the preceding 3-month period); symptoms included heartburn, early satiety, loss of appetite, and postprandial fullness (bloating).[1] These symptoms of indigestion can be attributed to a great many causes, including not only increased secretion of acid but also decreased secretion of acid and other digestive factors and enzymes.

Indigestion is commonly treated with antacids or acid-blocking drugs, either chosen by patients over-the-counter or prescribed by medical practitioners. The use of these agents will typically raise the gastric pH above 3.5, effectively inhibiting the action of pepsin, the enzyme involved in protein digestion that can be irritating to the stomach. Although raising the pH can reduce symptoms, it also substantially impairs protein digestion and mineral disassociation. In addition, the change in pH can adversely affect gut microbial flora, including the promotion of an overgrowth of *Helicobacter pylori*. Finally, most nutrition-oriented physicians believe that lack of acid, not excess, is the true culprit in most patients with indigestion.

According to surveys, most people use antacids to relieve symptoms of reflux esophagitis.[2] However, reflux esophagitis is most often caused by overeating, not excessive acid production. Other common causes are as follows:

- Obesity
- Cigarette smoking
- Chocolate
- Fried foods
- Carbonated beverages
- Alcohol
- Coffee

These factors either increase intra-abdominal pressure or decrease the tone of the esophageal sphincter.

Chronic heartburn may also be a sign of a hiatal hernia. However, although 50% of people older than 50 years have hiatal hernias, only 5% of patients with hiatal hernias actually experience reflux esophagitis. Perhaps the most effective treatment of chronic reflux esophagitis and symptomatic hiatal hernias is to

BOX 58-1 Common Signs and Symptoms of Low Gastric Acidity

Bloating, belching, burning, and flatulence immediately after meals
A sense of "fullness" after eating
Indigestion, diarrhea, or constipation
Multiple food allergies
Nausea after taking supplements
Itching around the rectum
Weak, peeling, and cracked fingernails
Dilated blood vessels in the cheeks and nose
Acne
Iron deficiency
Chronic intestinal parasites or abnormal flora
Undigested food in stool
Chronic *Candida* infections
Upper digestive tract gassiness

BOX 58-2 Diseases Associated with Low Gastric Acidity

Addison's disease	Hives (chronic)
Asthma	Myasthenia gravis
Celiac disease	Osteoporosis
Dermatitis herpetiformis	Pernicious anemia
Diabetes mellitus	Psoriasis
Eczema	Rheumatoid arthritis
Gallbladder disease	Rosacea
Graves' disease	Sjögren's syndrome
Chronic autoimmune disorders	Systemic lupus erythematosus
Hepatitis	Thyrotoxicosis
Hyperthyroidism/hypothyroidism	Vitiligo

utilize gravity. The standard recommendation is to simply place 4-inch blocks under the bedposts at the head of the patient's bed. This elevation of the head is very effective in many cases. Another recommendation to heal the esophagus is the use of deglycyrrhizinated licorice.

Enteric-coated peppermint oil has been shown to be very helpful in cases of nonulcer dyspepsia and reflux esophagitis. For more information, see Chapter 105, *Mentha piperita* (Peppermint).

Hypochlorhydria

In the patient with chronic indigestion, rather than focus on blocking the digestive process with antacids, the natural approach focuses on aiding digestion. Although much is said about hyperacidity conditions, a more common cause of indigestion is a lack of gastric acid secretion. Many symptoms and signs suggest impaired gastric acid secretion, and a number of specific diseases have been associated with insufficient gastric acid output.[3-13] They are listed in Boxes 58-1 and 58-2.

Several studies have shown that the ability to secrete gastric acid decreases with age.[14-16] Some studies found low stomach acidity in more than half of the subjects older than 60 years. The best method of diagnosing a lack of gastric acid is the Heidelberg gastric analysis (see Chapter 18).[17] Wright[18] suggested that the response to a bicarbonate challenge during Heidelberg gastric analysis, not simply resting pH, was the true test of the functional ability of the stomach to secrete acid.

Because the Heidelberg gastric acid analysis is not widely available, a clinical trial of hydrochloric acid (HCl) supplements can be used as described in Appendix 7.

Etiology

Like peptic ulcer disease, achlorhydria and hypochlorhydria have been linked to the overgrowth of the bacteria *H. pylori*. Approximately 90% to 100% of patients with duodenal ulcers, 70% of patients with gastric ulcers, and about 50% of people older than 50 years test positive for *H. pylori*.[19] The presence of *H. pylori* is determined by measuring the level of antibodies to *H. pylori* in the blood or saliva or by culturing material collected during an endoscopy as well as measuring the breath for urea. A breath test is also available for assessment of current *H. pylori* activity.

Low gastric output is thought to predispose to *H. pylori* colonization, and *H. pylori* colonization increases gastric pH, thereby setting up a positive feedback scenario and increasing the likelihood of colonization of the stomach and duodenum by other organisms.[20] Not surprisingly, HCl antisecretory drugs (H_2 receptor antagonists and proton pump inhibitors) may actually promote *H. pylori* overgrowth. Patients with *H. pylori* experience an exaggerated response in elevations of pH with antisecretory therapy.[21] Eradication of *H. pylori* is associated with a return to normal gastric acidity and pepsinogen ratio.[22]

Although the typical conventional medicine approach is to focus only on the infective agent, the usual host defense factors are equally or more important. Unfortunately, research has focused on eradicating the organism, and there is little information on protective factors against infectivity. Proposed protective factors against *H. pylori*-induced intestinal damage are maintaining a low pH and ensuring adequate antioxidant defense mechanisms.[23-25] Low levels of vitamin C and vitamin E and other antioxidant factors in the gastric juice appear not only to lead to the progression of *H. pylori* colonization but also contribute to ulcer formation, because the mechanism by which *H. pylori* damages the stomach and intestinal mucosa is oxidative.[26] Furthermore, antioxidant status and gastric acid output appear to explain the observation that most people infected with *H. pylori* do not experience peptic ulcer disease or gastric cancer; for more information on natural approaches for eradicating *H. pylori*, see Chapter 198.

One natural medicine that may be useful against *H. pylori* that is not discussed in Chapter 198 is bovine lactoferrin. Lactoferrin exerts broad-spectrum antimicrobial action because it has been shown to be effective in inhibiting the growth of disease-causing protozoa, yeast, bacteria, and viruses. More important than its ability to actually kill organisms is the discovery that lactoferrin prevents the attachment of disease-causing organisms to cells that line the mouth and entire gastrointestinal tract. At the same time, lactoferrin is a powerful booster of health-promoting bacteria like *Bifidobacteria* and *Lactobacillus* species. By preventing growth of harmful bacteria while promoting the growth of beneficial *Bifidobacteria*, lactoferrin assists in the development of proper intestinal flora.

The standard medical treatment of *H. pylori* infection is a 1- or 2-week course of treatment called triple therapy. It involves taking two antibiotics to kill the bacteria and an acid suppressor drug. On the basis of results of clinical trials, lactoferrin alone or in combination with triple therapy may soon be the treatment of choice. In one study, 151 patients testing positive for *H. pylori* with indigestion symptoms were given either triple therapy alone or with lactoferrin. *H. pylori* status assessed 8 weeks after the end of the treatment indicated a 95.9% eradication rate for

the group receiving the lactoferrin; the other group had only a 72.5% eradication rate.[27] The effective dose of lactoferrin in this application is 300 mg/day.

Pancreatic Insufficiency

The most severe level of exocrine pancreatic insufficiency (EPI) is seen in cystic fibrosis. Next in severity is the EPI associated with the late stages of pancreatitis. These more severe causes of EPI are most often easily recognized, but causes of mild EPI are more insidious and difficult to diagnose. Both physical symptoms and laboratory tests can be used to assess pancreatic function in patients in whom mild EPI is suspected. Common symptoms of EPI are abdominal bloating and discomfort, gas, indigestion, and the passing of undigested food in the stool. For laboratory diagnosis, a comprehensive stool and digestive analysis (discussed in Chapter 27) is quite useful. In addition, the measurement of fecal elastase 1 concentrations using an enzyme-linked immunosorbent assay is an accepted indirect test of the exocrine pancreatic function. It shows higher sensitivity and specificity for EPI than fecal chymotrypsin determination and is comparable to oral pancreatic function tests, such as the pancreolauryl test.[28]

Pancreatic Enzyme Supplements

Pancreatic enzyme products are an effective treatment for EPI and are widely used. Most commercial preparations are prepared from fresh hog pancreas (i.e., pancreatin) (see Chapter 111 for a full discussion).

The dosage of pancreatic enzymes is based on the level of enzyme activity of the particular product as defined by the United States Pharmacopoeia (USP). A 1× pancreatic enzyme (pancreatin) product has in each milligram no less than 25 USP units of amylase activity, no less than 2.0 USP units of lipase activity, and no less than 25 USP units of protease activity. Pancreatin of higher potency is given a whole-number multiple indicating its strength. For example, a full-strength undiluted pancreatic extract that is 10 times stronger than the USP standard would be referred to as 10× USP. Full-strength products are preferred to lower potency pancreatin products because lower potency products are often diluted with salt, lactose, or galactose to achieve desired strength (e.g., 4× or 1×). The dosage recommendation for a 10× USP pancreatic enzyme product is typically 350 to 1000 mg three times per day immediately before meals when used as a digestive aid and 10 to 20 minutes before meals or on an empty stomach when anti-inflammatory effects are desired.

Enzyme products are often enteric coated, primarily to protect the more fragile porcine lipase. However, some studies have shown that non–enteric-coated enzyme preparations actually outperform enteric-coated products if they are given before a meal (for digestive purposes) or on an empty stomach (for antiinflammatory effects). In general, there is no significant difference in clinical response to various delivery forms of pancreatin.[29]

Alternatives to porcine pancreatin include plants (e.g., bromelain, papain, etc.) and enzymes extracted from various microbes or yeast (e.g., *Aspergillus oryzae*). These enzymes are more resistant to digestive secretions and have a broader range of activity, including pH range (see Chapter 71, Bromelain; and Chapter 106, Microbial Enzyme Preparations). One double-blind, crossover trial in 17 patients with severe EPI and steatorrhea compared the effects of a non–enteric-coated pancreatic enzyme preparation (360,000 lipase U/day), an enteric-coated pancreatic enzyme preparation (100,000 lipase U/day), and a fungal enzyme preparation (75,000 lipase U/ day).[30] All three treatment preparations in both groups yielded significant reduction in total daily stool weight and total daily fecal fat excretion compared with controls. It is interesting to point out, however, that the fungal enzyme preparation produced similar benefit at three-fourths the dose of enteric-coated pancreatic enzyme and one-fifth the dose of the non–enteric-coated pancreatic enzyme preparation.

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CHAPTER 59

Sports Nutrition

Jade Teta, ND, CSCS, and Keoni Teta, ND, LAc, CSCS

CHAPTER CONTENTS

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Becoming leaner, faster, stronger, and performing better for longer all while staying healthy is the hope of every athlete from the weekend warrior to the elite professional. Sports nutrition is about fueling performance, recovering from stress, building skills quickly, and maintaining optimal body composition for the sport. In this chapter we will cover the pertinent issues around sports nutrition, including supplementation for performance, fitness, and fat loss.

NUTRITION AND PERFORMANCE

Performance Nutrition and Fat Loss

Before we begin the discussion of sports nutrition, it is useful to cover the topic of body composition. Excelling and participating in sports has much to do with achieving and maintaining an ideal body composition. Athletes seek to optimize the correct ratio of muscle tissue to fat weight that allows the best performance advantage in their sport. More times than not, simply participating in the sport improves body composition. However, when it does not, an athlete may, at times, seek to increase muscle mass or decrease their fat weight. In addition, the average recreational sport enthusiast, who is not engaged in the competitive side of athletics, will often adopt the eating habits of the elite athletes in the sport they participate in. This can be a point of confusion.

The "glycogen paradigm" is a way of thinking about sports performance that seeks to maximize muscle sugar storage. This, it is believed, is the best way to increase training intensity, accelerate recovery, and improve performance. This glycogen dogma has resulted in confusion for athletes and exercise enthusiasts regarding optimal exercise for improving body composition. It has been known for some time that maximizing glycogen storage increases the performance of endurance athletes. In a 1991 study, Wagenmakers et al[1] showed this effect conclusively. However, this study also showed a direct negative association between glycogen storage and fat burning. Other studies have shown that exercise done in a glycogen-depleted state may have benefits for increasing fat loss.[2-4]

This information has consequences for athletes and weekend warriors. At times, fat loss is the key aim of an athlete. When this becomes the case, it may be important to tweak the glycogen-centered philosophy of maximizing performance to an approach that instead focuses on fat loss. Health practitioners working with athletes and the general population would be wise to remember the positive association of glycogen with performance and the negative association with fat loss.

Diet Concerns for Athletes

Nutrition for exercise performance involves fueling the body for performance. This requires optimal energy resources to make up for caloric expenditure during exercise. Athletic activities can use significant resources. High intensity daily exercise can burn from 600 to 1200 calories/day.[5-8] Elite athletes, such as professional cyclists, can burn as high as 12,000 calories/day, necessitating a large compensatory calorie intake. Caloric needs this high can be extremely difficult to obtain through food.[5-12] This makes supplementation necessary for athletes undergoing heavy training.

Health care providers advising athletes on nutrition must take many things into account. In addition to the caloric issues just described there are several other issues.

Many athletes undergoing the intense stress of training can experience loss of appetite especially after intense exercise.[13] Athletes are often also under the constraints of tight schedules of competition and travel requirements that can interrupt scheduled meals. Given the already tight training schedules, athletes can quickly become overwhelmed by considerations of food.

To account for these issues, athletes engaged in heavy training should work to assure muscle is not lost and weight is maintained. This means eating calorie dense meals and snacks that are convenient for an athlete's lifestyle. Although real and whole foods should be emphasized, the use of protein bars, meal replacement shakes, electrolyte beverages, and nutritional vitamin and mineral supplements will often be needed. Athletes should eat between four and six meals per day and should eat in consistently timed intervals. Meal and snack timing around training is also an important consideration to replenish energy and aid recovery.[13] It is important to understand that without calorie balance many supportive training aids will not provide much advantage.

Macronutrient Ratios

In addition to the caloric considerations of athletes, balancing the protein, fat, and carbohydrate ratio is also important. Recreationally active individuals are usually advised to consume from 45% to 55% carbohydrates, 10% to 15% protein, and 25% to 35% fat.[5-8] The macronutrient needs of athletes can far exceed these numbers. Carbohydrate requirements for athletes can increase up to 10% to replenish and maximize liver and muscle glycogen storage.[7,8] These carbohydrates should come from low glycemic index sources that do not cause rapid fluctuations in blood glucose. Because higher levels of carbohydrate can be hard to consume, fruit juices, energy bars, and other convenience foods may be considered.

Research related to carbohydrate intake in athletes shows there might be what we call a "carbohydrate tipping point."[7] This is a level of carbohydrate beyond which there ceases to be a performance advantage. Research suggests the body can burn 1 to 1.1 g of carbohydrate per minute, amounting to roughly 60 g of carbohydrate per hour of exercise.[7] Harger-Domitrovich et al[14] showed approximately 50 g of carbohydrate for a 165 lb individual was the optimal intake of carbohydrates for athletes. This amounts to 0.27 g of carbohydrate needed per pound of body weight each hour during exercise.

It is also interesting to note that not all carbohydrates are created equal. Research suggests that sugars composed mainly of glucose (maltose, maltodextrin, and other polysaccharides) are burned at a higher rate compared with nonglucose sugar (fructose, galactose, etc.). The combinations of these sugars seem to be most advantageous.[7] Evaluating carbohydrate sources on the relative ratios of these sugars may be wise. The glucose/fructose ratio of close to 1:1 seems optimal.

Protein

Protein makes up about half the human body's dry weight and is the second most abundant compound in the body after water. Recent research on protein intake has shown that athletes require two times or more of the reference daily intake.[7,15-20] It is now recommended that athletes involved in very high volume training consume between 0.7 and 0.9 g of protein per pound of body weight per day. This amounts to between 115 and 150 g of protein per day for a 165 lb athlete. This would be the equivalent of about five to seven 3 oz servings of chicken, fish, or other lean protein per day. Protein considerations are especially important for endurance athletes who are more susceptible to protein malnutrition due to the catabolic hormonal environment created by their sport.[20-22]

Not all protein is the same. The amino acid content of protein sources can vary and has direct bearing on quality. Different types of protein can be described as fast proteins or slow proteins.[23, 24] Slow proteins are digested more evenly and take longer to process. Fast proteins are digested more rapidly and allow amino acids to be quickly available to the body. The typical fast and slow protein sources are whey and casein, respectively. Health care providers working with athletes may want to look at slow proteins as good meal options, whereas fast protein may be great options to aid performance and recovery by timing them for intake before and after exercise. The best sources of protein are low fat and have a high biological value with optimal amino acid ratios. These sources include skinless chicken, lean beef, fish, egg whites, skim milk, lean pork, and the supplemental milk proteins casein and whey.

The International Society of Sports Nutrition published its position stand on protein intake in 2007, highlighting the following points[25]: (1) highly active individuals should consume between 1.4 and 2 g of protein per kilogram of body weight; (2) concern that protein intake within this range is unhealthy is unfounded; (3) attempts should be made to get protein from whole foods, but supplemental protein is a safe and viable method of protein intake; (4) timing protein intake before and after exercise may have benefits, including enhanced recovery and development of muscle mass; and (5) certain proteins, such as branched chain amino acids (BCAAs) have been shown to be beneficial for increasing the rate of protein synthesis, decreasing protein breakdown, and increasing recovery from exercise.[6] Exercising individuals require more protein than their sedentary counterparts.

Fat

Fat intake for athletes has several important considerations and depends on the athlete's goals and training state. In general, athletes' fat recommendations should be at or slightly greater than their nonathlete sedentary counterparts.[7] High volume athletic training has been shown to lower testosterone concentrations, and decreasing fat intake can exacerbate this effect.[26-28] Most research suggests athletes should keep their dietary fat intake at around 30% of total calories. However, ultra-endurance athletes, in particular, may go much higher than this. Athletes undergoing very intense training regimes have been shown to safely tolerate and benefit from diets containing as much as 50% of total calories from fat.[29] As mentioned previously, weight loss is occasionally a concern for athletes. In these cases, a lower fat diet may be advisable, with research suggesting a diet of 0.25 to 0.5 g of fat per pound per day.[30] Fat quality is also a concern. The polyunsaturated fatty acid ratio of ω-6/ω-3 may be a concern in immune system function and inflammatory responses. Saturated fat intake may also be associated with more optimal testosterone responses.[28] Given these considerations of fat and the emerging understanding of the different function of fats, it is wise for athletes to consume a wide range of dietary fats, with a special eye towards balancing the ω-3/ω-6 ratio.

Performance, Recovery, and Nutrient Timing

Athletes and those working with them can benefit greatly from understanding how to time meals for performance and recovery. When it comes to performance nutrition, it is useful to think about first maximizing storage capacity (i.e., filling the liver and muscle glycogen stores) and fueling exercise (i.e., having nutrients more recently consumed to fuel exercise).[5-8] Complex

carbohydrates take about 4 to 6 hours to be digested, absorbed, and then stored in the liver and muscle as glycogen.[5-8,31] Recommendations regarding carbohydrate loading for training and competition should take this into account. Morning training sessions or competition will benefit from nighttime loading strategies, whereas afternoon competition and training sessions will benefit from morning loading strategies. A light carbohydrate and protein shake roughly 45 minutes (30 to 60 minutes) before activity has been shown to improve performance toward the end of high intensity activity. The inclusion of protein also serves to spare muscle tissue by decreasing the need for the body to cannibalize its own muscle tissue.[32,166]

Although exercise sessions less than an hour require no special nutritional or hydration strategies, exercise sessions lasting longer do. Strategies that manage pre-, post-, and within workout nutritional requirements can dramatically aid performance and recovery. This is where electrolyte solutions and sports drinks consumed before and during exercise have an important role to play. These beverages can help prevent low blood sugar, optimize hydration, replace lost minerals, and reduce the immune suppression that occurs after intense long duration exercise.[33,34] A carbohydrate beverage of 6% to 8% with an equal mixture of glucose and fructose taken every 20 minutes during exercise is advised.[7,35,36] In addition, adding protein to carbohydrate intake may result in higher rates of glycogen storage after exercise.[13,33,36,37] Research suggests consumption of approximately 20 g of a rich source of essential amino acids (e.g., whey protein) combined with 40 g of a good glucose source (e.g., grape juice) taken 40 minutes before exercise may be useful and within 3 hours after exercise may improve performance and aid recovery. The addition of a small amount of fat may also be helpful in stabilizing blood glucose levels.[36]

After exercise there is a unique opportunity to fuel the body for recovery. During this "recovery phase" nutritional strategies should be instituted as soon as possible, and at least within the first 30 minutes after the cessation of exercise. A mixed carbohydrate protein beverage containing close to a 3:1 ratio of carbohydrate/protein within 3 hours after exercise appears to provide greater recovery benefits than lesser amounts of carbohydrate.[13,33,36,37,38] Upon completion of this post-workout "snack," another more carbohydrate heavy post-workout meal should be eaten again within 90 minutes.

Most athletes will taper their training by one third to one half 2 to 5 days before their event. During this time, it may be beneficial to consume 200 to 300 extra grams of carbohydrate daily. This technique has been shown to maximize glycogen storage before the event and improve performance.[36]

Water

Easily the most beneficial ergogenic aid is water. Working to prevent dehydration during exercise is one of the most useful endeavors for improving exercise performance. Intense exercise can result in significant loss of water through sweat. When this fluid is not replaced, athletic performance will suffer. A loss of 2% water through sweat can impair the ability to compete and a loss of 4% can result in the inability of the body to cool itself during exercise.[39] Athletes can lose 1 to 2 L in sweat through exercise per hour. Unfortunately, athletes cannot rely on thirst perception to regulate fluid balance.[39] There are several objective ways for athletes to measure fluid loss.[39] One way to ensure adequate hydration recovery is for athletes to weigh themselves before and after exercise and drink 3 cups of liquids per pound of weight lost through exercise. During heavy exercise athletes should consume 1 to 2 L of water or glucose and/or electrolyte beverage per hour.[39,40]

Vitamins and Minerals

It is now recommended by most medical organizations that a low-dose multivitamin be consumed daily to assure optimal vitamin status.[7,41] Few, if any, vitamins and minerals have been shown conclusively in research to have any performance benefit. However, the nutritional status of an athlete can impact quality of performance, training, and recovery.[7,41-44] When considering vitamin and mineral supplementation for athletes, health care practitioners should view their recommendations in the context of nutrient adequacy. Athletes may be more susceptible to vitamin and mineral inadequacies given the previously mentioned issues on nutrition and potential caloric deficits. Although there may be no direct benefits to performance, many vitamins and minerals aid recovery and support.[7,41-44]

Vitamin C and zinc in particular have good research suggesting immune enhancement during intense training periods.[7] Vitamin C and E, along with other antioxidant nutrients, may also protect athletes from excessive oxidative damage, which could also lead to immune suppression.[7]

Mineral deficiencies are particularly problematic for athletes. Restoring any mineral deficiencies can aid performance.[7] Certain minerals may also provide benefit for optimizing performance. Calcium is one mineral that can aid athletes. Although there is no evidence that calcium supplementation improves performance, at supplement levels of approximately 1000 mg/day it has been shown to assist athletes susceptible to osteoporosis as well as improve body composition.[45,46] Phosphorus supplementation may have ergogenic effects when supplemented as sodium phosphate, but not other forms (calcium phosphate, potassium phosphate, etc.).[47] Levels of supplementation for phosphate are 4000 mg/day (1 gram tribasic dodecahydrate sodium phosphate 4 times/day) for 3 days for endurance improvement. Sodium intake has benefit for training in the heat and reduces the risk of hyponatremia.[48] With most minerals as with vitamins, the real benefit to athletes comes when identified deficiencies are corrected. Restoring vitamin and mineral status to optimal levels can aid exercise performance.[7,41-44]

Along these lines, vitamin D is a special consideration. Vitamin D deficiency is now epidemic, and athletes have the same rates of deficiency as the rest of the public.[49, 50] In one study of elite female gymnasts, 77% were found to have vitamin D levels lower than 35 ng/mL and a full third had levels lower than 10 ng/mL.[50] In a group of athletes susceptible to prolonged and constant bone stress (i.e., long distance runners), this finding was especially troubling and underscores the need for athletes to ensure adequate vitamin D status.

Although vitamin D supplementation in those with sufficient vitamin D does not appear to increase performance, vitamin D therapy delivered to deficient athletes may improve performance.[51, 52, 53] Vitamin D is known for its role in bone metabolism. The fact that skeletal muscle has vitamin D receptors is not commonly known. As far back as the 1930s, there have been numerous reports of the beneficial effects of ultra-violet therapy on athletic performance.[53,54] There are also studies that suggest the season of training makes a difference. One of these studies showed that training in the summer months creates greater gains than the same volume of training in autumn or winter despite the same stimulus.[54]

In both older and younger individuals, adequate vitamin D status impacts neuromuscular function and may have a specific relationship to the maintenance of the fast twitch type 2 muscle

fibers.[49,51,53,55,56] In a study on teenage athletes, vitamin D deficiency lowered muscle power and force.[57] Vitamin D levels are also related to myalgia, fatigue, and reduced motivation to exercise. Studies in older adults showed that levels of vitamin D were correlated with the propensity to fall.[58] A meta-analysis on vitamin D levels showed a 20% reduction in the risk of falling in those with higher levels.[59] This was likely due to vitamin D's ability to improve reaction speed, balance, and neuromuscular performance. Much of this may be explained by the ability of vitamin D to help maintain and even build type 2 muscle fibers.

Athletes should be tested for vitamin D levels with a serum 25-hydroxy vitamin D laboratory test with a target between 50 and 100 ng/mL. If they are found to be insufficient, a combination of supplementation and sun exposure is advisable. For quick restoration of adequate vitamin D levels, 50,000 IUs of vitamin D per week for 12 weeks has been shown to allay symptoms of vitamin D deficiency. Maintenance doses of between 1000 and 10,000 IU/day, depending on sun exposure and living latitude, should also be considered to prevent deficiencies.



ASSESSMENT

Laboratory Evaluations for Sports Nutrition

Nutrient deficiencies can impact many aspects of physical performance, recovery, and immune function. Athletes, because of the imposed increases in metabolism, can be at an increased risk for nutrient deficiencies. Serum testing is a reliable and useful tool for diagnosis of severe nutrient deficiencies, but may be inadequate for certain vitamins and minerals.[60] Therefore, it is useful for those working with athletes to have more functional tools for assessment of metabolic and nutritional needs.

Testing blood for nutritional levels can be misleading. Serum nutrient concentrations are closely regulated by the body and can fluctuate based on recent intake. Furthermore, some vitamins and minerals are almost entirely found intracellularly. As stated by Lord and Bralley in their textbook *Laboratory Evaluations for Integrative and Functional Medicine*, "for various reasons specific to each vitamin, it is possible for an individual to have normal serum levels of a vitamin while exhibiting signs of insufficiency for that vitamin owing to a lack of adequate intracellular concentration to meet the metabolic demands of the cells."[60] Given these factors, serum may not always be the best means of determining nutritional status for all nutrients. There are now a range of laboratory analyses that can give more functional assessments of nutrition status.[60] The ones that may be most beneficial are adrenal hormone profiles (cortisol and dehydroepiandrosterone [DHEA]), organic acid testing, and intracellular nutrient analysis.

Adrenal Hormone Testing

Analyzing the adrenal hormones cortisol and DHEA can give insight into training status and whether an athlete may be overtraining or overreaching.[61-63] Cortisol and DHEA provide a good indication of catabolic versus anabolic balance in the body as well as neuroendocrine adaptation to stress. The test is simple and noninvasive, involving salivary collection at four time points during the day (morning, noon, evening, and night). Depending on the laboratory, the cortisol and DHEA test may also provide markers of immune function, such as immunoglobulin-A. All these measures are important for athletes looking to compete at high levels for prolonged periods.

The body goes through four stages in response to stress. Stage 1 occurs in response to acute stress and involves elevations in cortisol with no changes in DHEA. Stage 2 involves continued stress and is marked by a sustained cortisol peak with a matching elevation of DHEA. At stage 3, when stress continues and becomes chronic, cortisol levels drop, whereas DHEA stays high. Finally, both cortisol and DHEA fall, a stage often referred to as adrenal exhaustion or stage 4.

Testing athletes for levels of adrenal hormones gives important guidance concerning nutritional therapy and supplementation. Cortisol is a highly catabolic agent, and increased cortisol levels with normal to low DHEA indicate excessive stress and potential muscle wasting.[60] This necessitates increased protein intake, especially increased glutamine.[64] High cortisol levels also give an indication of increased need for other nutrients that are easily depleted through increased metabolic activity (e.g., magnesium, zinc, and vitamin B_6).[60] Cortisol suppressing supplements, such as phosphatidyl serine, may also be indicated,[65] as is the potential for DHEA supplementation and/or immune support.[66] Changes in adrenal hormones may occur long before seeing clinical symptoms and can be used to monitor training status and recovery.

Organic Acid Testing

Organic acid testing is a useful analysis that looks at metabolic by-products in urine.[60] The test does not measure actual vitamins and minerals but assesses them indirectly by measuring excreted metabolic by-products. Although the test is not diagnostic, it can be used to analyze the metabolic consequences of insufficient nutrient intake. It can also give insight into toxic exposures, amino acid need, and neuroendocrine function.

Fats, proteins, and carbohydrates become carboxylic acids before they are completely burned to carbon dioxide. These acids, formed by the body's metabolic processes, are usually low or nonexistent in urine. When perturbations occur in metabolism due to inefficient enzymes as a result of genetic polymorphisms and/or lack of a vitamin or mineral cofactor, the metabolic by-products can build up in the cell, be released into the blood and then begin to show up in the urine. The organic acids that appear can then be traced back to known biochemical pathways, indicating a particular nutrient need.

Given the fact that almost all nutrients become ergogenic when there is a deficiency or increased need, organic acid testing may be useful in understanding what nutrients may be indicated for a particular athlete and if the supplements they are currently taking are actually doing the job. Using organic acid testing may provide health care practitioners working with athletes a way to pinpoint potential nutrient issues and bolster key metabolic pathways.

Intracellular Nutrient Analysis

Because many nutrients, like magnesium, are not well measured in serum, another useful functional analysis for athletes is intracellular nutrient analysis.[60] This testing involves drawing blood, and isolating white blood cells and growing them in a nutrient rich medium. Individual nutrient concentrations are then manipulated one by one while measuring cell growth rates. Cellular growth from an athlete with insufficient levels of a nutrient will be slower than from an athlete with sufficient levels.[67] This allows tailored nutrient supplementation to optimize intracellular levels of all nutrients.

Amino Acids Testing

Due to the high turnover of amino acids required in the participation and recovery from intense exercise, amino acid analysis can be useful for athletes.[60,68] When testing athletes for amino acids, it

may be useful to measure plasma levels, urine levels, and organic acids. Plasma levels give the best indication of protein utilization and are the most scientifically validated. However, urinary amino acids may give greater insight into protein breakdown from factors interfering with amino acid utilization (i.e., micronutrient deficiency or toxic exposures). These two measures along with the ability to map biochemical pathways through organic acid testing can provide an athlete with in-depth information as to protein utilization, breakdown, and metabolic needs.

CRITICAL EVALUATION OF ERGOGENIC AIDS

It is important for the health care practitioner to be aware of the large gap that often exists between supplement marketing and research. Given that nutritional supplements are not regulated to the same degree as pharmaceuticals, and little financial incentive exists to research natural compounds, it is important to look for valid and objective resources on nutritional supplements. When evaluating whether a nutraceutical might be useful, it is important to keep several things in mind.[7]

A good first question to ask is "does the basic science make sense?" Natural health practitioners need to be good students of biochemistry and physiology. Knowing the compound and its involvement in biochemical pathways is a necessary first step. If the mechanism of action "makes sense" from a biochemical perspective, the supplemental aid may have merit. A good example here is the use of the nutrient L-carnitine. Understanding the biochemistry of this nutrient as key in delivering fat to the mitochondria to be burned for energy allows suspicion that it may have fat loss and performance benefits.

The next question is "is it feasible to deliver the nutrient in a form that can actually be absorbed and utilized by the body?" Although a nutrient may seem like a perfect candidate for performance enhancement properties, if it cannot be delivered to the body in a safe, feasible, and usable form, it will not have much use. In the case of L-carnitine, there are several issues that warrant consideration. First, L-carnitine is not well absorbed; therefore, understanding the different delivery forms is essential. Would L-carnitine bound to tartrate, fumarate, or another molecule be most feasible for delivery? Also, in the case of amino acids like carnitine, there are two forms, L-carnitine and D-carnitine. L-carnitine is active in the body, whereas D-carnitine is not and can actually block the action of L-carnitine. Confidence would therefore be less on studies using the racemic mixture of this nutrient versus those using pure L-carnitine.

Another important consideration is "does any good research exist on the substance?" Are the studies in vitro or in vivo studies? Were they animal or human studies? Was the sample size big enough? Was the study designed appropriately? Was it well controlled? Human clinical trials with a large sample size that are double blinded and placebo controlled are obviously the gold standard and should be weighted heavier. However, these types of studies often do not exist for sports performance supplements, accounting for much of the skepticism regarding sports performance aids. Much of this skepticism is warranted, although discounting a supplement purely on the basis of lack of these types of trials is probably not wise.

Some final considerations would be whether or not the product is safe, legal, and appropriate. In 2006, the 109th Congress passed the Dietary Supplement and Nonprescription Drug Consumer Act. This law requires supplement companies to disclose all complaints about their products and make them available to the public. For supplement issues that are more serious in nature, the companies must notify the Food and Drug Administration within a 2-week time frame. There are also consumer bodies that help police the industry. These organizations independently test supplement products against claims of efficacy and issues with contamination and can be useful resources to those advising supplement use. Finally, there are always products that are completely safe that may present issues in certain populations. All these considerations should be evaluated when using nutritional supplementation.

GENERAL HEALTH CONCERNS FOR ATHLETES

The American Medical Association has suggested Americans use supplemental vitamins to maintain health; these recommendations seem especially prudent in the athletic world. Although there is no performance benefit to the use of multiple vitamins and minerals, as discussed previously, athletes can be susceptible to deficiencies and/or require more support in areas due to increased vulnerability of stress or injuries encountered during sports. Glucosamine can aid in the healing of damaged cartilage and lessen joint pain.[69] Supplements such as zinc, glutamine, vitamin C, lipoic acid, selenium, and other nutrients may support immune function and antioxidant capacity.[5-7,70-72] Amino acids are especially useful. Creatine, whey protein, BCAAs, and L-carnitine tartrate have all been shown to help athletes through the stress of intense training periods.[5-7] Finally, ω-3 fats can help balance inflammatory and anti-inflammatory reactions in the body.

NUTRITIONAL SUPPLEMENTS

Obviously, a full treatment of all the nutraceuticals purported to have beneficial effects in exercise and body composition could fill an entire book. We selected the compounds discussed here that demonstrated the most research supporting their use as ergogenic aids. We attempted to avoid looking at compounds that have strong theoretical support for their use, but have not yet been studied. We gave special consideration to compounds that have been studied in humans and have been evaluated under double-blinded and placebo-controlled conditions. Newer compounds that did not meet these criteria may not be covered. In certain cases, we covered compounds that are novel in their reported use as ergogenic substances.

Arginine

Arginine has several potential benefits for athletes, including increasing human growth hormone production, increasing blood flow, increasing mitochondrial biogenesis, and increasing fat loss and muscle gain. Many of these effects are related to nitric oxide, for which arginine is a precursor. However, several of these benefits are relatively new discoveries regarding arginine supplementation. Animal studies and human studies showed arginine might have particular benefit in improving exercise capacity and body composition.

Arginine may play a role in endurance performance. A 2010 study showed that a proprietary arginine supplement given to elderly male cyclists was able to positively impact performance. The arginine supplement significantly increased the anaerobic threshold within 1 week of beginning supplementation, with the effect lasting throughout the 3-week study.[73] There was no change in maximal oxygen consumption (VO_2max) in this particular study. However, in another study, this time on younger cyclists, oxygen kinetics were sped up in relation to L-arginine

supplementation.[74] Another study in 2010 showed arginine's potential role in illness associated with reduced cardiovascular capacity.[75] In this analysis, arginine supplementation improved exercise capacity in heart transplantation patients, resulting in furthering the distance walked and delaying the ventilatory threshold by 1.2 minutes.

In addition to endurance benefits, arginine may also have a role to play in strength training. An April 2010 study showed increased growth hormone and insulin-like growth factor 1 release in response to heavy resistance training.[76] This newer study lends credibility to older reports.

Research on rats, pigs, and humans showed arginine to be a potential antiobesity aid through several unique mechanisms.[78] Supplemental arginine appears to have activity that increases glucose and long-chain fatty acid oxidation while at the same time suppressing gluconeogenesis and lipogenesis. In rats, L-arginine was shown to increase muscle mass by 12% and increase glucose metabolism by 14% without impacting insulin. Most interestingly, arginine was shown to coax white adipose tissue to become brown adipose tissue and, as a result, significantly elevated the metabolic rate. Arginine appears to act partly via its conversion to nitric oxide. It may act via cyclic guanosine monophosphate and cyclic adenosine monophosphate dependent mechanisms. It was found to increase mitochondrial biogenesis, upregulate GLUT-4 receptors, and improve muscle mass.

A 21-day randomized and double-blind, placebo-controlled study of arginine in obese men was conducted in 2006 by Lucotti et al.[79] Thirty-three obese males were put on a low calorie diet (1000 kcal/day) and an exercise program (45 minutes of exercise twice per day for 5 days/week). They were then randomized to receive 8.3 g/day of arginine or placebo. As expected, the lifestyle intervention resulted in weight loss, waist circumference reduction, lowered fasting glucose, and reduced insulin in both groups. However, the arginine group had statistically better responses in most measures compared with the placebo group (P <0.0001). Most interestingly, the arginine group was able to maintain their muscle mass, whereas the placebo group had significant reduction in lean body mass. Forty-three percent of the weight lost in the placebo group was fat compared with a full 100% for the arginine group.

Dosage

The appropriate dose of arginine based on the animal and human studies appears to be 80 mg/kg body weight per day or 3 g three times daily for a 155 lb adult. Results of the National Health and Nutrition Examination Survey indicated arginine intake in the United States averages about 4.4 g/day with 25% of the population receiving suboptimal levels.[78]

Other Considerations

Both animal and human studies suggest there are no safety concerns related to arginine supplementation when taken in appropriate doses and in an appropriate form. There is a theoretical concern that increased arginine supplementation will alter the arginine/lysine ratio and possibly increase herpes virus activity. Arginine is also known to increase the inducible form of nitric oxide synthase resulting in potential negative cytokine activity and immune consequences. This is a special concern for those suffering from autoimmunity.

Beta-Alanine

Beta-alanine is a precursor, along with histidine, of carnosine and is found in high concentration in skeletal muscle. It is widely assumed carnosine has performance benefits due to its ability to resist pH changes in muscle. In one study, oral intake of β-alanine for 4 weeks was shown to increase carnosine levels.[80] Another study showed supplementation with β-alanine for 10 weeks significantly elevated carnosine levels at weeks 4 and 10.[81] Subjects taking β-alanine have been shown to complete a greater number of repetitions during resistance exercise,[81-82] resist fatigue, [81,83,104] generate greater force with the legs,[84] optimize the hormonal response to exercise,[84,85] and even improve body composition.[82]

Dosage

Typical doses in studies range between 400 and 800 mg given multiple times throughout the day to achieve between 4 and 8g. Doses above 800 mg at any given time may cause transient paresthesias. β-alanine appears to have a low toxic profile and is generally considered a safe nutraceutical.

Beta-Hydroxy Beta-Methylbutyrate

Beta-hydroxy beta-methylbutyrate (HMB) is derived from the BCAA leucine. HMB use at levels from 1 to 3 g/day while undergoing weight training may increase strength results and have positive impacts on lean muscle gains.[86-88] The largest and most beneficial responses come from studies in the untrained. Older individuals may also enjoy benefits from supplementation. Volkovich et al, in 2001, showed 3 g of HMB daily over 8 weeks given to elderly men and women led to significantly greater loss in fat compared with a placebo group.[89] Muscle mass gains usually ranged from 1 to 2.2 lbs over 3 to 6 weeks of training for those taking HMB versus placebo.[7]

Performance benefits in athletes or well-trained individuals are not as convincing as results in untrained subjects. However, at least one quality study by Knitter et al, in 2000, showed HMB might protect against muscle damage from exercise.[90] Well-trained runners were supplemented with 3 g/day over 6 weeks. Compared with placebo, HMB supplemented runners had lower markers of muscle damage.

Dosage

The dose of HMB shown to be effective is 1 to 3 g/day.

Other Considerations

HMB supplementation along with creatine may behave in a synergistic fashion.[91] HMB is generally considered safe to use.

Branched Chain Amino Acids

BCAAs are perhaps the most beneficial aspect of increased protein intake. They have been shown to increase protein synthesis, decrease protein breakdown, and speed recovery from exercise.[92,93,94] Newer research suggests they may have some acute performance enhancement effects and play a key role in body composition.[95,96,97]

BCAAs include leucine, isoleucine, and valine. The body is not able to synthesize these amino acids, making their dietary intake essential. BCAAs are necessary for production of other amino acids, most notably alanine and glutamine, two of the most important amino acids used in gluconeogenesis. Low calorie diets and stress can greatly increase the need of amino acids precursors for gluconeogenesis. A large pool of BCAAs through dietary intake spares muscle protein breakdown and likely promotes muscle protein synthesis.[98,99, 165]

BCAA supplementation has shown some impact on exercise performance, perceived exertion, and recovery. Matsumoto et al[97] had subjects drink either a BCAA beverage or a placebo 6 days

before performing high intensity cycling until exhaustion. The trial was a double-blinded, crossover, placebo-controlled study with a 1-week washout period between exercise sessions. BCAA increased plasma levels of leucine, isoleucine, and valine during the exercise test. The contribution of fat burned during the exercise session was significantly greater for BCAA compared with placebo, as was the oxygen uptake and lactate thresholds at equivalent work levels. VO_2max was also greater in the BCAA supplementation. Taken together, these results suggest BCAA supplementation may improve endurance exercise performance.

Another study by Greer et al[94] looked at BCAA for endurance exercise improvement. This study did not show an acute performance advantage for BCAA during exercise, but did show reduced damage. BCAA supplementation was significantly better than either a carbohydrate beverage or placebo at reducing markers of muscle damage. An earlier study by the same group showed comparable findings.[96] There are similar findings on enhanced recovery from exercise using BCAA in response to high intensity weight lifting.[93]

One of the more intriguing aspects of BCAA supplementation may be its role in optimizing body composition. Low calorie diets and aerobic exercise are both known to reduce lean muscle tissue. BCAA supplementation attenuates this response and helps maintain muscle mass.[95] In addition, BCAAs, specifically leucine, have unique actions as metabolic signaling molecules that may be able to increase energy expenditure,[100] suppress appetite,[103] and lower insulin.[102] Although all these relatively new mechanisms have only been shown in mice, one small pilot study including BCAA supplementation suggested that the same mechanisms may be at play in humans.[101] Fifty-nine healthy subjects participated in the study and were divided into a placebo group (fiber) and then given either a high concentration (12 g/day) or low concentration (6 g/day) BCAA supplement. Subjects were supplemented for 14 days and were encouraged not to modify either eating behavior or exercise habits.

Degree of weight loss was directly correlated with dose of BCAA given, with the largest weight loss being achieved in those who received the 12 g/day dose. Given the short time of the study, statistical significance was not achieved. The authors noted, "Design of this pilot study has more effects than can be analyzed satisfactorily with available sample sizes. An analysis with 'best possible' outcome did show that significance would have been possible with maximum weight loss difference from one group to another." Based on this study, it is not yet possible to make a determination as to BCAA supplementation in weight loss. However, given the new understanding of BCAA signaling, the promising results in animals, and the interesting, although not significant, findings of this study, further study certainly seems warranted.

Dosage

Most research suggests a dose of between 6 and 12 g/day of BCAA.

Other Considerations

Given that the dosages of BCAA are so high, it may be impractical to recommend this supplement in capsule form. BCAA powders are widely available and may provide convenience. Mixing BCAA powder in a small amount of high glucose fruit juice, such as grape juice, may help increase compliance by masking the bitter taste and increasing absorption and utilization.

Caffeine

Perhaps the most well-known performance-enhancing aid is caffeine. The consensus of studies show caffeine has value in endurance exercise performance, anaerobic exercise outcomes, exercise recovery, and weight loss.[105-107] In the body, caffeine absorption occurs rapidly and is then metabolized in the liver into theophylline, theobromine, and paraxanthine. Caffeine is lipid soluble, giving it quick access to the brain and other tissues. Caffeine is detectable in blood within 15 minutes of intake, reaching peak levels at 1 hour. Caffeine is cleared from the system in 1 to 12 hours depending on the individual's activity of CYP1A2.

Caffeine exerts strong influence on the nervous system, impacting both the central nervous system and peripheral nervous system. Several reviews on caffeine suggest this is the most beneficial action of caffeine related to performance enhancement.[105-107] It acts to increase mental focus and fine motor skills. Beta-endorphin concentrations also rise with caffeine consumption, possibly resulting in decreased pain perception during intense activity. Also, the nervous system activation plays a strong role in sports, requiring bursts of speed and intensity.

Caffeine spares muscle glycogen and shifts metabolism toward the increased use of fat both from subcutaneous and intramuscular compartments.[107-109] Given that fat oxidation is a key component of endurance sports, caffeine can improve outcomes in long distance events. It also has an interesting impact when dosed along with carbohydrate. A carbohydrate electrolyte beverage (6% glucose) spiked with caffeine (5 mg/kg of body weight) was able to bolster endurance performance by 9%.[109]

In high intensity exercise, caffeine raises catecholamine production, increasing both lipolysis and glycogenolysis.[105-107] This, along with increased activation of the central nervous system, may be the mechanism responsible for better performance in high intensity endeavors. In 2006, Schneiker et al[110] compared 6 mg/kg of body weight caffeine ingestion to placebo in amateur male athletes. In this study, either caffeine or placebo was taken 60 minutes before two 36-minute exercise sessions consisting of multiple short sprints separated by 2 minutes of recovery. Caffeine intake increased sprint performance 8.5% and 7.6% over placebo in the first and second bouts, respectively. Caffeine also increased power output compared with placebo.

This same combination, carbohydrate and caffeine, may also have a role to play in recovery from activity. In a study comparing a carbohydrate recovery beverage alone versus one spiked with caffeine, glycogen synthesis was increased by 66% in the carbohydrate plus caffeine group.[111] This may be mostly due to caffeine's ability to increase the absorption of glucose from the digestive tract into the bloodstream.

Caffeine's suspected activity as a fat loss aid comes from its epinephrine inducing effects. Studies as far back as 1990 showed as little as 100 mg of caffeine, the equivalent to a cup of coffee, could increase thermogenesis in even habitual coffee drinkers.[112] Other studies on caffeine showed increased fat oxidation with one older study showing a 30% greater blood free fatty acid level 2 hours after workout compared with placebo.[105-108]

Dosage

Caffeine intake appears to be different from coffee intake. Although the research on pure supplemental caffeine consumption is fairly clear on performance benefits, coffee consumption is less clear. Caffeine consumption shows impact when taken from 15 to 60 minutes before exercise at a dose of 6 mg/kg of body weight. For a 160 lb individual, this is the equivalent of about 430 mg of caffeine. An 8 oz cup of coffee has about 150 mg of caffeine on the high end. This amounts to close to 3 cups of drip coffee as the dose for a 160 lb individual.[105-107]

Other Considerations

Concerns about coffee intake and risk of dehydration are unfounded. There is no good evidence to suggest caffeine intake leads to an increased risk of dehydration. Users of caffeine will develop some tolerance. Nonhabitual users experience slightly better benefits from coffee intake versus regular users. Coffee intake can also have a negative impact on digestive function.[105-107]

Coleus Forskohlii (Forskolin)

Coleus forskohllii is a native plant of India and has been used in Ayurvedic medicine for centuries as a skin aid and respiratory tonic. It has seen renewed interest in the west as a potential aid for fat loss. Forskolin is an interesting compound that seems to have catecholamine-like action by increasing cyclic adenosine monophosphate without the stimulatory effect on the cardiovascular system.[113] This, theoretically, could enhance fat loss.

Henderson et al[114] looked at a group of 23 females supplemented with the herb. The subjects were randomized in a double-blinded fashion and given 250 mg *Coleus forskolhlii* standardized to 10% forskolin for a period of 12 weeks. The supplement did not aid fat loss, but did attenuate weight gain during the study. A study by Krieder et al[115] showed that forskolin reduced the loss of lean muscle tissue that occurs on low calorie diets.

A 2005 article by Godard et al[116] may be the most promising study on the potential of forskolin. The study tracked 30 men who consumed 250 mg standardized coleus extract or a placebo for 12 weeks. The study did not mention changes in diet or exercise. Before supplementation, subjects had body fat, muscle mass, bone mass, and testosterone levels analyzed. At the end of the 12 weeks, the 15 men receiving the forskolin had improvements in all measures. They reduced their fat weight by 4.5 kg (9.9 lbs) on average and their muscle weight increased 3.7 kg (8.1 lbs) on average. Bone mass was positively impacted, and testosterone levels increased by 16%. Although the marked lean mass gains bring up many questions (gains of this magnitude in such a short time are highly unlikely), this study does provide interest in the outcomes of future and better-controlled trials on this compound.

Dosage

Most studies have used extracts of *Coleus forskohlii* between 100 and 250 mg standardized to between 10% and 20% forskolin.

Creatine Monohydrate

The International Society of Sports Nutrition has called creatine "the most effective nutritional supplement available to athletes to increase high intensity exercise capacity and muscle mass during training."[7] All the performance-enhancing benefits are hypothesized to come down to two factors, increasing the amount of energy available in the form of adenosine triphosphate and increasing cellular hydration.

Creatine has been under investigation for over 60 years. It is highly concentrated in muscle tissue, with all but 4% to 5% of body creatine residing in the muscle. Most of the creatine in the body is in a phosporylated form called phosphocreatine. The major function of this supplement is to provide a rapid source of energy.

Although creatine can be made in the body, it requires significant resources, including the amino acids arginine and glycine, magnesium, methionine, vitamin B_{12}, and folate, among others. Creatine is also present in the food supply and is especially rich in animal protein. The highest concentrations are found in lean cuts of red meat, game meat, and fish, including salmon and tuna. Two pounds of lean red meat contains close to 5 g of creatine. Cooking food may have a negative impact on the availability of creatine.

Phosphocreatine is able to supply adenosine triphosphate for the energy required for quick bursts of activity lasting around 10 seconds. Once these high energy phosphates are depleted, the body relies more heavily on anaerobic metabolism. Supplementation of creatine is thought to "supersaturate muscle" and allow for greater performance of short explosive exercise.

Another benefit of creatine that may be key is cellular hydration. Creatine storage in the muscle is thought to increase muscle water content. Research has shown hydrated muscle tissue may be better able to both synthesize new muscle tissue and resist protein breakdown.[5,7,8,116]

Studies on weight training and high intensity interval exercise showed creatine as a reliable and beneficial training aid. Rawson et al[117] in an April 2011 study showed that compared to placebo a low dose creatine supplement (approximately 2 g daily) taken for 6 weeks significantly enhances the ability of muscle to resist fatigue.[117] Kerksick et al[118] showed 4 weeks of creatine supplementation significantly improved both strength and lean body mass when loaded at 20 g/day for 5 days followed by 5 g/day. In another study on creatine, 23 young males were divided into a creatine group or a placebo group.[119] The creatine dose was 5 g four times daily for 6 days. Both before and 7 days after supplementation, participants did 30 seconds of maximal sprinting on a bicycle ergometer. This was repeated five times with 2 minutes rest in between. The creatine group enjoyed greater power output and less fatigue compared with the placebo group. There was 7.6% increased power in the creatine group from the first to the second test, whereas the placebo group saw no improvement.

Creatine may also increase recovery from intense exercise and increase lean body mass.[77,101-103] Lean body mass gains can be significantly greater with creatine than with controls while weight training. A review by Krieder et al[77,120] determined creatine supplementation could generate a 2 to 5 lb greater muscle gain over 4 to 12 weeks of training compared with nonsupplementation.

Dosage

Creatine monohydrate is the most studied form of creatine. Dosage of creatine is usually prescribed in two ways, a loading dose "fast dose" or a maintenance dose "slow dose." Creatine loading, or "fast dosing," is the most studied protocol and reliably saturates muscle creatine stores. This dose entails 0.3 mg/kg of body weight daily taken in divided doses every 2 to 4 hours over 3 to 5 days. This essentially amounts to 20 to 30 g of creatine monohydrate daily for a 160 and 220 lb individual, respectively. Thereafter, the maintenance dose is used and consists of 3 to 5 g of creatine daily. Dosing the maintenance dose from the beginning or "slow dosing" involves consuming 2 to 5 g/day over 3 to 4 weeks. Dosing creatine with a small amount of glucose rich juice, such as grape juice, can improve muscle saturation, but has not been shown to increase performance benefits.[7,116]

Other Considerations

Creatine has now been studied extensively in several reviews, and long-term studies on safety have shown it to be safe in adults and adolescents. The only potential drawback to creatine use may be in those predisposed to fat gain.[116,121-123] There also may be implications for testosterone metabolism with creatine, because one study showed increased testosterone to dihydrotestosterone conversion with creatine intake.[124]

Green Tea Extract

Tea catechins from green tea have been consumed in Asian countries for centuries. Habitual green tea consumption has been shown to be correlated with lower body weights and less body fat.[125] Studies have shown extracts of catechins from green tea can increase oxidation of fat both at rest[126] and while exercising.[127]

Dulloo et al[126] showed green tea intake elevated 24-hour resting energy expenditure with increased fatty acid oxidation compared with an equal amount of caffeine taken alone. A 90 day-clinical trial combining green tea extract (GTE) with a low calorie diet resulted in significantly greater weight loss compared with a non-treatment group (30 vs 11 lbs).[125] Interestingly, the activity of GTE may have particular use against abdominal fat.[128]

Ichnose et al[129] conducted a double-blind placebo-controlled trial of GTE intake over a 10-week period. Exercise testing was done before and after the 10-week supplementation. Subjects received either a placebo or GTE (573 mg total of green tea catechins). Both the placebo and GTE contained equal caffeine content. In addition to the supplement, both groups exercised by cycling at 60% VO_2max 60 min/day, 3 days/week. At the conclusion of 10 weeks, no changes in performance parameters were noted between groups. However, there was a statistically significant increase in fat utilization for the GTE group, but no change in the placebo group.

Dosage

GTE dosage is usually 300 to 500 mg of a standardized extract daily.

Other Considerations

GTE can cause nausea in susceptible populations. It is also frequently combined with caffeine.

Pickle Juice

Athletic trainers have used acetic acid given in the form of pickle juice (PJ) anecdotally for some years. Several studies in the last several years have hinted there may be some benefit. Cramping due to electrolyte perturbations is something athletes and their trainers seek to mitigate. PJ compared with other electrolyte beverages contains high amounts of sodium, thereby replenishing sodium concentrations with very small volumes.

PJ tends to be high in sodium, requiring significant dilution to meet the guidelines for the regulatory body of the National Athletic Trainers Association (NATA). Dale et al,[130] in 2003, showed analysis of two brands of PJ greatly exceeded NATA guidelines for sodium and would require significant volumes of fluid for dilution. Here is a statement from that article explaining dilution criteria with PJ: "The NATA fluid-replacement guidelines suggest that the Na^+ concentration in rehydration beverages should range from 0.3 to 0.7 g Na^+/L. A hypothetical 0.06-L (2 fl oz) loading dose of 390 mg PJ contains 1.026 g Na^+, which would require 1.47 L of water (about 50 fl oz) to dilute the PJ to the upper limit of 0.7 g Na^+/L. Whether some athletes would ingest this large quantity of water before or during exercise is questionable, and if multiple doses of PJ are ingested, the volume of water needed to dilute the PJ to reasonable Na^+ concentrations would need to increase."

The concerns raised in the Dale et al study seem to be inconsequential according to two newer studies by Miller et al in 2009 and 2010. In the first study, 1 mL/kg body mass of PJ was ingested by nine well-hydrated men.[131] This was compared in crossover design with tap water and a carbohydrate electrolyte beverage. Resting blood samples were then taken in 5-minute increments up until 45 minutes and then again at 60 minutes. Plasma electrolytes were analyzed as well as blood volume and other measures. It was determined that the volumes tested of the PJ or carbohydrate drink did not create substantial changes in plasma electrolytes. The conclusion of the study was: "Concern that ingesting these volumes of pickle juice might exacerbate an athlete's risk of dehydration-induced hypertonicity may be unwarranted."

A second study by Miller et al[132] showed that PJ was effective at allaying muscle cramps in athletes, but that the mechanism might be neural and not electrolyte mediated. In this study, dehydrated subjects had cramps induced using electrical stimulation to determined length of cramping. They were then stimulated a second time after ingestion of water or PJ. The PJ induced statistically significant cramping reduction times. The researchers determined this mechanism was not coming from fluid volume shifts or restoration of electrolytes, but rather through neurally mediated signals originating in the mouth that were inhibiting the firing of α motor neurons.

Dosage

The effective dose of PJ to decrease cramping is 1 mL/kg or about one third of a cup for a 160 lb individual.

Quercetin

Quercetin is a bioflavonoid present in a variety of foods, including black and green tea, capers, apples, onions, grapes, citrus fruit, tomato, broccoli, leafy green vegetables, and a number of berries. Davis et al[133] conducted a small double-blinded, placebo-controlled crossover trial on quercetin's impact on endurance capacity. Baseline VO_2max and time to exhaustion were determined for 12 participants before 7 days of supplementation with either quercetin (500 mg twice daily) or placebo. On follow-up testing, the quercetin group saw statistically significant increases in time to fatigue (13.2%) and VO_2max (3.9%) compared with placebo. Similar but more modest results were seen by Nieman et al[134] in untrained subjects. Dumke et al[135] showed no effect of quercetin on trained subjects.

Dosage

The dosage of quercetin based on the previously mentioned studies is 1000 mg/day in divided doses.

Rhodiola

Rhodiola rosea is widely regarded as an "adaptogen." Adaptogens are defined as substances that aid the physiology in the proper adaptation to stress, increasing function where it may be low and lowering it when it may be high. Anecdotal, animal, and some human research has hinted *Rhodiola* may have ergogenic properties.[136-139] Several studies on *Rhodiola* suggest it may have benefit for performance, but the consensus leans more towards increased ability to adapt and recover.[137-139]

The most recent study on *Rhodiola* was completed by Parisi et al,[140] in which 14 competitively active males between the ages of 20 and 35 were supplemented daily for 4 weeks with 170 mg of *Rhodiola rosea* extract. All subjects completed VO_2max testing before supplementation. At the conclusion of 4 weeks, 30 minutes of cycling at 75% of VO_2max was completed. The subjects then had a 2-week washout period where no supplementation was taken. This was followed by 4 more weeks of supplementation of placebo. At this point, the testing was repeated.

During the pretrial tests as well as the testing post *Rhodiola* and placebo supplementation, participants had blood drawn before, during, and after testing. Their rating of exertion was also monitored via the Borg exertion scale. There were no differences in this test in any performance parameters, including perceived exertion. Both lactate and creatine kinase levels were reduced post-exercise in the *Rhodiola* group. The *Rhodiola* group also had increased levels of total antioxidants compared with placebo.

Dosage

Typical dose ranges are between 100 and 600 mg/day of *Rhodiola rosea* extract standardized to 3% rosavin + 1% salidroside. *Rhodiola* appears to have very low occurrences of side effects, and clinical evidence suggests it has a low toxicity.

Sodium Bicarbonate

Due to the fast accumulation of protons (hydrogen [H^+]) and carbon dioxide (CO_2) during high intensity anaerobic activity, buffering capacity in muscle and blood is essential. The chief buffering compound is the bicarbonate ion (HCO_3^-). HCO_3^- buffers by the following reaction: $H^+ + HCO_3^- \longleftrightarrow H_2CO_3 \longleftrightarrow H_2O + CO_2$. The CO_2 can then be off-loaded in the lungs.

Sodium bicarbonate provides a reservoir of HCO_3^- theoretically giving greater capacity to resist fatigue induced pH changes at the muscle cell. Several studies have shown supplemental sodium bicarbonate can stabilize pH changes for exercise lasting from 60 seconds to several minutes and improve performance.[141-144]

Dosage

Sodium bicarbonate can be taken in a performance dose before exercise or a loading dose several days before an event. The pre-exercise dose is 0.3 g/kg body weight of sodium bicarbonate taken in water between 60 and 90 minutes before an exercise bout. The loading dose of bicarbonate is taken over a 5-day period and consists of 5 g taken twice a day for 5 days.

Other Considerations

There appears to be no safety issues with sodium bicarbonate intake aside from digestive upset.

Spirulina

The consumption of the well-known algae *Spirulina* has been a practice among athletes from diverse cultures such as India, China, and Cuba.[145] *Spirulina* is considered a member of the "blue-green algae family" along with another popular algae, *Chlorella*. *Spirulina* differs from *Chlorella* based on the lack of a cell wall, rendering it more digestible. There is little research on this compound except for the anecdotal use and benefit reported from athletes in the countries mentioned and some positive outcomes in mice.[146] Although there is very little supportive evidence for its use, we include it here in this chapter as a novel compound that shows some promise and may have some beneficial effects.

A 2006 study by Lu et al[145] followed up on anecdotal reports from athletes and positive outcomes in animals that *Spirulina* may aid in decreasing oxidative stress from exercise. Sixteen student volunteers were divided into two groups. One group added approximately 7 g *Spirulina* to their regular diet, whereas the control group was given the same amount of soy protein. The supplementation lasted for 3 weeks. Blood was collected before and after supplementation in both groups. Both groups also participated in a treadmill run to exhaustion the day before and day after supplementation. After 3 weeks, the *Spirulina* group saw positive changes in blood chemistry as well as significant improvement in treadmill running time to exhaustion (713 versus 765 seconds). No significant change was seen in the soy group.

A 2010 study by Kalafati et al[147] looked at *Spirulina* supplementation in a small double-blinded, placebo-controlled and counterbalanced trial. Each subject received 6 g *Spirulina* or placebo for 4 weeks and then underwent exercise testing. The exercise challenge involved a moderate intensity run at 70% to 75% of VO_2max for 120 minutes followed by a 95% of VO_2max run until exhaustion. *Spirulina* supplementation decreased carbohydrate oxidation by 10.3% while improving fat burning by 10.9% during the 2 hour run. Time to fatigue was also significantly improved in the *Spirulina* group. These performance enhancements were also complimented by multiple positive changes in exercise antioxidant status up to 24 hours after exercise.

Dosage

Spirulina dose, based on these limited studies, appears to be 6 to 7 g/day.

Other Considerations

Quality of algae in products is a concern, because these compounds can easily accumulate heavy metals present in the environment. Clean sources of *Spirulina* should be sought.

Whey Protein

Whey protein is one of the most popular meal replacements and protein sources for athletes. The protein present in whey mimics many of the proteins present in human breast milk. Whey is very rich in essential amino acids and has an exceptionally high biological value. It is a rich source of sulfur-containing amino acids (methionine and cysteine), high in glutamine, and contains large amounts of the BCAAs leucine, isoleucine, and valine. The large amount of BCAA present in whey protein may be one of its key benefits (see section on "Branched Chain Amino Acids").[148]

Whey moves through the stomach rapidly and is absorbed quickly. For this reason, it has been designated as a "fast protein." Casein, on the other hand, transits the stomach slowly and is referred to as a "slow protein."[149] The different speed of absorption between whey and casein protein fractions can be harnessed when used in muscle building protocols as described in the "Protein" section.

No studies exist comparing the impact of different protein sources on nitrogen balance, body composition, or performance in trained athletes. However, whey has been shown to promote growth and enhance nitrogen balance in experimental animals and burn victims.[150,151]

Whey protein supplies many precursors related to the synthesis of glutathione.[152] It has one of the highest concentrations of cysteine, which is a required precursor in glutathione production. Any supplement that can aid the body's endogenous production of antioxidants may play a role in lessening damage and speeding recovery from exercise. Although free radical generation during exercise has been shown to be a normal consequence,[153] and training, in and of itself, increases antioxidant systems in the body, supplementation can further aid endogenous antioxidant systems. Although this may help with recovery, it has not been shown to aid performance.[154]

Glutathione levels are reduced during exercise.[155,156] Ultra-endurance events, such as marathons and triathlons, can increase oxidized glutathione levels by 189%.[157] Because whey protein

provides factors that increase glutathione production, a higher intake could play a role in protecting against damage during exercise and recovery after exercise.[158]

Another benefit of whey protein may be its ability to bolster the content of other important amino acids. Whey enhances body levels of cysteine, taurine, glutamine, and BCAAs among others.[159] This could have consequences in several areas, including immune function.[160, 161] Nothing interrupts training more than illness.

Whey protein also has merit as a fat loss and muscle building aid. Twenty grams of whey protein taken 20 minutes before exercise increased the amount of calories burned after exercise by a hundred compared with no supplementation.[162] This may make it a useful preworkout meal compared with carbohydrate, which may slow fat loss.[1]

Whey protein also shows a powerful ability to regulate hunger and binge eating for weight control. Pal et al[163] carried out a randomized crossover study on 22 males given equivalent gram doses of four liquid protein meals. The four protein meals were whey, tuna, turkey, and egg albumin. Four hours after the liquid protein meals, participants were given access to an all-you-can-eat buffet style meal. The whey protein group had much greater satiety response and consumed significantly less food than any other group, showing whey protein as having a potential role in appetite regulation. A similar study by Akhavan et al[164] showed whey protein taken before an all-you-can-eat pizza meal significantly lowered food intake, postmeal glucose, and insulin levels in response to the meal.

Dosage

As discussed in this section as well as in the sections on protein and meal timing, whey protein can provide benefit when timed appropriately with exercise. Whey protein post-workout may be one of the most beneficial things an athlete can do to maximize lean body mass. Whey protein is low glycemic, but insulinogenic at the same time.[161,163] Immediately after a workout up until about 2 hours after the workout, the body is uniquely sensitized to insulin. This may create a unique opportunity for muscle growth without fat gain, especially in a post-workout setting.[161]

The addition of a small amount of carbohydrate may be more beneficial in terms of muscle gain. In studies analyzing post-workout intake of protein alone, carbohydrate alone, or a combination of both, protein and carbohydrate together generated the greatest insulin response.[127-130] This enhances muscle glycogen synthesis and storage and has benefit for athletes in terms of recovery.[127,128] Adding fat to the mix is not beneficial and may blunt this response.[167,168]

Combining whey protein with creatine may have synergistic benefit as well. Men supplementing their diets with a combination of whey protein and creatine together (1.2 g/kg per day of whey with 0.1 g/kg per day creatine) enjoyed greater improvements in strength and muscle mass compared with placebo.[169]

Other Considerations

Although many individuals are dairy intolerant, whey protein seems to be handled well by most people. This is probably due to the fact that pure whey protein has low levels of lactose and is easily digested. However, people with known dairy sensitivities or allergies should be cautious with their intake of whey.

Bovine serum albumin (BSA) protein in whey has been suggested as a potential cause or possible contributing factor to insulin-dependent diabetes mellitus.[170,171] Anti-BSA antibodies have been found in those with insulin-dependent diabetes mellitus. Proteins on the β-cells of the pancreas may "mimic" the BSA proteins in whey, causing immune reactivity against both the whey protein and the β-cells.[170] Theoretically, this is "protein mimicry" at work, and an ongoing debate that has not yet been resolved.

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CHAPTER 60

Stress Management

Michael T. Murray, ND

CHAPTER CONTENTS

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INTRODUCTION

Stress is defined as any disturbance—e.g., heat or cold, chemical toxin, microorganisms, physical trauma, strong emotional reaction—that can trigger the "stress response." How an individual handles stress plays a major role in determining their level of health. Comprehensive stress management involves a truly holistic approach designed to counteract the everyday stresses of life. Most often the stress response is so mild it goes entirely unnoticed. However, if stress is extreme, unusual, or long-lasting, the stress response can be overwhelming and quite harmful to virtually any body system.

Before one can discuss methods for helping patients deal effectively with stress, it is important to understand the stress response. Ultimately, the success of any stress management program depends on its ability to improve an individual's immediate and long-term responses to stress.

THE GENERAL ADAPTATION SYNDROME

The stress response is actually part of a larger response known as the general adaptation syndrome, a term coined by the pioneering stress researcher, Hans Selye. To fully understand how to combat stress, one must understand the general adaptation syndrome. The syndrome is composed of three phases: alarm, resistance, and exhaustion.[1] These phases are largely controlled and regulated by the adrenal glands.

The initial response to stress is the alarm reaction, which is often referred to as the fight-or-flight response. The fight-or-flight response is triggered by activation of the sympathetic nervous system and, ultimately, the hypothalamic-pituitary-adrenal (HPA) axis, which causes the adrenals to secrete adrenaline and other stress-related hormones.

The fight-or-flight response is designed to counteract danger by mobilizing the body's resources for immediate physical activity. As a result, the heart rate and force of contraction of the heart increase to provide blood to areas necessary for response to the stressful situation. Blood is shunted away from the skin and internal organs, except the heart and lungs, whereas the amount of blood supplying required oxygen and glucose to the muscles and brain is increased. The rate of breathing rises to supply necessary oxygen to the heart, brain, and exercising muscle. Sweat production increases to eliminate toxic compounds produced by the body and to lower body temperature. Production of digestive secretions is severely reduced because digestive activity is not critical for counteracting stress. Blood sugar levels rise dramatically as the liver converts stored glycogen into glucose for release into the bloodstream.

Although the alarm phase is usually short-lived, the next phase—the resistance reaction—allows the body to continue fighting a stressor long after the effects of the fight-or-flight response have worn off. Other hormones, such as cortisol and other corticosteroids secreted by the adrenal cortex, are largely responsible for the resistance reaction. For example, these hormones stimulate the conversion of protein to energy, so that the body has a large supply of energy long after glucose stores are depleted, and promote the retention of sodium to keep blood pressure elevated.

As well as providing the necessary energy and circulatory changes required to deal effectively with stress, the resistance reaction provides the changes required to meet emotional crisis, perform strenuous tasks, and fight infection. The effects of adrenal cortex hormones are quite necessary when the body is faced with danger, but prolongation of the resistance reaction or continued stress increases the risk of significant

BOX 60-1 Diseases Strongly Linked to Stress

Angina
Asthma
Autoimmune disease
Cancer
Cardiovascular disease
Common cold
Depression
Diabetes (adult onset—type 2)
Headaches
Hypertension
Immune suppression
Irritable bowel syndrome
Menstrual irregularities
Premenstrual tension syndrome
Rheumatoid arthritis
Ulcerative colitis
Ulcers

Data from Benson H. The relaxation response. New York: William Morrow, 1975.

disease (including diabetes, high blood pressure, and cancer) and results in the final stage of the general adaptation syndrome, exhaustion.

Exhaustion may manifest as a partial or total collapse of a body function or specific organ. Two of the major causes of exhaustion are loss of potassium ions and depletion of adrenal glucocorticoid hormones, like cortisone. Loss of potassium results in cellular dysfunction and, if severe, cell death. Adrenal glucocorticoid store depletion diminishes glucose control, leading to hypoglycemia.

Another cause of exhaustion is weakening of the organs. Prolonged stress places a tremendous load on many organ systems, especially the heart, blood vessels, adrenals, and immune system, and is associated with many common diseases, as listed in Box 60-1.

STRESS: A HEALTHY VIEW

The father of modern stress research was Hans Selye. Having spent many years studying this subject, Selye developed valuable insights into the role of stress in disease. According to Selye, stress in itself should not be viewed in a negative context. It is not the stressor that determines the response; instead, it is the individual's internal reaction that triggers the response. This internal reaction is highly individualized. What one person may experience as stress, the next person may view entirely differently. Selye perhaps summarized his view best in the following passage from his book *The Stress of Life*[2]:

> *No one can live without experiencing some degree of stress all the time. You may think that only serious disease or intensive physical or mental injury can cause stress. This is false. Crossing a busy intersection, exposure to a draft, or even sheer joy are enough to activate the body's stress mechanisms to some extent. Stress is not even necessarily bad for you; it is also the spice of life, for any emotion, any activity causes stress. But, of course, your system must be prepared to take it. The same stress which makes one person sick can be an invigorating experience for another.*

The key statement Selye made may be "your system must be prepared to take it." A significant body of knowledge has been accumulated delineating methodologies for helping patients develop healthful, rather than disease-facilitating, responses to both short- and long-term stress.

DIAGNOSTIC CONSIDERATIONS

Evaluating the impact of stress on a patient's health status requires a complete clinical assessment (e.g., review of systems, medical history, physical examination, sleep history, etc.). Many people who are "stressed out" may not be able to identify exactly what is causing them to feel stressed. Typical presenting symptoms are insomnia, depression, fatigue, headache, upset stomach, digestive disturbances, and irritability.

One useful tool to assess the role that stress may play is the "social readjustment rating scale" developed by Holmes and Rahe[3] (Table 60-1). The scale was originally designed to predict the risk of a serious disease due to stress. Various life-changing events are numerically rated according to their potential to cause disease. Notice that even events commonly viewed as positive, such as an outstanding personal achievement, carry stress.

If a person is under a great deal of immediate stress or has endured a fair amount of stress for a few months or longer, it is appropriate to assess adrenal dysfunction more accurately with laboratory methods.

The standard interpretation of the social readjustment rating scale is that a total of 200 or more units in 1 year are considered to be predictive of a high likelihood of experiencing a serious disease. However, rather than using the scale solely to predict the likelihood of serious disease, the clinician can use the scale to evaluate a patient's level of stressor exposure, because everyone reacts differently to stressful events.

Laboratory assessment generally involves evaluating aspects of the HPA axis. The gold standard for diagnosing dysfunction of the HPA axis is the combined dexamethasone/corticotropin-releasing hormone test. This test is often used in research studies to monitor the clinical course of depression. More popular in the clinical setting are assessment tools based on salivary cortisol levels.[4,5] Salivary hormone levels are reproducible, comparable to plasma levels, and easy to assess.[21,22]

One straightforward test that is a reasonably good predictor of HPA dysregulation is the cortisol-awakening response. Salivary levels generally show a sharp rise upon awakening and during the first hour after wake-up. Generally, an initially hyperactive HPA response results in elevated cortisol levels, whereas more chronic stress, insomnia, or depression may blunt this effect.[6,7,23,24]

Another popular test is measuring salivary cortisol levels at awakening and in the evening usually along with dehydroepiandrosterone (DHEA). The classic pattern associated with chronic stress is elevated cortisol combined with reduced DHEA, indicating a shift toward glucocorticoid production and away from sex hormone steroid production. This pattern is often associated with anxiety and depression. Adrenal exhaustion is characterized by low cortisol and low DHEA. Adrenal exhaustion is a common side effect of continual high stress as well as steroid drugs, like prednisone, which are used in the treatment of allergic or inflammatory diseases.

THERAPEUTIC APPROACH

Whether currently aware of it or not, the patient has developed a pattern for coping with stress. Unfortunately, most people have found patterns and methods that ultimately do not support good health. Negative coping patterns must be identi-

TABLE 60-1 **The Social Readjustment Rating Scale**

RANK	LIFE EVENT	MEAN VALUE
1	Death of spouse	100
2	Divorce	73
3	Marital separation	65
4	Jail term	63
5	Death of a close family member	63
6	Personal injury or illness	53
7	Marriage	50
8	Fired at work	47
9	Marital reconciliation	45
10	Retirement	45
11	Change in health of family member	44
12	Pregnancy	40
13	Sex difficulties	39
14	Gain of a new family member	39
15	Business adjustment	39
16	Change in financial state	38
17	Death of a close friend	37
18	Change to different line of work	36
19	Change in number of arguments with spouse	35
20	Large mortgage	31
21	Foreclosure of mortgage or loan	30
22	Change in responsibilities at work	29
23	Son or daughter leaving home	29
24	Trouble with in-laws	29
25	Outstanding personal achievement	28
26	Spouse begins or stops work	26
27	Beginning or end of school	26
28	Change in living conditions	25
29	Revision of personal habits	24
30	Trouble with boss	23
31	Change in work hours or conditions	20
32	Change in residence	20
33	Change in schools	20
34	Change in recreation	19
35	Change in church activities	19
36	Change in social activities	18
37	Small mortgage	17
38	Change in sleeping habits	16
39	Change in number of family get togethers	15
40	Change in eating habits	15
41	Vacation	13
42	Christmas	12
43	Minor violations of the law	11

Data from Holmes TH, Rahe RH. The social readjustment rating scale. J Psychosom Res 1967;11:213-218.

fied and replaced with positive ways of coping. The clinician should try to identify any negative or destructive coping patterns, listed in Box 60-2, that the patient may have developed and try to replace that pattern with more positive measures for dealing with stress.

BOX 60-2 Negative Coping Patterns

Dependence on chemicals: legal and illicit drugs, alcohol, smoking
Overeating
Too much television
Emotional outbursts
Feelings of helplessness
Overspending
Excessive behavior

BOX 60-3 The Stress Response

- The heart rate and force of contraction of the heart increase to provide blood to areas necessary for response to the stressful situation.
- Blood is shunted away from the skin and internal organs, except the heart and lungs, whereas the amount of blood supplying required oxygen and glucose to the muscles and brain is increased.
- The rate of breathing rises to supply necessary oxygen to the heart, brain, and exercising muscle.
- Sweat production increases to eliminate toxic compounds produced by the body and to lower body temperature.
- Production of digestive secretions is severely reduced because digestive activity is not critical to counteracting stress.
- Blood sugar levels are raised dramatically as the liver dumps stored glucose into the bloodstream.

Stress management can be substantially improved by assisting the patient in the following six equally important areas:

- Techniques to calm the mind, promote parasympathetic tone, and promote a positive mental attitude
- Lifestyle factors
- Exercise
- A healthful diet designed to nourish the body and support physiologic processes
- Dietary and botanical supplements designed to support the body as a whole, but especially the adrenal glands
- Supervised stress management program

Calming the Mind and Body

Learning to calm the mind and body is extremely important in relieving stress. Among the easiest methods for the patient to learn are relaxation exercises. The goal of relaxation techniques is to produce a physiologic response known as a relaxation response—a response that is exactly opposite to the stress response that reflects activation of the parasympathetic nervous system. Although an individual may relax by simply sleeping, watching television, or reading a book, relaxation techniques are designed specifically to produce the relaxation response.

Relaxation response was a term coined by Harvard professor and cardiologist Herbert Benson in the early 1970s to describe a physiologic response that is just the opposite of the stress response.[1] With the stress response (Box 60-3), the sympathetic nervous system dominates. With the relaxation response (Box 60-4), the parasympathetic nervous system dominates. The parasympathetic nervous system controls bodily functions such as digestion, breathing, and heart rate during periods of rest, relaxation, visualization, meditation, and sleep. Although the sympathetic nervous

BOX 60-4 The Relaxation Response

- The heart rate is reduced and the heart beats more effectively. Blood pressure is reduced.
- Blood is shunted towards internal organs, especially those organs involved in digestion.
- The rate of breathing decreases as oxygen demand is reduced during periods of rest.
- Sweat production diminishes, because a person who is calm and relaxed does not experience nervous perspiration.
- Production of digestive secretions is increased, greatly improving digestion.
- Blood sugar levels are maintained in the normal physiologic range.

BOX 60-5 Instructions to Help Patients Learn Diaphragmatic Breathing

1. Find a comfortable and quiet place to lie down or sit.
2. Place your feet slightly apart. Place one hand on your abdomen near your navel. Place the other hand on your chest.
3. You will be inhaling through your nose and exhaling through your mouth.
4. Concentrate on your breathing. Note which hand is rising and falling with each breath.
5. Gently exhale most of the air in your lungs.
6. Inhale while slowly counting to four. As you inhale, slightly extend your abdomen, causing it to rise about 1 inch. Make sure that you are not moving your chest or shoulders.
7. As you breathe in, imagine the warmed air flowing in. Imagine this warmth flowing to all parts of your body.
8. Pause for 1 second, then slowly exhale to a count of four. As you exhale, your abdomen should move inward.
9. As the air flows out, imagine all your tension and stress leaving your body.
10. Repeat the process until a sense of deep relaxation is achieved.

system is designed to protect against immediate danger, the parasympathetic system is designed for repair, maintenance, and restoration of the body.

The relaxation response can be achieved through a variety of techniques. The methodology should be determined by patient interest, because all techniques have the same physiologic effect—a state of deep relaxation. The most popular techniques are meditation, prayer, progressive relaxation, self-hypnosis, and biofeedback. To produce the desired long-term health benefits, the patient should use the relaxation technique for at least 5 to 10 minutes each day.

Breathing

Producing deep relaxation with any technique requires learning how to breathe. One of the most powerful methods of producing less stress and more energy in the body is by breathing with the diaphragm. Diaphragm breathing activates the relaxation centers in the brain and the parasympathetic nervous system. Box 60-5 lists a 10-step technique for teaching diaphragmatic breathing.

Progressive Relaxation

One of the most popular techniques for producing the relaxation response is progressive relaxation. The technique is based on a very simple procedure of comparing tension with relaxation. Many people are not aware of the sensation of relaxation. In progressive relaxation, an individual is taught what it feels like to relax by comparing relaxation with muscle tension.

The basic technique is to have the patient contract a muscle forcefully for a period of 1 to 2 seconds and then give way to a feeling of relaxation in that muscle. The procedure systematically goes through all the muscles of the body, progressively producing a deep state of relaxation. The procedure begins with contracting the muscles of the face and neck, then the upper arms and chest, followed by the lower arms and hands. The process is repeated progressively down the body, from the abdomen through the buttocks, the thighs, and calves to the feet. This whole process is repeated two or three times. This technique is often used in the treatment of anxiety and insomnia.

Progressive relaxation, deep breathing exercises, or some other stress reduction technique is an important component of a comprehensive stress management program.

BOX 60-6 Patient Tips for Improved Time Management

Set priorities. Realize that you can only accomplish so much in a day. Decide what is important, and limit your efforts to that goal.

Organize your day. There are always interruptions and unplanned demands on your time, but create a definite plan for the day on the basis of your priorities. Avoid the pitfall of always letting the "immediate demands" control your life.

Delegate authority. Delegate as much authority and work as you can. You cannot do everything yourself. Learn to train and depend on others.

Tackle tough jobs first. Handle the most important tasks first, when your energy levels are high. Leave the busy work or running around for later in the day.

Minimize meeting time. Schedule meetings to bump up against the lunch hour or quitting time; that way they cannot last forever.

Avoid putting things off. Work done under pressure of an unreasonable deadline often has to be redone. That creates more stress than if it had been done right the first time. Plan ahead.

Do not be a perfectionist. You can never really achieve perfection anyway. Do your best in a reasonable amount of time, then move on to other important tasks. If you find time, you can always come back later and polish the task some more.

Lifestyle Factors

A patient's lifestyle is a major determinant of his or her stress levels. The two primary areas of concern (other than addressing negative coping patterns) are time management and relationship issues.

One of the biggest stressors for most people is time. They simply do not feel they have enough of it. Box 60-6 provides tips on time management for patients.

Another major cause of stress for many people is interpersonal relationships. Interpersonal relationships can be divided into three major categories: marital, family, and job-related. The quality of any relationship ultimately comes down to the quality of the communication. Learning to communicate effectively goes a very long way in reducing the stress and occasional (or frequent) conflicts of interpersonal relationships. Box 60-7 lists seven tips for effective communication, regardless of the type of interpersonal relationship.

BOX 60-7 Keys to Assist Patients in Improving Communication

- The first key to successful communication is the most important: learn to be a good listener. Allow the person you are communicating with to really share his or her feelings and thoughts uninterrupted. Empathize with the person; put yourself in his or her shoes. If you first seek to understand, you will find yourself being better understood.
- Be an active listener. This means that you must be truly interested in what the other person is communicating. Listen to what he or she is saying instead of thinking about your response. Ask questions to gain more information or clarify what he or she is telling you. Good questions open lines of communication.
- Be a reflective listener. Restate or reflect back to the other person your interpretation of what he or she is telling you. This simple technique shows the other person that you are both listening to and understanding what he or she is saying. Restating what you think is being said may cause some short-term conflict in some situations, but it is certainly worth the risk.
- Wait to speak until the person you want to communicate with is listening. If the person is not ready to listen, your message will not be heard no matter how well you communicate.
- Do not try to talk over somebody. If you find yourself being interrupted, relax; do not try to out-talk the other person. If you are courteous and allow him or her to speak, eventually (unless extremely rude) he or she will respond likewise. If that does not happen, point out that the other person is interrupting the communication process. You can do this only if you have been a good listener. Double standards in relationships seldom work.
- Help the other person become an active listener. This can be done by asking whether he or she has understood what you were communicating. Ask him or her to tell you what he or she heard. If the other person does not seem to be understanding what you are saying, keep trying until he or she does.
- Do not be afraid of long silences. Human communication involves much more than human words. A great deal can be communicated during silences; unfortunately, in many situations silence can make us feel uncomfortable. Relax. Some people need silence to collect their thoughts and feel safe in communicating. The important thing to remember during silences is that you must remain an active listener.

Exercise

The immediate effect of exercise is stress on the body. However, with a regular exercise program, the body adapts, and exercise becomes an effective stress reduction technique. With regular exercise, the body becomes stronger, functions more efficiently, and has greater endurance. Exercise is a vital component of a comprehensive stress management program and overall good health.

People who exercise regularly are much less likely to experience fatigue and depression. Tension, depression, feelings of inadequacy, and worries diminish greatly with regular exercise.

Exercise alone has been demonstrated to have a tremendous effect in terms of improving mood and the ability to handle stressful life situations. This effect is seen in adolescents as well as adults. In one study, 2223 boys and 2838 girls (mean age, 16.3 years) from 10 teams and 25 different individual sports were studied for the relationship between emotional well-being and psychological well-being. The sport and vigorous recreational activity index was positively associated with emotional well-being independent of other variables.[8]

Dietary Guidelines

An individual with stress or anxiety must support the biochemistry of the body by following some important dietary guidelines. Specifically, the patient must:

- Eliminate or restrict the intake of caffeine.
- Eliminate or restrict the intake of alcohol.
- Eliminate refined carbohydrates from the diet.
- Eat a diverse range of whole foods.
- Increase the potassium-to-sodium (K/Na) ratio.
- Eat regular planned meals in a relaxed environment.
- Control food allergies.

According to Selye,[2] whether or not stress is harmful is based on the strength of the system. From a purely physiologic perspective, it can be strongly argued that delivery of high-quality nutrition to the cells of the body is the critical factor in determining the strength of the system.

When the eating habits of Americans are examined as a whole, it is little wonder that so many people have stress, anxiety, and fatigue. Most Americans are not providing their bodies with the high-quality nutrition they need. Instead of eating foods rich in vital nutrients, most Americans focus on refined foods high in calories, sugar, fat, and cholesterol.

Caffeine

The average American consumes 150 to 225 mg of caffeine daily, or roughly the amount of caffeine in two cups of coffee. Although most people can handle this amount, some people are more sensitive to the effects of caffeine than other people, owing to decreased activity of phase I detoxification enzymes. Even small amounts of caffeine can affect sensitive people, whereas those with normal sensitivity respond to large amounts. Excessive caffeine consumption can produce "caffeinism characterized by symptoms of depression, nervousness, irritability, recurrent headache, heart palpitations, and insomnia." People prone to feeling stress and anxiety tend to be especially sensitive to caffeine.[9,10]

Alcohol

Alcohol produces chemical stress on the body. It also increases adrenal hormone output and interferes with both normal brain chemistry and normal sleep cycles. Although many people believe that alcohol has a calming effect, a study of 90 healthy male volunteers given either a placebo or alcohol demonstrated significant increases in anxiety scores after consumption of alcohol.[10]

Refined Carbohydrates and Glycemic Volatility

One of the consequences of the stress response is abdominal fat cell growth and loss of muscle mass, a scenario that obviously leads to insulin resistance and obesity. It is a complex set of events orchestrated by cortisol released as a result of the stress response that is ultimately responsible for the fact that stress promotes weight gain. Cortisol is also a contributing factor in a high degree of glycemic volatility. Rapidly fluctuating blood sugar levels are generally related to some degree of insulin resistance and made worse by more than moderate consumption of foods with a high glycemic impact. Refined carbohydrates (e.g., sugar and white flour) are known to contribute to problems in blood sugar control, especially hypoglycemia as well as glycemic volatility. The association between hypoglycemia and impaired mental function is well known. Numerous studies have shown a high percentage of hypoglycemia in depressed patients.[11,12] Since depression is one of the most common causes of anxiety, this finding provides a link between hypoglycemia and feelings of stress. Simply eliminating

refined carbohydrates from the diet is occasionally all that is needed for effective therapy in patients who have depression or anxiety due to hypoglycemia.

Potassium-to-Sodium Ratio

One of the key dietary recommendations to support the adrenal glands is to ensure adequate potassium levels within the body. This can best be done by consuming foods rich in potassium and avoiding foods high in sodium. Most Americans have a dietary K/Na ratio of less than 1:2. In contrast, most researchers recommend a dietary K/Na ratio higher than 5:1 for health. However, even this recommendation may not be optimal. A natural diet rich in fruits and vegetables can produce a K/Na ratio higher than 50:1, since most fruits and vegetables have a K/Na ratio of more than 100:1.

Meal Planning

Mealtimes should be spent in a relaxed environment. As noted previously, digestion is a process largely controlled by the parasympathetic nervous system. Eating in a rushed manner or in a noisy or hurried environment is not conducive to good digestion or good health.

Food Allergies

People with symptoms of anxiety or chronic fatigue must be concerned about food allergies. As far back as 1930, pioneering allergist Albert Rowe began noticing that anxiety and fatigue were key features of food allergies.[13] Originally, Rowe described a syndrome known as "allergic toxemia" to describe a syndrome that included the symptoms anxiety, fatigue, muscle and joint aches, drowsiness, difficulty of concentration, and depression. Around the 1950s, this syndrome began to be referred to as the "allergic tension-fatigue syndrome." Due to the popularity of chronic fatigue syndrome, many physicians and other people are forgetting that food allergies can lead to anxiety as well as chronic fatigue.

NUTRITIONAL AND BOTANICAL SUPPORT

Nutritional and botanical support for the individual experiencing signs and symptoms of stress largely involves supporting the adrenal glands. Long-term stress and corticosteroids cause the adrenal glands to shrink and become dysfunctional, aggravating the stress symptoms of anxiety, depression, and chronic fatigue.

An abnormal adrenal response, either deficient or excessive hormone release, significantly alters an individual's response to stress. Often the adrenals become "exhausted" as a result of constant demands put on them. An individual with adrenal exhaustion usually experiences chronic fatigue and may complain of feeling "stressed out" or chronically anxious. He or she typically has a reduced resistance to allergies and infection.

Nutritional Supplements

The nutrients especially important for supporting adrenal function are vitamin C, vitamin B_6, zinc, magnesium, and pantothenic acid. All of these nutrients play a critical role in the health of the adrenal gland as well as the manufacture of adrenal hormones. During stress, the levels of these nutrients in the adrenals decrease substantially.

For example, during chemical, emotional, psychological, or physiologic stress, the urinary excretion of vitamin C is increased. Examples of chemical stressors are cigarette smoke, pollutants, and allergens. Extra vitamin C in the form of supplementation and a higher intake of vitamin C–rich foods is often recommended to keep the immune system working properly during times of stress.

Equally important during high periods of stress or in individuals needing adrenal support is pantothenic acid (vitamin B_5). Pantothenic acid deficiency results in adrenal atrophy, characterized by fatigue, headache, sleep disturbances, nausea, and abdominal discomfort. Pantothenic acid is found in whole grains, legumes, cauliflower, broccoli, salmon, liver, sweet potatoes, and tomatoes. In patients who have chronic stress or a history of corticosteroid (prednisone) use, the typical level of supplementation is 100 to 500 mg/day.

The appropriate daily dose of vitamin B_6 is 50 to 100 mg; of zinc, 20 to 30 mg; and of magnesium, 250 to 500 mg.

Gamma-aminobutyric Acid

Gamma-aminobutyric acid (GABA) is a major neurotransmitter that is abundantly and widely distributed throughout the central nervous system. Low levels or decreased GABA function in the brain are associated with several psychiatric and neurologic disorders, but most primarily anxiety, depression, insomnia, and epilepsy. Currently, many popular antianxiety drugs—the sedative-hypnotics—interact primarily with GABA receptors. These drugs include the benzodiazepine drugs like alprazolam (Alprazolam, Xanax) and diazepam (Valium), as well as drugs like flurazepam (Dalmane), quazepam (Doral), temazepam (Restoril), triazolam (Halcion), zolpidem tartrate (Ambien), and baclofen (Kemstro and Lioresal).

Clinical studies with PharmaGABA, a naturally manufactured supplement via a fermentation process that utilizes *Lactobacillus hilgardii*, have shown it to produce significant antistress effects.[14,15] Specifically, PharmaGABA has been shown to produce relaxation as evidenced by changes in brain wave patterns, pupil diameter, and heart rate, as well as reduce markers of stress, including salivary cortisol and chromogranin A levels. These effects are thought to be the result of activation of the parasympathetic nervous system rather than PharmaGABA crossing the blood–brain barrier. The typical dosage is 100 to 200 mg up to three times daily. As a general guideline, it is recommended to take no more than 1000 mg within a 4 hour period and no more than 3000 mg within a 24 hour period.

Botanical Medicines

Several botanical medicines support adrenal function. Most notable are the ginsengs; Chinese ginseng (*Panax ginseng*) and Siberian ginseng (*Eleutherococcus senticosus*), rhodiola (*Rhodiola rosea*), and ashwagandha (*Withania somnifera*). All of these plants exert beneficial effects on adrenal function, enhance resistance to stress, and are often referred to as "adaptogens." These plants have historically been used to:

- Restore vitality in debilitated and feeble individuals
- Increase feelings of energy
- Improve mental and physical performance
- Prevent the negative effects of stress and enhance the body's response to stress

Both Siberian and Chinese ginsengs possess this kind of equilibrating, tonic, antistress action, and so the term adaptogen is quite appropriate in describing their general effects.

The ginsengs have been shown to enhance the ability to cope with various stressors, both physical and mental.[16-18] Presumably, this antistress action is mediated by mechanisms that control the adrenal glands. Ginseng delays the onset and reduces the severity of the alarm phase response of the general adaptation syndrome.

People taking either of the ginsengs typically report an increased sense of well-being. Clinical studies have confirmed that both Siberian and Chinese ginsengs significantly reduce feelings of stress and anxiety. For example, in one double-blind clinical study, nurses who switched from day to night duty rated themselves for competence, mood, and general well-being, and were given a test for mental and physical performance along with blood cell counts and blood chemistry evaluation.[19] The group who were given *P. ginseng* demonstrated higher scores in competence, mood parameters, and mental and physical performance compared with those receiving placebos. The nurses taking the ginseng felt more alert, yet more tranquil, and were able to perform better than the nurses who were not taking the ginseng.

In addition to these human studies, several animal studies have shown the ginsengs to exert significant antianxiety effects. In several of these studies, the stress-relieving effects were comparable to those of diazepam (Valium); however, diazepam causes behavior changes, sedative effects, and impaired motor activity, but ginseng has none of these negative effects.[20]

On the basis of the clinical and animal studies, ginseng appears to offer significant benefit to people experiencing stress and anxiety. *P. ginseng* is generally regarded as being more potent than *E. senticosus*. *P. ginseng* is probably better for the patient who has experienced a great deal of stress, is recovering from a longstanding illness, or has taken corticosteroids, such as prednisone, for a long time. For the patient who is under mild to moderate stress and is experiencing less obvious impairment of adrenal function, *E. senticosus* may be the better choice.

Another useful botanical medicine to support stress management is *R. rosea* (artic root), a popular plant in traditional medical systems in Eastern Europe and Asia, where it has traditionally been recommended to help combat fatigue and restore energy. Modern research has confirmed these effects and its qualities as an adaptogen. However, the adaptogenic actions of *R. rosea* are different from those of Chinese and Siberian ginsengs, which act primarily on the HPA axis. *R. rosea* seems to exert its adaptogenic effects by working on neurotransmitters and endorphins. *R. rosea* appears to offer an advantage over other adaptogens in circumstances of acute stress because it produces a greater feeling of relaxation and antianxiety effects. A single dose of *Rhodiola* extract before acute stressful events has been shown to prevent stress-induced disruptions in function and performance, but like the ginsengs, *R. rosea* has also shown positive results with long-term use.[21-24] In one randomized, placebo-controlled trial of 60 patients with stress-related fatigue, *Rhodiola* was found to have an antifatigue effect that increased mental performance, particularly the ability to concentrate, as well as decreased the cortisol response to awakening stress.[25]

On the basis of results of clinical trials with a standardized *R. rosea* extract, the therapeutic dose varies according to the rosavin content. For a dosage target of 3.6 to 7.2 mg of rosavin, the daily dose would be 360 to 600 mg for an extract standardized for 1% rosavin, 180 to 300 mg for 2% rosavin, and 100 to 200 mg for 3.6% rosavin. When *R. rosea* is used as an adaptogen, long-term administration is normally begun several weeks before a period of expected increased physiologic, chemical, or biological strain and continued throughout the duration of the challenging event or activity. When *R. rosea* is used as a single dose for acute stress (e.g., for an examination or athletic competition), the suggested dose is three times the dose used for long-term supplementation. No side effects have been reported in the clinical trials, but at higher doses, some individuals might experience greater irritability and insomnia.

Lastly, clinical studies with Sensoril, a patented proprietary extract of roots and leaves from *Withania somnifera* (ashwagandha), have shown considerable antistress and adaptogenic effects. In one human double-blinded study, chronically stressed subjects taking Sensoril had significant reductions in a modified Hamilton anxiety scale, serum cortisol, C-reactive protein, pulse rate, and blood pressure, and significant increases of serum DHEA-S and hemoglobin, compared with the placebo group. In addition, there were dose-dependent responses in lowering fasting blood glucose and improving the serum lipid levels. Dosage is 125 to 250 mg/day.[26]

Stress Management Programs

Supervised stress management programs are thought to offer greater compliance and better results than unsupervised, patient-directed programs. In one study, stress management experts evaluated six widely used occupational stress management interventions (relaxation, physical fitness, cognitive restructuring, meditation, assertiveness training, and stress inoculation) on the basis of ten practicality criteria and seven effectiveness objectives. They found that relaxation was the most practical intervention, and that meditation and stress inoculation were the least practical. Physical fitness was chosen to be the most effective intervention, and both meditation and assertiveness training were rated overall as the least effective. What these results imply is that although relaxation training may be the most practical intervention, physical exercise was the most effective intervention.[27]

Meditation was shown to be the least practical and least effective method in this evaluation, but when it is part of supervised program it can be very effective. In one trial of 103 adults, 59% and 61% of the meditation and control groups, respectively, completed the study.[28] The intervention program consisted of an 8-week group stress reduction program in which subjects learned, practiced, and applied "mindfulness meditation" to daily life situations. The control group received educational materials and was encouraged to use community resources for stress management. Compared with the control group, intervention subjects reported significant decreases from baseline in effect of daily hassles (24%), psychological distress, (44%), and medical symptoms (46%) that were maintained at the 3-month follow-up.

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SECTION 5

PHARMACOLOGY OF NATURAL MEDICINES

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Careful review of the scientific literature reveals a considerable amount of research documenting the clinical efficacy, pharmacologic activity, and toxicology of numerous "natural" medicines. An important purpose of this section is the critical evaluation, from a scientific standpoint, of the historical use of botanical medicines. Although plants have been used as medicines since antiquity, appreciation of them as effective medicinal agents was greatly diminished until recently. Hopefully, this section will further revive the appreciation for and the safe and effective use of botanical medicines.

Although some plant constituents are discussed as separate entities and in many situations may be the most appropriate therapeutic substances, we believe that the whole herb should be used whenever possible. It has been amply demonstrated that, in many instances, physiologic and pharmacologic effects of a particular plant constituent are diminished when it is given as an isolated

component rather than in its naturally occurring environment. Furthermore, besides synergistic and enhancing effects, there appear to be factors in many plants that prevent many of the side effects of isolated plant constituents. In understanding the pharmacology, pharmacognosy, and historical use of plants, the student of natural medicine is once again inspired by the miracle of nature as well as the intuition and empiricism that ancient herbalists possessed.

We hope that this section will help better inform our readers of the impressive uses, and potential dangers, of these natural medicines. We also want to stress that botanical medicine should not be used simply as a substitute for the drugs commonly used to treat disease. The true physician of natural medicine will use them as part of the treatment of the whole person and in the context of removing the causes of the disease and promoting health, not simply treating symptoms.

Finally, considering the unfortunate, continuing trend of forever increasing use of prescription drugs—and in too many instances polypharmacy with unpredictable results—the astute physician of natural medicines needs to be expert in the potential for interaction between natural and conventional medicines. These interactions can take many forms, such as enhancing or inhibiting a drug's rate of absorption, the intended pharmaceutical effect, and the rate of detoxification.

Glossary of some terms used in section 5

Abortifacient: a substance that induces abortion.

Acrid: a pungent, biting taste that causes irritation.

Adaptogen: a substance that is safe, increases resistance to stress, and has a balancing effect on body functions.

Adjuvant: a substance that enhances the effect of the medicinal agent or increases the antigenicity of a cancer cell.

Alkaloids: naturally occurring amines, arising from heterocyclic and often complex structures, that display pharmacologic activity. Their trivial names usually end in *-ine*. They are usually classified according to the chemical structure of their main nucleus: phenylalkylamines (e.g., ephedrine), pyridine (e.g., nicotine), tropine (e.g., atropine, cocaine), quinoline (e.g., quinine), isoquinolone (e.g., papaverine), phenanthrene (e.g., morphine), purine (e.g., caffeine), imidazole (e.g., pilocarpine), and indole (e.g., physostigmine, yohimbine).

Alterative: a substance that has a balancing effect on a particular body function.

Analgesic: a substance that reduces the sensation of pain.

Androgens: hormones that stimulate male characteristics.

Anthelminthic: a substance that causes the elimination of intestinal worms.

Anthocyanidin: a particular class of flavonoids that gives plants, fruits, and flowers colors ranging from red to blue.

Antidote: a substance that neutralizes or counteracts the effects of a poison.

Aphrodisiac: a substance that increases sexual desire.

Astringent: an agent that causes the contraction of tissue.

Balm: a soothing or healing medicine applied to the skin.

Beta-carotene provitamin A: a plant carotene that can be converted to two vitamin A molecules.

Carminative: a substance that promotes the elimination of intestinal gas.

Carotenes: fat-soluble plant pigments, some of which can be converted into vitamin A by the body.

Cathartic: a substance that stimulates the movement of the bowels, more powerful than a laxative.

Cholagogue: a compound that stimulates the contraction of the gallbladder.

Choleretic: a compound that promotes the flow of bile.

Cholestasis: the stagnation of bile within the liver.

Cholinergic: pertaining to the parasympathetic portion of the autonomic nervous system and the release of acetylcholine as a transmitter substance.

Coenzyme: a necessary nonprotein component of an enzyme, usually a vitamin or mineral.

Compress: a pad of linen applied under pressure to an area of skin and held in place.

Decoctions: dilute aqueous extracts prepared by boiling the botanical material with water for a specified period, followed by straining or filtering.

Demulcent: a substance soothing to irritated mucous membranes.

Emulsify: to disperse large fat globules into smaller uniformly distributed particles that can remain in suspension in water.

Enteric-coated: a special way of covering a tablet or capsule to ensure that it does not dissolve in the stomach, so it can reach the intestinal tract.

Enzyme: an organic catalyst that speeds chemical reactions.

Essential oils: also known as volatile oils, ethereal oils, or essences. They are usually complex mixtures of a wide variety of organic compounds (e.g., alcohols, ketones, phenols, acids, ethers, esters, aldehydes, oxides) that evaporate when exposed to air. They generally represent the odoriferous principles of plants.

Extracts: concentrated forms of natural products obtained by treating crude materials containing these substances with a solvent and then removing the solvent completely or partially from the preparation. The most commonly used extracts are fluid extracts, solid extracts, powdered extracts, tinctures, and native extracts.

Flavonoid: a generic term for a group of flavone-containing compounds that are found widely in nature. They include many of the compounds that account for plant pigments (anthocyanins, anthoxanthins, apigenins, flavones, flavonols, bioflavonols, etc.). These plant pigments exert a wide variety of physiologic effects in the human body.

Fluid extracts: these extracts are typically hydroalcoholic solutions with a strength of one part solvent to one part herb. The alcohol content varies with each product. They are, in essence, concentrated tinctures, constructed to represent 1 grain of the crude drug to 1 minim of fluid extract.

Glycosides: sugar-containing compounds composed of a glycone (sugar component) and an aglycone (non–sugar-containing component) that can be cleaved upon hydrolysis. The glycone portion may be glucose, rhamnose, xylose, fructose, arabinose, or any other sugar. The aglycone portion can be any kind of organic compound (e.g., sterols, triterpenes, anthraquinones, hydroquinones, tannins, carotenoids, anthocyanidins).

Infusion; tea produced by steeping a botanical in hot water.

Laxative: a substance that promotes the evacuation of the bowels.

LD_{50}: the dosage that will kill 50% of the animals taking the substance.

Lipotropic: promoting the flow of lipids to and from the liver.

Menstrums: solvents used for extraction (e.g., water, alcohol, acetone).

Metalloenzyme: an enzyme that contains a metal at its active site.

Native extracts: high-potency extracts prepared via concentration under reduced pressure at low temperatures until all solvent is removed.

Oleoresins: primarily mixtures of resins and volatile oils. They either occur naturally or are made by extracting the oily and resinous materials from botanicals with organic solvents (e.g., hexane, acetone, ether, alcohol). The solvent is then removed

under vacuum, leaving behind a viscous, semisolid extract that is the oleoresin. Examples of prepared oleoresins are paprika, ginger, and capsicum.

Powdered extract: a solid extract that has been dried to a powder.

Putrefaction: the process of breaking down protein compounds by rotting.

Recommended dietary allowance (RDA): recommended dietary allowance.

Resins: complex oxidative products of terpenes that occur naturally as plant exudates or are prepared by alcohol extraction of botanicals that contain resinous principles.

Saponins: non-nitrogenous glycosides, typically with sterol or a triterpene as the aglycone, that possess the common property of foaming, or making suds, when strongly agitated in aqueous solution.

Solid extracts: thin to thick, viscous liquids or semisolids prepared from native extracts by adjusting the latter to the specific strength with suitable diluents. Typically, these extracts are 4:1, that is, one part extract is equivalent to, or derived from, four parts of crude herb.

Strength: the potency of an extract or strength of a botanical extract is generally expressed in two ways. If they contain known active principles, their strength is commonly expressed in terms of their content of active principles. Otherwise their strength is expressed in terms of their concentration of the crude drug. Thus, a strength of 4:1 means one part of extract is equivalent to, or derived from, four parts of crude drug. A strength of 1:5 represents one part of extract comparable to 0.2 parts of the crude drug. This ratio method of expressing drug strength does not accurately measure potency because there may be wide variation between manufacturers.

Tinctures: alcoholic or hydroalcoholic solutions usually containing the active principles of botanicals in low concentrations. They are usually prepared by maceration or percolation or by dilution of their corresponding fluid or native extracts. The strengths of tinctures are typically 1:10 or 1:5. Alcohol content varies.

Tonic: a substance that exerts a gentle strengthening effect on the body.

CHAPTER 61

Alkylglycerols

Michael T. Murray, ND, and Peter T. Pugliese, MD

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INTRODUCTION

Sharks have existed, virtually unchanged, for some 450 million years. Some scientists attribute this long staying power to the well-developed immune system in the shark, an immune system that is quite similar to our own. This chapter explores the use of alkylglycerols from sharks, both as immune stimulants and as powerful agents in the treatment of neoplastic disorders.

HISTORY

Alkylglycerols are ether-linked biologic compounds that have a long and fascinating history. Much of their early history is found in the literature of histochemistry and is related to methods of staining specific cellular components. One of the greatest histologists was Robert Feulgen (1884-1955), a German physiologic chemist who devised the Feulgen reaction. (The Feulgen reaction, or test, is a method to detect animal nucleic acids. It involves acid hydrolysis with hydrogen chloride followed by a 1% solution of decolorized rosaniline, which yields a red color in the presence of nucleic acids.) Feulgen and Voit discovered plasmalogens in 1924,[1] at the time they thought they had discovered an aldehyde, which they called plasmal. The origin of plasmal was believed to be an unknown substance, which they called plasmalogen. They demonstrated the presence of this compound in many tissues, from protozoa to humans.

Plasmalogens, it was learned later, were ether lipid compounds that are formed in the metabolic pathway of phosphoglycerides. They differ from phosphoglycerides in that they contain an ether linkage on the C-1 of the glycerol molecule. Intensive work on the structure and formation of the plasmalogens continued over the next 35 years. It was many years before a formula for plasmalogens was finally agreed on; the biological function of plasmalogens and their role in organisms were finally discovered after 1960.

BASIC CHEMISTRY OF ALKYLGLYCEROL ETHERS FROM SHARK LIVER OIL

Some Definitions

The term alkoxyl refers to an organic group RO, which is part of an ether group ROR. The term has been shortened to alkyl, so we denote ether lipid as alkylglyceride. The ether bond is the key to understanding the unique functioning of the alkylglycerol versus the common ester linkage of triglycerides. Figures 61-1 and 61-2 illustrate typical triglycerides and alkylglycerols, respectively.

One of the major sources of natural alkylglycerols is obtained from the Greenland shark, *Somniosus microcephalus*, which contains up to 50% of alkylglycerols. Other sources include the elasmobranch fish, such as the small shark, *Chimaera monstrosa*, and the dogfish, *Squalus acanthias*. Cod liver oil and certain mollusks are additional sources of alkylglycerols. These compounds have been found in various animal organs, including bone marrow fat, spleen, liver, plasma, and erythrocytes, and in milk. These compounds are found in the unsaponifiable fraction of the oils obtained from these animals. Three major natural alkylglycerols obtained from the Greenland shark are batyl alcohol, chimyl alcohol, and selachyl alcohol. Figure 61-3 illustrates the chemical structure of these compounds. Although chimyl and batyl

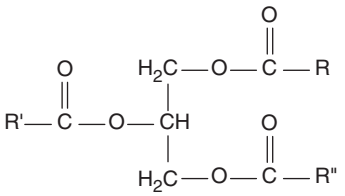


FIGURE 61-1 Triglyceride.

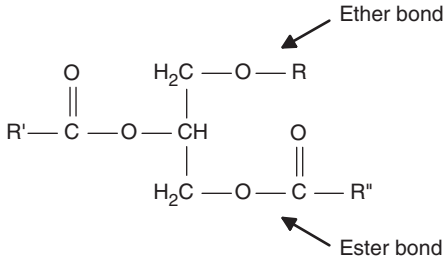
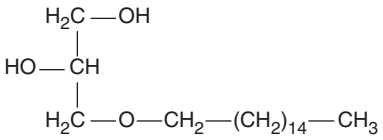
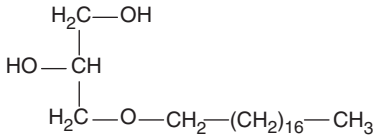


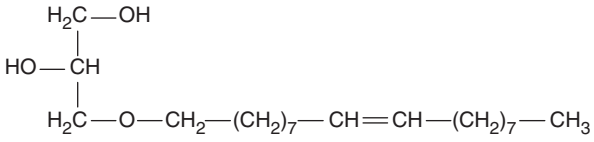
FIGURE 61-2 Alkylglycerol.



Chimyl alcohol



Batyl alcohol



Selachyl alcohol

FIGURE 61-3 Chimyl, batyl, and selachyl alcohol.

alcohol are saturated chains, selachyl alcohol contains one unsaturated bond. All the ether bonds are on the number 3 carbon of glycerol. In the natural state, these compounds are usually present as ester compounds, with carbons 1 and 2 esterified with C16 or C18 saturated fatty acids. A fourth natural compound is a methoxy-substituted alkylglycerol, shown in Figure 61-4. This active compound comprises only a small percentage of natural shark liver oil–derived alkylglycerols (about 3%).[2-4]

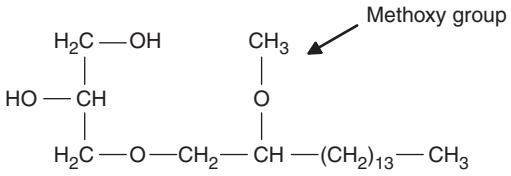


FIGURE 61-4 Methoxy-substituted alkylglycerol.

Absorption, Fate, and Excretion

About 95% of radioactive (C14-labeled) chimyl alcohol administered orally is absorbed in the intestine, with 5% being excreted in the feces in one study.[5] In the gastrointestinal tract, a large proportion of the ingested ether lipid in the form of 1-O-alkylglycerols is cleaved at the ether bond with the alkyl moieties, giving rise to fatty acids. The remainder is incorporated into 1-O-alkyl,2,3-diacyl-sn-glycerols, 1-O-alky-l-2-acyl-sn-glycerols, and 1-O-alkyl-2-acyl-sn-glycerol-3-phosphoethanolamines.[6] Ether lipids are only minor components of the human diet, so that the major portion of ether lipids in the body is synthesized in the body. Absorption of the intact ether lipid is the rule, because ether lipids are not subject to the action of lipase, which is specific for the ester bond. After feeding chimyl alcohol to rats, analysis of the lymph fluid showed that 2% to 4% of the ether lipids are found as fatty acids combined in phospholipids. About 50% is found in the triglyceride fraction, whereas another 40% is found as the free chimyl alcohol or an esterified alcohol. In the triglyceride fraction, most of the original compound is found as palmitic acid, which indicates that the ether bound in the chimyl alcohol is split during the absorption process. The cetyl alcohol (a C 15 fatty alcohol) moiety of chimyl alcohol is oxidized to palmitic acid (a C 16 fatty acid) during its passage through the intestinal mucosa.

BIOLOGICAL EFFECTS

Hemopoietic Effects

The erythropoietic, thrombopoietic, and granulopoietic stimulatory activities of 1-octadecylglycerol ethers have been demonstrated in several animal studies.[6,7] Interestingly, chimyl alcohol can stimulate hemopoiesis, but selachyl alcohol cannot.[2,3,8]

Protection Against Radiation Damage

The effects of 1-alkylglycerols in the treatment of radiation-induced leukopenia have been studied extensively. Some investigators confirmed these beneficial effects,[9] whereas others have not.[10,11] Work by Lorenz et al[12] found that lethal irradiation in mice and guinea pigs was counteracted by postirradiation injection of bone marrow. Sandler[10] believed that batyl alcohol might be the

active factor in bone marrow that prevented irradiation leukopenia. His observations, however, noted an increase mainly in erythropoiesis. Additional studies by Arturson and Linback,[13] using intraperitoneal injections of batyl alcohol in mice, showed an increase in the production of both erythrocytes and reticulocytes.

Other studies confirmed the positive effect of the alkoxyglycerols on postirradiation damage. The work of Brohult and Homberg[6] showed that lethal irradiation was counteracted by postirradiation injections of batyl alcohol. In 1963, Brohult[14] published a thesis on the use of alkylglycerols in radiation treatment. A summary of the major findings in this paper follows:

- The postirradiation decrease in thrombocytes and white cells was notably less in patients treated with alkylglycerols than in those not given alkylglycerols.
- Patients with low thrombocyte counts due to radiation treatment or chemotherapy had increased counts after treatment with alkylglycerols.
- In irradiated rats pretreated with alkylglycerols, there was less of a decrease in megakaryocytes and nucleated cells in the bone marrow compared with untreated irradiated controls.
- Selachyl alcohol was more effective than batyl alcohol in preventing megakaryocyte decrease.
- A dose-related response with a maximum response at a certain level occurred, and then a decreased response occurred when that level was exceeded.
- The alkylglycerols increased the growth rate of rats after treatment and irradiation compared with untreated irradiated rats.
- Batyl alcohol had a greater effect than selachyl alcohol on increasing growth rate in rats.
- In a series of 350 patients with cervical cancer treated with alkylglycerol and given radiation therapy, there was a greater survival rate for 1 and 5 years than in untreated irradiated controls (see "Clinical Uses of the Alkylglycerols" for discussion in further detail).

IMMUNOLOGIC ASPECTS OF ALKYLGLYCEROLS

Early in the investigation and study of ether lipids, an augmentation of the immune system seen in animals that ingested these compounds was evident. Apparently the macrophage was the key cell in this reaction. Inflamed cancerous tissue releases alkyllysophospholipids and other alkylglycerols, which are degradation products of alkyl phospholipids and alkyl neutral lipids. These compounds are found in cancerous tissue in high concentration but are in low concentration in normal tissues. One of these products, dodecylglycerol, is among the most potent macrophage activators known.[15-18] The use of the natural sn-3-octylglycerol, or batyl alcohol, found in shark liver oil produced the same effect as dodecylglycerol.[19] The mechanism of macrophage activation by the natural alkylglycerols is most likely identical to the action of lysophospholipids. Keeping in mind that activated macrophages exhibit increased phagocytosis, one method of assaying substances for activation potency is to measure the ingestion of various particles. Erythrocytes coated with immunoglobulin-G (IgG) are common target particles used in this assay.

Lysophosphatidylcholine has been shown to be effective in increasing macrophage ingestion of IgG-coated erythrocytes.[15,16] Mice were treated with intraperitoneal injections of batyl alcohol in saline, and the macrophages were harvested 4 to 5 days later. Sheep erythrocyte coated with IgG showed a greatly increased ingestion of erythrocytes. There was no increased ingestion when the cells were coated with IgM or complement, which suggests that batyl alcohol activates the macrophages for Fc-mediated ingestion only. It was interesting that batyl alcohol was more effective at a lower dose than the synthetic compound.[17]

Evidence indicates that oral intake of natural alkylglycerols results in higher levels of plasmalogens in the erythrocytes in human subjects. (Plasmalogens are ether compounds that are formed in the metabolic pathway of phosphoglycerides. They differ from phosphoglycerides in that they contain an ether linkage on the C-1 of the glycerol molecule.) Plasmalogens protect animal cell membranes against oxidative stress. In rat studies, batyl alcohol was incorporated into all tissues except brain tissue, and this action was a stereospecific incorporation.[10] It has been shown that alkylglycerols are present in human and cow milk,[19-21] along with other immunologic factors.[22] Because the neonate has not developed a mature immune system,[23] the prospect of transmitting immune functional components in the milk is a practical way to provide some protection for the newborn.[24] In one study, lactating rats were fed alkylglycerols dissolved in corn oil; the composition of the alkylglycerols was similar to that found in shark liver oil, in that batyl alcohol, chimyl alcohol, and selachyl alcohol were the major constituents.[24] The findings from this study showed that although peripheral blood granulocytes were elevated, there was no elevation of peripheral lymphocytes. Plasma levels of Igs were elevated in pups whose dams were fed alkylglycerols, but not in the controls. Both IgG and IgM were elevated to a significant degree.

CLINICAL USES OF ALKYLGLYCEROLS

Cancer

Alkylglycerols have been used primarily to treat various types of cancer, usually as adjunct therapy combined with radiation.[2,3] This section covers the work of Brohult et al[25] on cervical cancer tumor regression and on the decrease of complications resulting from irradiation therapy. It also addresses a new alkylglycerol, a methoxy-substituted alkylglycerol that occurs naturally at only 3% in shark liver oil, but may be available as a synthetic compound.

Tumor Regression with Alkylglycerol Treatment

Patient selection was determined by stages that were defined by the International Federation of Gynecology and Obstetrics as follows:

- Stage I—carcinoma strictly confined to the cervix (early stage)
- Stage IA—cases of early stromal invasion
- Stage IB—all other cases of stage I
- Stage IIA—the carcinoma extends beyond the cervix but has not extended onto the pelvic wall; the carcinoma involves the vagina except for the lower third; no parametrial involvement
- Stage IIB—the carcinoma extends beyond the cervix but has not extended onto the pelvic wall; the carcinoma involves the vagina except for the lower third; parametrial involvement is noted
- Stage III—the carcinoma has extended onto the pelvic wall; on rectal examination there is no cancer-free space between the tumor and the pelvic wall; the tumor involves the lower third of the vagina
- Stage IV—the carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum

Patients were treated with shark liver oil–derived alkylglycerol containing 100 mg of alkylglycerol, given as two capsules three times a day for a total dose of 600 mg/day. The treated group received 600 mg/day for 7 days before irradiation and for 1 to 3

months after radiation therapy. The study covered three time periods: period 1, from September 1, 1964, to February 15, 1964, comprising 458 patients; period 2, from 1970 to 1973, comprising 137 patients in a double-blind study; and period 3, from late 1973 to 1975, comprising 245 patients who were treated with alkylglycerols on "every second patient."

The control group consisted of all patients who received radiation therapy for cervical cancer but did not receive alkylglycerols.

The control group in this study consisted of 4404 patients treated during the same periods, whereas the total treated group was 841 patients. Mortality after 5 years was 31% for the group treated with alkylglycerols and 39.6% for the control group. The difference was statistically significant (P <0.001).[25]

Protection Against Radiation Injuries

Studies of patients treated from 1963 to 1966 and 1970 to 1972 by Brohult et al[26] were aimed at further evaluating the protective effects of ether lipids against irradiation injuries in patients with uterine cervix cancer. Alkylglycerols derived from Greenland shark liver oil were administered to one group of patients at 600 mg/day during the radiation treatment and 300 mg/day for 1 to 3 months after treatment. Another group of patients was treated the same way during and after radiation, but was also treated prophylactically 8 days before radiation with 600 mg/day of alkylglycerols.[28] The patients receiving alkylglycerols during and after radiation treatment were referred to as the nonprophylactic group, and the patients given alkylglycerols before the radiation as the prophylactic group. The system proposed by Kottmeier and Gray[27] was used to evaluate radiation injuries that occurred in the bladder, rectum, uterus, and intestine. Radiation injuries of grade I, with minimal objective changes in the mucosa, were excluded. Patients with radiation injuries of grades II to IV were treated as a single group: "patients with radiation injuries."

Grade II was characterized by moderate to severe changes, such as necroses, ulcerations, moderate stenoses, and reactions with lengthy bleeding. Radiation complications of grade III included injuries to the bladder, radiation fistulas from the ureters, and rectal and intestinal stenoses of such severity that colostomy or resection was needed. Grade IV was characterized by rectal and intestinal fistulas. Complications included patients with clinical features of radiation injury in whom the symptoms were found to be caused by tumor growth or a combination of tumor growth and radiation injury. These complications were termed complex injuries and represented a serious situation. All patients with complex injuries were dead after 5 years.

The incidence of radiation injuries varies with the spread of the cancer and radiation technique. The incidence is higher in the more advanced tumor stages than in the less advanced ones. It is also higher after 60 cobalt three-beam treatment of combined high-voltage and x-ray treatment than after conventional radiographs or radium alone. When comparing the groups statistically, standardized proportions have been used to cancel out differences with regard to stage distribution and radiation technique.

The total incidence of injuries was lower in the groups that received alkylglycerols (18.1% in the prophylactic group and 24.4% in the nonprophylactic group) than in the controls (37.1%). The prophylactic group had a considerably lower incidence of complex injuries and multiple injuries than both the controls and the nonprophylactic groups. The differences were highly significant (P <0.001). Analysis of the patients divided into groups according to tumor stage or radiation technique showed that the incidence of complex injuries was lower in all subgroups of prophylactically treated patients than in the corresponding control groups. A double-blind study from 1970 to 1972 showed a pronounced protective effect of prophylactic treatment against injuries after radiation therapy.[26] The use of increased doses of radium in intracavitary irradiation was followed by a high incidence of radiation injuries, which was considerably reduced by treatment with alkylglycerols, especially when these compounds were administered prophylactically.[28]

Alkylglycerols in Other Medical Conditions

Although few studies support the use of natural alkylglycerols in disease states other than cancer, it seems appropriate to consider these agents in any condition that would benefit from stimulation of an immune component. Currently, the alkylglycerols are viewed as adjunct therapy rather than primary therapeutic agents, except for the methoxy-substituted alkylglycerols. Newer forms of the alkylglycerols have been synthesized and are being tested successfully with a wide range of tumor types. Conditions that are characterized by a hyperproliferative state may benefit from treatment with alkylglycerol.

Considering that one possible effect of the alkylglycerols is competitive inhibition of diacylglycerol, it is plausible that protein kinase C would also be inhibited by this same action, because diacylglycerol is a stimulator of protein kinase C. Protein kinase C is essential to the oxidative burst in neutrophils, and agents that inhibit protein kinase C inhibit this action.[29] By inhibition of 12-O-tetradecanoylphorbol-13-acetate (TPA)–mediated arachidonic acid release, studies examining the effects of synthetic alkylglycerols on the release of arachidonic acid and arachidonate metabolites from Madin Darby canine kidney cells in response to TPA have suggested this same mechanism of protein kinase C inhibition.[30] The work by Yamamoto et al[17] supports the role of ether analogs as activators of macrophages and as primary cytotoxic agents. This dual role would suggest a wider application of alkylglycerol as adjunct therapy. Oth and Jadhav[31] observed that alkylglycerols given to lactating mice increased the peripheral granulocyte count, as well as the serum immunoglobulins in the pups. This action suggests the possible use of alkylglycerols in most infectious disorders.

Antiangiogenesis

Although more clinical and in vitro studies are necessary to fully examine the usefulness of alkylglycerols, a strong body of research is being gathered. In one research project, the antitumor effects of shark liver oil and more refined alkylglycerols were analyzed in mice with Lewis lung carcinoma tumors. Purified alkylglycerols were found to significantly decrease plasmalogen content in tumors, although the shark liver oil had no such effect. In alkylglycerol-treated mice, metastasis dissemination was reduced by 64 ± 8%, whereas the shark liver oil demonstrated a 30 ± 9% effect below control. Lastly, after a 5-day treatment with alkylglycerols, there was an attenuated presence in tumors of von Willebrand factor, a marker of endothelial cells.[34] The authors of this study believed these data might suggest an antiangiogenic effect of alkylglycerols. Another study of shark liver oil, as a standardized concentration of alkylglycerols and their methoxy derivates, found that prostate cancer cells demonstrated a marked colony inhibition following relatively small doses of 0.5 and 0.1 mg/mL of medium. Using flow cytometry to elucidate the mode of cell death, ovarian and prostate carcinoma exhibited an increased percentage of apoptotic cells. Interestingly, mammary carcinoma cells showed a predominantly necrotic effect.[35]

Blood–Brain Barrier Permeability

The treatment of central nervous system cancer with chemotherapeutic drugs is fraught with difficulty because low-toxicity methods that effectively traverse the blood–brain barrier are not well characterized. Alkylglycerols have demonstrated multiple biological activities with a prominent effect on blood–brain barrier permeability,[36] including increasing the permeability of tight junctions.[37] Clinically, this effect may prove useful to improve the brain uptake of cancerostatic agents. Testing the ability to transfer methotrexate in normal rats, intracarotid short-chain alkylglycerols were shown to constitute an effective and low-toxic strategy for transient opening of the blood–brain barrier.[38] Another study employing intracarotid coadministration of methotrexate and 1-O-pentylglycerol in nude mice resulted in a significant increase in delivery of small and large compounds to normal brain and brain tumors, including methotrexate concentrations. These increases were found in the ipsilateral brain, compared with controls without 1-O-pentylglycerol ($P < 0.005$).[37]

Experimental Antitumor Activity with Methoxy-Substituted Alkylglycerol

About 3% of the alkylglycerols in Greenland shark liver oil consist of methoxy-substituted alkylglycerols, which have been found to inhibit tumor growth in cultured cells. Two cell lines were used, a methylcholanthrene-induced murine sarcoma (MCGI-SS) and a juvenile osteogenic sarcoma. Marked growth inhibition was noted for the mixture of 2-methoxy alkylglycerols from Greenland shark liver oil, different single components derived from this oil (2-methoxy hexadecyl glycerol, 2-methoxy hexadecenyl glycerol, and 2-methoxy octadecenyl glycerol), and various synthetic compounds, including, for example, 2-ethoxy hexadecyl glycerol, 2-methoxy hexadecenyl glycerol, and 3-methoxy hexadecyl glycerol.[39]

In several tumor-host systems including solid tumors, leukemias, and lymphomas, the methoxy-substituted alkylglycerols were incorporated into the feed in different concentrations (0.1% to 2%, w/w). Growth inhibition was noted for melanoma B16, for a methylcholanthrene-induced sarcoma and Lewis lung tumor in C57BL/6J mice, for lymphoma-associated antigen in A/Sn mice with synthetic 2-methoxy hexadecyl glycerol, and for a spontaneous mammary carcinoma in C3H mice with methoxy-substituted alkylglycerols from Greenland shark liver oil. The survival time of DBA/2J mice transplanted with lymphatic leukemia P1534 was increased by synthetic 2-methoxy hexedecyl glycerol.[39,40] Metastases induced by the injection of MCGI-SS cells into a tail vein or into the portal vein were inhibited in the liver by methoxy-substituted alkylglycerols from Greenland shark liver oil.[40] Spontaneous metastasis formation from a methylcholanthrene-induced sarcoma (MCGI-SS) in lymph nodes and lungs of CBA mice was inhibited by methoxy-substituted alkylglycerols derived from Greenland shark liver oil, as well as by synthetic 2-methoxy hexadecyl glycerol.[39] Spontaneous metastasis formation from melanoma B16 was inhibited by synthetic 2-methoxy hexadecyl glycerol.[40]

The same substance can both stimulate the immune system and inhibit tumors. This has also been proven for alkyl-lysophospholipids synthesized with a methoxy group in the 2-position of the glycerol part of the molecule. These substances have been studied at the Max-Planck Institute for Immunobiology at Freiburg and at the Department of Haematology and Oncology of the University of Munich.

The German research groups showed that even alkyl-lysophospholipids without the 2-methoxy group in the glycerol part can activate macrophages in the bone marrow. This shows that ordinary glycerol ethers, after incorporation into phospholipids, can activate the body's immune defense system. These investigators thought that the macrophage-stimulating effects of alkyl-lysophospholipids explained the effects of these substances on tumors and tumor spread. Tumor cells have only a low activity of enzymes that can break down ethers. This means that alkyl ethers are incorporated into the cell membrane's phospholipids, which are then recognized and attacked by macrophages, which have a high activity of ether catabolic enzymes.

Interactions between different types of alkylglycerols and human neutrophil granulocytes were studied by Palmblad et al.[41] Platelet-activating factor (PAF) was the most potent with regard to the ability to produce an oxidative response, followed by the methoxy-substituted alkylglycerols. The study showed that there was a dissociation between the ability of an alkylglycerol to initiate oxidative and calcium responses, indicating strict structure activity relationships for the different alkylglycerols studied.

Male Infertility

In the near future, alkylglycerols may also be known to help in cases of poor sperm motility and fertility. Alkylglycerols are known to amplify PAF biosynthesis.[32] The PAF produced by mammalian sperm is an important activator of sperm motility. In one in vitro study of boar spermatozoa, alkylglycerol treatment improved percentage of motility, as well as velocity parameters after 24 hours and number of boars produced. Those boars treated with PAF receptor antagonist did not show these effects.[33]

INDICATIONS AND DOSAGE

Currently, shark liver oil–derived alkylglycerols are not used as specific therapy for any medical condition. However, they may be used as ancillary, auxiliary, or augmentative agents in many disorders. In cancer chemotherapy or irradiation therapy, they are not only protective but also additive in the overall therapeutic effect. Any disorder that has a proliferative component, which includes most inflammatory disorders, responds to alkylglycerols. Immune disorders in particular can be treated effectively with alkylglycerols. In the prevention of infection or neoplastic diseases, 50 mg of alkylglycerol three times a day is suggested. For aggressively treated disorders, 300 mg/day or more may be necessary. The use of the methoxy-derived alkylglycerols must await further research and availability of this powerful alkylglycerol.

TOXICOLOGY OF THE ALKYLGLYCEROLS

Toxicity in Animals

Oral toxicity studies with alkylglycerols have been conducted in rats, mice, and dogs. Alexander et al[42] reported that mice given a diet containing 18% alkyldiacylglycerols showed no ill effects after 2 years. Work by Brohult,[14] Peifer et al,[43] Carlson,[44] and Bandi[45] on oral feeding of alkylglycerols to rats showed that they are relatively nontoxic. Carlson[44] tested dogs with chimyl, batyl, and selachyl alcohols by feeding levels of 2.4 g/kg of body weight and found no ill effects.

Toxicity in Humans

Brohult[14] observed that a healthy human being consumes about 10 to 100 mg/day of alkylglycerols in an average diet and even higher in people who eat shark meat and shark byproducts. Only

the consumption of shark liver has been reported to produce ill effects, mainly diarrhea, due to the high squalene content. Alkylglycerols from the Greenland shark have been used for more than 30 years without undesirable side effects.

CONCLUSIONS

Ether lipids are well known as a new class of tumoricidal compounds, producing strong biological signals. Although many new compounds have been synthesized, natural compounds have been known for a long time, beginning with the work of Hanahan on PAF, a 1-O-alkylglycerol. This class of compound, know as plasmalogens, is known to inhibit phosphorylation reactions, particularly those catalyzed by protein kinase C. The dual action of alkylglycerols on both the physical structure of the cell, such as the cell membrane, and the complex biochemical pathways makes them extremely interesting as modulators of cell functions.

The biological action of the alkylglycerols suggests they may have both prophylactic and inhibitory properties against tumors. This action is highly selective and appears to be related mainly to the chemical structure of the alkylglycerol. Most clinical trials with alkylglycerols have been with advanced cases, but these results are encouraging. The mechanisms involved in antitumor activity are many and include macrophage activation, immune cytotoxicity, natural killer cell activation, enzyme inhibition and activation, and cell membrane disturbances. Other actions include the anti-infective properties, as well as the radiation protective properties of these agents.

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CHAPTER 62

Allium cepa (Onion)

Michael T. Murray, ND

Allium cepa (family: Amaryllidaceous or Liliaceous)
Common name: onion

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GENERAL DESCRIPTION

Numerous forms and varieties of onion exist, since this perennial or biennial herb is cultivated worldwide. The part used is the fleshy bulb. Common varieties are white globe, yellow globe, and red globe.

Onions range in size, color, and taste depending on their variety. The two general types of large, globe-shaped onions are classified as spring/summer or storage onions. The former class includes those grown in warm weather climates and mild or sweet in flavor. Included in this group are the Walla Walla, Vidalia, and Maui Sweet onion. Storage onions are grown in colder weather climates. After harvesting, they are dried out for several months to attain dry, crisp skins. They generally have a more pungent flavor and are usually named by their color: white, yellow, or red. Spanish onions fall into this classification. In addition to these large onions, there are smaller varieties, such as the green onion, or scallion, and the pearl onion.

CHEMICAL COMPOSITION

Onions, like garlic, contain various organic sulfur compounds:

- S-methylcysteine sulfoxide
- Trans-S-(1-propenyl) cysteine sulfoxide
- S-propylcysteine sulfoxide
- Dipropyl disulfide

Onions also contain the enzyme alliinase, which is released when the onion is cut or crushed, causing conversion of trans-S-(1-propenyl) cysteine sulfoxide to the so-called lacrimatory factor (propanethial S-oxide). Other constituents include the following[1,2]:

- Flavonoids (primarily quercetin)
- Phenolic acids (e.g., caffeic, sinapic, and p-coumaric)
- Sterols
- Saponins
- Pectin
- Volatile oils

HISTORY AND FOLK USE

Although not as valued a medicinal agent as garlic, onion has been used almost as widely. Like garlic *(Allium sativum),* onion has been used as an antispasmodic, carminative, diuretic, expectorant, stomachic, anthelmintic, and anti-infective agent. Externally, it has been used as a rubefacient and poultice, giving relief for skin diseases and insect bites.[1-3]

Onions originated in the central part of Asia, from Iran to Pakistan, and northward into the southern part of Russia. Onions have been revered throughout time not only for their culinary use but also for their therapeutic properties. As early as the sixth century, onions were used as medicine in India. Although they were popular with the ancient Greeks and Romans, they were often dressed with extra seasonings, because many people did not find them spicy enough. Yet it was their pungency that made onions popular among poor people throughout the world, because this

inexpensive vegetable could spark up meals. Onions were an indispensable vegetable in the cuisines of many European countries during the Middle Ages and later even served as a classic healthy breakfast food. Christopher Columbus brought onions to the West Indies, and then their cultivation spread throughout the Western hemisphere. Today, China, India, the United States, Russia, and Spain are among the leading producers of onions.

World onion production has increased dramatically, with current production around 44 million tons per year, making onions the second most important horticultural crop after tomatoes. Because of their storage characteristics and durability for shipping, onions have always been traded more widely than most vegetables. Onions are versatile, often used in many dishes, and accepted by almost all traditions and cultures.[4]

PHARMACOLOGY

Onions and garlic, due to their similar constituents, have many of the same pharmacologic effects. However, significant differences make one more advantageous than the other in certain conditions.

One of the key nutritional qualities of onions is their high content of quercetin. To determine uptake as well as in vivo antioxidant effects of quercetin from onions, six healthy nonobese, normocholesterolemic female volunteers participated in a randomized two-phase crossover supplementation trial to compare the antioxidant effects associated with (1) a meal of fried onions and (2) a meal of fried onions and fresh cherry tomatoes.[5] Plasma flavonoids, lymphocyte DNA damage, plasma ascorbic acid, tocopherols and carotenoids, urinary malondialdehyde, and 8-hydroxy-2-deoxyguanosine were determined to assess flavonoid absorption and antioxidant efficacy. The results indicated that the flavonoid glucosides (quercetin-3-glucoside and isorhamnetin-4-glucoside) were significantly elevated in plasma after ingestion of the onion meal, and the increases were associated with an increased resistance of lymphocyte DNA to DNA strand breakage.

A significant decrease in the level of urinary 8-hydroxy-2-deoxyguanosine was evident 4 hours after ingestion of the onion meal. After the combined tomato and onion meal, only quercetin was detected in plasma. Endogenous base oxidation was decreased, but resistance to strand breakage was unchanged. No significant change in the excretion of urinary malondialdehyde occurred after either meal. The conclusions from the study were that both meals—onions and onions with tomatoes—led to transient decreases in biomarkers of oxidative stress, although the particular biomarkers affected differed. It is possible that the differences in patterns of response reflect the different uptakes of flavonoids, but the underlying mechanism is not yet understood.

Antimicrobial Activity

Although onions exhibit antibacterial, antifungal, and anthelmintic activity, it is not nearly as potent as that of garlic. This suggests that garlic may be better indicated in cases of infection,[2,3,6] but onion can usually be consumed in larger quantities than garlic, which may increase the concentration of antimicrobial constituents in vivo to approximate those of garlic.

Cardiovascular Effects

Like garlic, onions and onion extracts were shown to decrease blood lipid levels, increase fibrinolysis, decrease platelet aggregation, and lower blood pressure in several clinical studies.[7-9] Onion oil, compared with garlic oil, was a stronger inhibitor of the enzymes cyclooxygenase and lipoxygenase, which mediate eicosanoid metabolism (prostaglandins, thromboxanes, and leukotrienes).[10] This suggests that onions would also have a greater effect on inhibition of platelet aggregation and other events mediated by eicosanoids. Garlic and onion consumption was associated with lower levels of cholesterol and triglycerides, as well as an increase in fibrinolytic activity[11] (see Chapter 63 for details). Since the quantity of onion consumed in the study cited was so much larger than that of garlic (600 g of onion per week compared with 50 g of garlic), an argument could be made that onion consumption was the major determinant.

Onion consumption may also reduce the risk of cardiovascular disease due to its quercetin content. Epidemiologic data suggested that those who consumed a diet rich in quercetin-containing foods might have a reduced risk of cardiovascular disease. In a double-blind randomized cross-over study, subjects ingested an onion soup containing either a high or a low amount of quercetin. Plasma quercetin concentrations and platelet aggregation and signaling were assessed after soup ingestion. The high-quercetin soup contained 69 mg total quercetin compared with the low-quercetin soup containing 5 mg total quercetin. Plasma quercetin concentrations were significantly higher after high-quercetin soup ingestion than after low-quercetin soup ingestion, and the high quercetin soup also influenced some aspects of platelet aggregation and signaling.[12]

Diabetes

Onions were shown to have significant oral hypoglycemic action, comparable to that of the prescription oral hypoglycemic agents tolbutamide and phenformin.[13,14] The active hypoglycemic principle in onions is believed to be allyl propyl disulphide, although other constituents such as quercetin and anthocyanidin may play a significant role as well. Experimental and clinical evidence suggested that allyl propyl disulphide lowered glucose by competing with insulin (also a disulfide) for degradation sites, thereby increasing the half-life of insulin. Other mechanisms, such as increased hepatic metabolism of glucose or increased insulin secretion, have been proposed.

In one assessment of the hypoglycemic activity of onion consumption in type 1 and type 2 diabetic patients, ingestion of 100 g of onion caused a considerable reduction in fasting blood glucose levels by about 89 mg/dL in relation to insulin (145 mg/dL) in type 1 diabetic patients, and it reduced fasting blood glucose levels by 40 mg/dL compared with glibenclamide (81 mg/dL) in type 2 diabetic patients, 4 hours later. The same dose of onion produced a significant reduction in induced hyperglycemia (glucose tolerance test) by about 120 mg/dL compared with water (77 mg/dL) and insulin (153 mg/dL) in type 1 diabetic patients, and considerably reduced the glucose tolerance test by 159 mg/dL in relation to water (55 mg/dL) and glibenclamide (114 mg/dL) in type 2 diabetic patients, after 4 hours.[15]

Antiasthmatic Action

Onions have historically been used as antiasthmatic agents.[2,3] Their action in asthma, as well as in other conditions associated with increased lipoxygenase derivatives (leukotrienes), such as psoriasis and atopic dermatitis, appears to be greater than that of garlic. (As mentioned previously, onion oil is a much greater inhibitor of cyclooxygenase and lipoxygenase.[10]) The net effect is similar to that of cortisol, which inhibits all eicosanoid metabolism via inhibition of phospholipase. Inhibition of leukotriene

formation and onion's quercetin and isothiocyanate content are probably the primary factors responsible for onion's antiasthmatic effects. These effects have been confirmed in experimental studies.[16,17]

Antitumor Effects

An onion extract was found to be cytotoxic to tumor cells in vitro and to arrest tumor growth when tumor cells were implanted in rats.[18] The onion extract was shown to be unusually nontoxic, because a dose as high as 40 times that of the cytotoxic dose for the tumor cells had no adverse effect on the host. Another species, *Allium ascalonicum* (shallots), was shown to exhibit significant antileukemic activity in mice.[19]

One human study evaluated onion consumption and stomach cancer in more than 120,000 men and women between 55 and 69 years of age. After a 3.3-year follow-up, 139 stomach cancers were diagnosed. The researchers found a strong inverse association between onion consumption and stomach cancer incidence, but no association with the use of leeks or garlic.[20]

Hair Tonic Effects

Topical application of onions has been shown to help alopecia areata—a patchy, nonscarring hair loss condition. Any hair-bearing surface may be involved in alopecia areata, and different modalities of treatment have been used to induce hair regrowth. One study compared the effectiveness of topical crude onion juice in the treatment of patchy alopecia areata in comparison with tap water.[5] The patients were divided into two groups. The onion juice treated group consisted of 23 patients (16 males and 7 females) ranging in age from 5 to 42 years old (mean, 22.7 years). The control group consisted of 15 patients (8 males and 7 females) ranging in age from 3 to 35 years old (mean, 18.3 years). The two groups were advised to apply the treatment twice daily for 2 months. Regrowth of terminal coarse hairs started after 2 weeks of treatment with crude onion juice. At 4 weeks, hair regrowth was seen in 17 patients (73.9%). At 6 weeks, hair regrowth was observed in a total of 20 patients (86.9%) and was significantly higher among males (93.7%) compared with females (71.4%). In contrast, with tap water, hair regrowth was apparent in only two patients at 8 weeks of treatment with no sex differences. These results indicate that crude onion juice can be an effective topical therapy for patchy alopecia areata.

CLINICAL APPLICATION AND DOSAGE

This chapter highlights the medicinal value of onions, particularly in cardiovascular disease, diabetes mellitus, and inflammatory conditions. Onions can be eaten liberally as part of a nutritious diet. Therapeutic dosages in the various forms are typically equal to 50 to 150 g/day of raw onion.

TOXICOLOGY

Virtually no reports of toxicity have been documented. However, people with heartburn may note an aggravation of symptoms. One study evaluated symptoms of acid reflux in 16 normal subjects and 16 heartburn patients. Subjects were studied with an esophageal pH probe for 2 hours after eating a plain hamburger and a glass of ice water, then on another day after an identical meal plus a slice of raw onion. In the normal patients, ingestion of onions did not increase any of the variables measured (number of reflux episodes, pH less than 4, time of pH less than 4, heartburn episodes, and belches). In contrast, heartburn subjects experienced a significant increase in all variables. Although the authors of the study concluded that onions could be a potent and long-lasting reflexogenic agent in heartburn patients,[21] an alternative explanation might be that onions simply improved digestive acid secretion, making the symptoms of reflux more noticeable.

DRUG INTERACTIONS

There are no confirmed drug interactions with onion consumption. Theoretically, because onion consumption may improve blood sugar control, patients with type 2 diabetes taking oral hypoglycemic drugs need to monitor glucose levels because dosage levels of the medication might need to be changed.

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CHAPTER 63

Allium sativum (Garlic)

Michael T. Murray, ND

Allium sativum (family: Amaryllidaceous or Liliaceous)
Common names: garlic, allium

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GENERAL DESCRIPTION

Garlic, a member of the lily family, is a perennial plant that is cultivated worldwide. The garlic bulb is composed of individual cloves enclosed in a white skin. It is the bulb, either fresh or dehydrated, that is used as a spice or medicinal herb.

CHEMICAL COMPOSITION

Garlic contains 0.1% to 0.36% of a volatile oil composed of sulfur-containing compounds including the following:

- Allicin
- Diallyl disulfide
- Diallyl trisulfide

Garlic oil is obtained by steamed distillation of the crushed fresh bulbs.[1] These volatile compounds are generally considered responsible for most pharmacologic properties of garlic. Other constituents of garlic include the following[1,2]:

- Alliin (S-allyl-L-cysteine sulfoxide)
- S-methyl-L-cysteine sulfoxide
- Protein (16.8%, dry weight basis)
- High concentrations of trace minerals (particularly selenium)
- Vitamins
- Glucosinolates
- Enzymes (alliinase, peroxidase, and myrosinase)

Allicin is mainly responsible for garlic's pungent odor. It is formed by the action of the enzyme alliinase on the compound alliin. The essential oil of garlic yields approximately 60% of its weight in allicin after exposure to alliinase. The enzyme is inactivated by heat, which accounts for the fact that cooked garlic produces neither as strong an odor as raw garlic nor nearly as powerful physiologic effects.[1]

HISTORY AND FOLK USE

Garlic has been used throughout history for the treatment of a wide variety of conditions. Its usage predates written history. Sanskrit records document the use of garlic remedies approximately 5000 years ago, whereas the Chinese have been using it for at least 3000 years. *The Codex Ebers*, an Egyptian medical papyrus dating to about 1550 BC, mentions garlic as an effective remedy for various ailments, including hypertension, headache, bites, worms, and tumors. Hippocrates, Aristotle, and Pliny cited numerous therapeutic uses for garlic. In general, garlic has been used throughout the world to treat coughs, toothache, earache, dandruff, hypertension, atherosclerosis, hysteria, diarrhea, dysentery, diphtheria, vaginitis, and many other conditions.[1-3]

Stories, verse, and folklore (such as its alleged ability to ward off vampires) give historical documentation to garlic's power. Sir John Harrington, in writing *The Englishman's Doctor* in 1609, summarized garlic's virtues and faults[3]:

Garlic then have power to save from death
Bear with it though it maketh unsavory breath,
And scorn not garlic like some that think
It only maketh men wink and drink and stink.

In 1721, during a widespread plague in Marseilles, France, four condemned criminals were recruited to bury the dead. The gravediggers proved to be immune to the disease. Their secret was a concoction they drank consisting of macerated garlic in wine. This became known as vinaigre des quatre voleurs ("four thieves" vinegar), and it is still available in France today.

Garlic's antibiotic activity was noted by Pasteur in 1858. Garlic was used by Albert Schweitzer in Africa to treat amebic dysentery and as an antiseptic in the prevention of gangrene during World Wars I and II.

PHARMACOLOGY

Although garlic has a wide range of well-documented effects, its most important clinical uses are in the areas of infection, cancer prevention, and cardiovascular disease.

Antimicrobial Activity

Garlic has broad-spectrum antimicrobial activity against many genera of bacteria, viruses, worms, and fungi, as summarized in several works.[4-7] These findings support the historical use of garlic in the treatment of various infectious conditions.

Antimicrobial Effects

Antibacterial Activity

Dating back to 1944, studies demonstrated that both garlic juice and allicin inhibited the growth of *Staphylococcus, Streptococcus, Bacillus, Brucella,* and *Vibrio* species at low concentrations.[7-9] In more recent studies, using serial dilution and filter paper disk techniques, fresh and vacuum-dried powdered garlic preparations were found to be effective antibiotic agents against many bacteria, as listed in Box 63-1.[4-7,10,11] In these studies, the antimicrobial effects of garlic were compared with commonly used antibiotics, including penicillin, streptomycin, chloramphenicol, erythromycin, and tetracyclines. Besides confirming garlic's well-known antibacterial effects, the studies demonstrated its efficacy in inhibiting the growth of bacteria that had become resistant to one or more of these antibiotics.[7]

Garlic administration has also been shown to significantly reduce the number of coliforms and anaerobes in the feces.[12] One clinical application of garlic's antibacterial activity may be in the treatment of *Helicobacter pylori*, because a clinical investigation indicated that garlic intake for long durations (years) was associated with a significantly lower average antibody titer. This suggests an indirect inhibitory effect on the reproduction of *H. pylori* and possibly progression to more serious peptic ulcer diseases.[13]

BOX 63-1 Clinical Relevant Microbes Inhibited by Garlic

- Bacteria
- Alpha- and β-hemolytic Streptococcus
- *Citrobacter* spp.
- *Escherichia coli*
- *Helicobacter pylori*
- *Klebsiella pneumoniae*
- Mycobacteria
- *Proteus vulgaris*
- *Salmonella enteritidis*
- *Staphylococcus aureus*
- Fungi
- *Candida albicans*
- *Cryptococcus neoformans*
- Helminths
- *Ascaris lumbricoides*
- Hookworms
- Viruses
- Herpes simplex types 1 and 2
- Human rhinovirus type 2
- Parainfluenza virus type 3
- Vaccinia virus
- Vesicular stomatitis virus

Data from references 4-7, 10, 11.

Antifungal Activity

Garlic demonstrated significant antifungal activity in many in vitro and in vivo studies.[4,14-19] From a clinical perspective, inhibition of *Candida albicans* has the most significance, because both animal and in vitro studies showed garlic to be more potent than nystatin, gentian violet, and six other reputed antifungal agents.[4,15-17] Although allicin and the volatile oil fraction are clearly the most potent active anticandida components,[20,21] aqueous garlic extracts have been shown in vivo to be effective, even at a dilution of 1:100, against the common tinea corporis, capitis, and cruris fungal skin infections.[15]

In one study at a major Chinese hospital, garlic therapy alone was used effectively in the treatment of cryptococcal meningitis, one of the most serious fungal infections imaginable.[18]

Anthelmintic Effects

Garlic extracts have anthelmintic activity against common intestinal parasites, including *Ascaris lumbricoides* (roundworm) and hookworms.[12,22]

Antiviral Effects

Garlic's antiviral effects have been demonstrated by its protection of mice from infection with intranasally inoculated influenza virus and by its enhancement of neutralizing antibody production when given with influenza vaccine.[23]

The in vitro virus-killing effects of fresh garlic, allicin, and other sulfur components of garlic were determined against herpes simplex types 1 and 2, parainfluenza virus type 3, vaccinia virus, vesicular stomatitis virus, and human rhinovirus type 2. The order for virucidal activity was the following:

ajoene > allicin > allyl methyl thiosulfinate > methyl allyl thiosulfinate

Ajoene was found in oil macerates of garlic but not in fresh garlic extracts. No antiviral activity was found for alliin, deoxyalliin, diallyl disulfide, or diallyl trisulfide. Fresh garlic extract was virucidal against all viruses tested. Virucidal activity of commercial products was dependent on their preparation processes. Those producing the highest level of allicin and other thiosulfinates had the best virucidal activity.[24] The antiviral activity of an allicin-containing garlic supplement was investigated in 146 subjects randomized to receive a placebo or an allicin-containing garlic supplement, one capsule daily, over a 12-week period.[25] The garlic-treatment group had significantly fewer colds than the placebo group (24 vs 65 patients). The placebo group, in contrast, recorded significantly more days challenged virally (366 vs 111 patients) and a significantly longer duration of symptoms (5.01 vs 1.52 days). This study indicates that allicin-containing garlic supplements can prevent the common cold virus.

Immune-Enhancing Effects

Extensive research has shown that garlic has many immune-potentiating properties, most of which are thought to be due to volatile factors composed of sulfur-containing compounds: allicin, diallyl disulfide, diallyl trisulfide, and others. For example, in vitro studies with allicin showed that it stimulated enhanced

cell-mediated cytotoxicity in human peripheral mononuclear cells. In animal models, multiple administration of allicin elicited marked antitumor effects via immunostimulatory mechanisms.[26] Fresh garlic, commercial products containing allicin, and aged garlic preparations have all shown these immune-enhancing properties. Garlic has been shown to enhance the pathogen-attacking activity of T cells, neutrophils, and macrophages, which increase the secretion of interleukin and natural killer (NK) cell activity.[27-30] The increase in killer cell activity was a remarkable 140% in those who ate the equivalent of two bulbs a day and 156% in those who consumed 1800 mg of odorless, aged garlic.

Anticancer Effects

The famous Greek physician Hippocrates prescribed eating garlic as a treatment for cancer. Animal research and some human studies suggest this may have been well-founded advice. It must be kept in mind that much of garlic's anticancer effect is likely an indirect effect via its impact on the immune system. Nonetheless, several garlic components have displayed significant anticancer effects, including enhancing phase II metabolizing enzymes, antioxidant properties, inhibition of the formation of nitrosamines, direct tumor growth inhibition, and the ability to induce apoptosis.[31-49] Human studies showing garlic's anticancer effects are largely based on epidemiologic studies.[31-35] These studies typically show an inverse relationship between cancer rates and garlic consumption. Human studies have also shown that garlic inhibits the formation of nitrosamines (powerful cancer-causing compounds formed during digestion).[45,46]

Cardiovascular Effects

Garlic appears to be an important protective factor against heart disease and strokes via its ability to affect the process of atherosclerosis at many steps. Since there is substantial clinical information on garlic's beneficial effects on the cardiovascular system, the pharmacology is discussed later in the section on "Clinical Applications".

Other Effects

Antiinflammatory Effects

Garlic extract has demonstrated significant antiinflammatory activity in experimental models of inflammation.[2,12] This activity is probably a result of garlic's inhibition of the formation of inflammatory compounds.

Hypoglycemic Action

Garlic and onions have often been used in the treatment of diabetes. Allicin has been shown to have significant hypoglycemic action. This effect is thought to be due to increased hepatic metabolism, increased release of insulin, and the insulin-sparing effect.[50] The latter mechanism appears to be the major factor, because allicin and other sulfhydryl compounds in garlic and onions compete with insulin (also a disulfide protein) for insulin-inactivating compounds, which results in an increase in free insulin.

Interestingly, when allicin was administered to groups of rats fed a high-fructose diet, the control group that was fed a diet enriched by fructose alone continued to gain weight, whereas the groups fed allicin did not.[51] This study indicates that garlic may have some practical use in weight control.

Miscellaneous Effects

Garlic possesses diuretic, diaphoretic, emmenagogue, and expectorant action.[1,10] It is also a carminative, antispasmodic, and digestant, making it useful in cases of flatulence, nausea, vomiting, colic, and indigestion.[12,52]

COMMERCIAL PREPARATIONS

The modern use of garlic primarily features the use of commercial preparations designed to offer the benefits of garlic without the odor. The marketplace is swamped with garlic products, and each manufacturer claims its product is the best. However, there are vital considerations when choosing a garlic product to prescribe. First, if the primary goal is to lower cholesterol or blood pressure, as well as exert immune-enhancing or antimicrobial effect, it is important to ensure that the product provides a sufficient level of allicin. Because allicin is not actually in the product at significant levels, manufacturers often refer to the allicin potential or allicin yield. These terms signify the amount of allicin produced when allinase is activated in the garlic tablet or powder.

The next issue is not so simple to tell from a label. It involves the quality and character of the enteric coating of the tablet. For the allicin to be liberated within the intestinal tract, the tablet must not only be resistant to the stomach's acid, it must disintegrate rapidly when it reaches the small intestine. According to research conducted by the renowned garlic experts Lawson et al,[53] when 24 brands of enteric-coated garlic were analyzed for tablet dissolution using an approved method (U.S. Pharmacopoeia dissolution method 724A), only one brand released the amount of allicin claimed on the label. The second-best brand released only 44% of its label claim, and 75% of the brands released less than 10% of their label claim. Failure to deliver an effective dosage of allicin most assuredly does not lower cholesterol or blood pressure.

Why so many garlic products fail to deliver allicin is basically due to two major problems. First, many of the garlic products contained little alliinase activity. Alliin was plentiful, but because the activity of alliinase was low, the level of allicin formed was also low. Next, many tablets contained excipients (e.g., binders and fillers) that actually inhibit alliinase activity. The alliinase activity in 63% of the brands was less than 10% of the expected activity. The inability to release an effective dose of allicin would explain why so many studies on garlic supplements fail to show benefits in lowering cholesterol or blood pressure.[54] For example, studies done on one particular garlic supplement before 1993 were mostly positive. The results from these positive studies were the main reason garlic supplements have been allowed to refer to cholesterol-lowering activity in Germany and the United States. However, most studies published since 1995 have failed to show a consistent effect in lowering cholesterol.[55-57]

Although the authors of the negative studies on garlic believed that the underlying reason for the results was a better-designed study, a more likely explanation is that they were due to a poorer quality tablet. Specifically, research conducted by Lawson showed that tablets manufactured before 1993 were twice as resistant to disintegration in acid as tablets manufactured after 1993, and that the older tablets released three times the amount of allicin than the more recently manufactured tablets.[53] Examination of package labels shows several changes in tablet excipients between the pre-1993 and post-1993 tablets. Again, these excipients are believed to block allinase activity.

Importantly, most studies that show a positive effect of garlic and garlic preparations in reducing cholesterol and blood pressure are those that use products that deliver a sufficient dosage of

allicin, other garlic components such as S-allylcysteine, and garlic extracts (e.g., aged garlic extract [AGE]) that protect against atherosclerosis via additional mechanisms, including protection against low-density lipoprotein (LDL) oxidation and improvement of endothelial cell function.

Kyolic, the AGE manufactured by the Wakunaga Wakunaga Pharmaceutical Co., Ltd. (Osaka, Japan), is a highly standardized AGE produced by extraction and aging of organic fresh garlic, at room temperature, for 20 months. The process increases antioxidant levels and converts allicin to mostly stable water-soluble organosulfur compounds, such as S-allylmercaptocysteine and S-allylcysteine. These compounds have a high bioavailability and considerable antioxidant effects.[58,59] AGE has minimal cholesterol-lowering and antimicrobial effects, but based upon good clinical data, it does have antiatherosclerotic, antiaging, and anticancer effects.

The antioxidant effects of AGE have been shown to prevent LDL oxidation[96] as well as improve endothelium-dependent vasodilation via increased nitric oxide production and decreased output of inflammatory cytokines. In a double-blind, placebo-controlled, cross over study in 15 men with angiographically proven coronary artery disease, AGE supplementation for 2 weeks significantly improved brachial artery flow-mediated endothelium-dependent dilation by 44%.[97] In a double-blind study of AGE in normal, healthy individuals, dosages between 2.4 and 7.2 g/day were shown to produce a dose-dependent selective inhibition on platelet aggregation and adhesion.[60] In a 1-year study, AGE was shown to produce a modest reduction in the calcium score of 7.5, determined by electron beam tomography, whereas the placebo group demonstrated an average increase in calcium scores of 22.2.[61,62]

Epidemiologic and animal studies suggest AGE and its organosulfur constituents, such as S-allylcysteine and S-allylmercaptocysteine, have anticarcinogenic effects. Several clinical studies validated an anticancer effect for AGE. In one double-blinded study in patients with colorectal polyps using high-AGE (AGE 2.4 mL/day) and low-AGE (AGE 0.16 mL/day) doses, in 37 patients chosen as efficacy evaluated subjects, 47.4% (9/19 patients) in the high-AGE and 66.7% (12/18 patients) in the low-AGE group had at least one new adenoma for the first and second interval (0 to 12 months after intake). The decrease rate of at least one adenoma was 50.0% (7/14 patients) in the high-AGE group for the second interval (6 to 12 months after intake), whereas there was no decrease in subjects in the low-AGE group.[63] The difference from baseline for total size of adenomas increased in the low-AGE group, whereas an increase in the high-AGE group was suppressed for the second interval. The difference from baseline for the total size of adenomas in subjects who had adenomas at baseline increased in the low-AGE group and decreased in the high-AGE group for the second interval. The results of this study suggest the possibility of preventive and therapeutic effects of AGE on colorectal adenomas, although it would be necessary to investigate these results in larger scale and longer term trials.

In a double-blind study in patients with advanced cancer, the primary end point used was a quality of life (QOL) questionnaire based on the Functional Assessment of Cancer Therapy. The subend points were changes in the NK cell activity and the salivary cortisol levels before and after administering AGE. The group consisted of 42 patients with liver cancer (84%), 7 patients with pancreatic cancer (14%), and 1 patient with colon cancer (2%). Drug compliance was relatively good in both the AGE and placebo groups. Although no difference was observed in QOL, both the number of NK cells and the NK cell activity increased significantly in the AGE group.[64]

CLINICAL APPLICATIONS

Although garlic has long been used in infectious conditions, a use supported by its antimicrobial and immune-enhancing properties, the primary clinical use of garlic has focused on its role in cardiovascular disease. Specifically, garlic is recommended primarily for its ability to lower cholesterol and blood pressure in the attempt to reduce the risk of dying prematurely from a heart attack or stroke.

In addition to the use of garlic preparations, garlic consumption as a food should be encouraged in patients with high cholesterol levels, high blood pressure, and diabetes.

Cholesterol-Lowering Activity

One of the major areas of focus in garlic's ability to offer significant protection against heart disease and strokes has been the evaluation of its ability to lower blood cholesterol levels.[1,65-69] Unfortunately, the results are inconsistent. Most, but not all, of the double-blind, placebo-controlled studies in patients with initial cholesterol levels greater than 200 given a commercial garlic preparation, providing a daily dose of at least 10 mg alliin or a total allicin potential of 4000 mcg, showed an ability to lower total serum cholesterol levels by about 10% to 12%. In addition, LDL cholesterol decreased by about 15%, high-density lipoprotein (HDL) cholesterol levels usually increased by about 10%, and triglyceride levels typically dropped by 15%,[1,53,54,69-76] whereas most trials not using products that delivered this dosage of allicin failed to produce a lipid-lowering effect.[53-57] However, based upon recent clinical trials, even using a well-defined garlic preparation is not sufficient assurance that positive results will be seen.[77-80]

One study worth mentioning evaluated the effect of raw garlic and two commonly used garlic supplements against a placebo on cholesterol concentrations in adults with moderate hypercholesterolemia. In the trial, 192 adults with low-density lipoprotein cholesterol (LDL-C) concentrations of 130 to 190 mg/dL were randomly assigned to one of the following four treatment arms: raw garlic, powdered garlic supplement, AGE supplement, or placebo. Garlic product doses equivalent to four average-sized garlic cloves a day were given 6 days/week for 6 months. None of the forms of garlic used, including raw garlic, had statistically or clinically significant effects on LDL-C or other plasma lipid concentrations in adults with moderate hypercholesterolemia.[80]

At present it can be concluded that the cholesterol-lowering effects of supplemental garlic preparations on cholesterol levels are extremely variable and modest at best. Nonetheless, the combination of lowering LDL and raising HDL can greatly improve the HDL/LDL ratio, a significant goal in the prevention of heart disease and strokes. Garlic preparations exert several other beneficial effects in preventing heart disease and strokes (discussed in "Platelet Aggregation Inhibition") and have also been shown to improve blood sugar control in diabetics with hyperlipidemia.[81]

In addition to taking a garlic supplement, individuals with high cholesterol levels should eat more garlic and onions, because increased dietary intake of garlic and onions can also lower cholesterol levels.[65-68,82] In a 1979 population study, researchers studied three populations of vegetarians in the Jain community in India who consumed differing amounts of garlic and onions.[83,84] Numerous favorable effects on blood lipids, as shown in Table 63-1, were observed in the group that consumed the largest amount. Blood fibrinogen (discussed in "Fibrinolytic Activity") levels were highest in the group eating no onions or garlic. The study was quite significant because the subjects had nearly identical diets, except in garlic and onion ingestion.

TABLE 63-1 **Effects of Garlic and Onion Consumption on Serum Lipids Under Carefully Matched Diets**

GARLIC/ONION	CHOLESTEROL	TRIGLYCERIDE
None	208 mg/dL	109 mg/dL
10/200 g/wk	172 mg/dL	75 mg/dL
50/600 g/wk	159 mg/dL	52 mg/dL

Hypertension

Garlic has demonstrated hypotensive action in both experimental animal models and humans with hypertension.[65-68,85-89] An early meta-analysis of published and unpublished randomized controlled trials of garlic preparations was conducted to determine the effect of garlic on blood pressure relative to placebo.[85] Eight trials (seven double-blind, one single-blind) were identified as meeting analytic criteria. A total of 415 subjects were included in the analysis. All trials used a dried garlic powder standardized to contain 1.3% alliin at a dosage of 600 to 900 mg/day (corresponding to 7.8 and 11.7 mg of alliin or the equivalent of approximately 1.8 to 2.7 g of fresh garlic daily).The meta-analysis concluded that garlic preparations designed to yield allicin lowered systolic and diastolic blood pressures over a 1- to 3-month period. The typical drop from pooled data was 11 mm Hg in the systolic and 5 mm Hg in the diastolic. This degree of blood pressure reduction in hypertensives can be quite significant. If blood pressure–lowering effects of garlic can be maintained, the risk of stroke may be reduced by an estimated 30% to 40% and the risk of heart attack by 20% to 25%.

Platelet Aggregation Inhibition

Excessive platelet aggregation is strongly linked to atherosclerosis, heart disease, and strokes. Garlic preparations standardized for alliin content, as well as garlic oil and AGE, have all demonstrated significant inhibition of platelet aggregation.[60,65-68,90,91] In one study, 120 patients with increased platelet aggregation were given either 900 mg/day of a dried garlic preparation containing 1.3% alliin or a placebo for 4 weeks.[90] In the garlic group, spontaneous platelet aggregation disappeared, the microcirculation of the skin increased by 47.6%, plasma viscosity decreased by 3.2%, diastolic blood pressure dropped from an average of 74 to 67 mm Hg, and fasting blood glucose concentration dropped from an average of 90 to 79 mg/dL.

Fibrinolytic Activity

Epidemiologic studies have suggested that excessive fibrinogen formation is a major primary risk factor for cardiovascular disease.[92] Garlic preparations standardized for alliin content and garlic oil and both fried and raw garlic have been shown to significantly increase serum fibrinolytic activity in humans.[93,94] This increase occurs within the first 6 hours after ingestion and continues for up to 12 hours.

Prevention of Low-Density Lipoprotein Oxidation and Other Vascular Effects

Growing evidence indicates that LDL oxidation plays a significant role in the development of atherosclerosis. Accordingly, substances that prevent oxidation of LDL may slow down atherosclerosis.

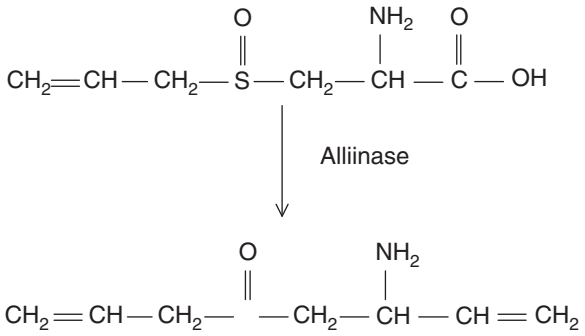


FIGURE 63-1 Conversion of alliin to allicin.

Garlic is known to exert antioxidant activity and has recently been shown to exert significant effects on preventing LDL oxidation.[95-100] In one study, healthy human volunteers given 600 mg/day of a garlic preparation providing 7.8 mg alliin for 2 weeks had a 34% lower susceptibility to lipoprotein oxidation compared with controls.[95] These results are significant given the short amount of time in which they were produced, coupled with the importance of reducing lipoprotein oxidation.

Another study was a placebo-controlled, double-blind trial of 23 subjects with coronary artery disease who had one to three major coronary arteries that were at least 75% blocked. After the subjects ingested 300 mg of garlic powder, 2 and 4 hours after a single dose, the atherogenicity of their sera was markedly decreased. Less cholesterol accumulated, and there were lower levels of oxidized LDL in human aortic smooth muscle cells cultured with patients' sera after treatment compared with those cultured with sera obtained before administration of garlic. After 3 weeks of therapy at 300 mg, three times daily, blood serum atherogenicity was decreased twofold compared with initial levels.[101]

Since AGE has also shown an ability to prevent LDL oxidation[99] it is likely that S-allylcysteine and other nonallicin components of garlic play a major role in the protection against LDL oxidation.

Studies have also shown garlic or garlic components to exert positive effects on endothelial function, vascular reactivity, and peripheral blood flow.[102-104]

DOSAGE

On the basis of extensive clinical research, a commercial garlic product should provide a daily dose equal to at least 4000 mg of fresh garlic. This dosage translates to at least 10 mg alliin or a total allicin potential of 4000 µg (Figure 63-1). Alternatively, AGE at a dosage of 2.4 to 7.2 g/day can be used.

TOXICITY

For the vast majority of individuals, garlic is nontoxic at the dosages commonly used. For some, however, it can irritate the digestive tract and cause heartburn. Others are apparently unable to effectively detoxify allicin and other sulfur-containing components. Prolonged feeding of large amounts of raw garlic to rats resulted in anemia, weight loss, and failure to grow.[105] Although the exact toxicity of garlic has yet to be definitively determined, side effects are rare at the recommended dosage. Garlic is thought to be safe during pregnancy and breastfeeding. Two studies showed that babies liked breast milk better from mothers who ate garlic.[106,107]

DRUG INTERACTIONS

Generally, garlic supplements should not be used in patients taking anticoagulant drugs (e.g., Coumadin) or in those scheduled for an elective surgery because of garlic's effects on platelet aggregation. The exception to this warning is AGE, because it appears safe for use in patients on warfarin therapy.[108]

Although garlic components have shown an ability to affect cytochrome P450 enzymes, they do not appear to interfere with drug metabolism.[109,110]

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CHAPTER 64

Aloe vera (Cape Aloe)

Michael T. Murray, ND

Aloe vera (family: Liliaceous)
Common name: cape aloe

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GENERAL DESCRIPTION

More than 300 species of aloe plants exist, but the most popular medicinal variety is currently *Aloe vera*. The nomenclature of *A. vera* is somewhat confusing, because the plant has been known by various names, most notably *A. barbadensis* and *A. vulgari*. The geographic origination of the plant is unclear. Historical records indicate that it may have originated from Egypt or the Middle East. Aloe has been introduced and naturalized throughout most of the tropics and warmer regions of the world, including the Caribbean, southern United States, Mexico, Latin America, the Middle East, India, and Asia.[1]

A. vera is a perennial plant with yellow flowers and tough, fleshy triangular or spear-like leaves arising in a rosette configuration. The leaves are up to 20 inches long and 5 inches across at the base, tapering to a point. There may be as many as 30 leaves per plant. The margins of the leaf are characterized by saw-like teeth. Inside, the meaty leaf is filled with gel that arises from a clear, central mucilaginous pulp. Mature aloe measures 1.5 to 4 feet long and has a base of 3 inches or greater in diameter.

The leaf is composed of three distinct layers: an outer layer of tough tissue; a corrugated lining just beneath the outer layer; and the major portion of the leaf, the inner layer consisting of parenchymal cells containing large vacuoles of a semisolid, gelatinous, transparent gel. The bitter latex of the corrugated layer protects the plants from predators. Should an animal bite the leaf, the sap causes irritation. The dried latex (juice) derived from the corrugated layer is the source of the laxative properties of aloe. The parenchymal tissue or gel is the portion of the aloe used in other applications.[2]

Aloe vera Terminology

- *A. vera gel*—naturally occurring, undiluted parenchymal tissue obtained from the decorticated leaves of *A. vera*
- *A. vera concentrate*—*A. vera* gel from which the water has been removed
- *A. vera juice*—an ingestible product containing a minimum of 50% *A. vera* gel
- *A. vera latex*—the bitter yellow liquid derived from the pericyclic tubules of the rind of *A. vera*, the primary constituent of which is aloin.

CHEMICAL COMPOSITION

The main feature of all aloe plant portions is a high water content. Aloe gel contains 99% water, whereas the skin and fillet fractions contain 90% and 98% water, respectively. *A. vera* contains numerous compounds possessing biological activity. Although many botanical medicines have substantial geographic variation in content, commercial aloe is quite consistent. One study found that the composition of the major compounds was remarkably invariable, with aloeresin A, aloesin, and aloin (both epimers A and B) contributing between 70% and 97% of total dry weight in a ratio of approximately 4:3:2, respectively. Minor compounds were less evenly distributed, with aloinoside A and aloinoside B found in higher concentrations in Western countries. The aloin content of the exudate varied, but there were no distinct geographic discontinuities.[3]

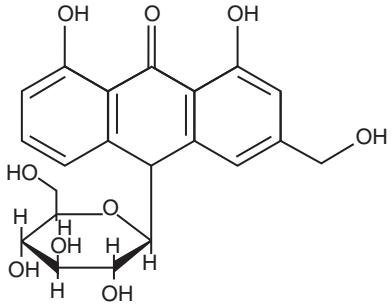


FIGURE 64-1 Aloin and aloe-emodin.

Anthraquinones

In 1851, the cathartic action of aloe was discovered to be due to aloin, a lemon yellow powder formed from drying of the bitter latex (Figure 64-1). From this material several anthracenes have been isolated, the major anthraquinone being barbaloin. Barbaloin and aloin are often referred to synonymously. Although aloe contains other anthraquinone derivatives, including the anthracene known as aloe-emodin, barbaloin is considered the most potent cathartic. As a whole, the anthraquinone compounds are water-soluble glycosides easily separated from the water-insoluble resinous material.[1-5]

Saccharides

Recent research on *A. vera* has focused on the glycoprotein, mucopolysaccharide, and polysaccharide constituents. Aloe contains the polysaccharides galactose, xylose, arabinose, and acetylated mannose. The latter, similar to guar and locust bean, has received considerable clinical research attention as an antiviral and immunopotentiating agent, especially in the treatment of acquired immunodeficiency syndrome (AIDS). Acemannan is a water-soluble, long-chain polydispersoid β(1,4)-linked mannan polymer interspersed with *O*-acetyl groups found mainly in aloe gel.[6]

Prostanoids

Several prostanoid compounds have been discovered in *A. vera* extracts.[7] The conversion of essential fatty acids to prostanoids by the enzyme cyclooxygenase in a plant such as *A. vera* is rare. The major unsaturated fatty acid in the plant is γ-linolenic acid (C18:3), which can be converted to icosatrienoic acid, the precursor to prostaglandins of the 1 series. The 1 series prostaglandins are known to exert more favorable effects on inflammation, allergy, platelet aggregation, and wound healing. The presence of γ-linoleic acid or prostaglandins, or both, in a stable medium, along with inhibitors of thromboxane synthesis, may be another important chemical characteristic of aloe responsible for its antiinflammatory and wound-healing effects.

Superoxide Dismutase

Extracts from the parenchymatous leaf gel and the rind of aloe (*A. barbadensis* Miller) have been shown to contain seven electrophoretically identifiable superoxide dismutases (SODs). Two of these seven are mangano SODs, whereas the other five activities are cupro-zinc SODs.[8]

BOX 64-1 Chemical Composition of Aloe Vera

Anthraquinones: Aloin, barbaloin, isobarbaloin, anthranol, aloetic acid, anthracene, ester of cinnamic acid, aloe-emodin, emodin, chrysophanic acid, ethereal oil, resistannol
Saccharides: Cellulose, glucose, mannose, L-rhamnose, aldopentose
Prostanoids: Gamma-linolenic acid
Enzymes: Oxidase, amylase, catalase, lipase, alkaline phosphatase
Amino acids: Lysine, threonine, valine, methionine, leucine, isoleucine, phenylalanine
Vitamins: Vitamins B_1, B_2, B_6, C, and E; folic acid; choline; β-carotene
Minerals: Calcium, sodium, manganese, magnesium, zinc, copper, chromium
Miscellaneous: Cholesterol, triglycerides, steroids, uric acid, lignins, β-sitosterol, gibberellin, salicylic acid

Data from Shelton RM. Int J Dermatol 1991;30:679-683.

Other Constituents

Other biological active compounds found in *A. vera* include the following:

- A serine carboxypeptidase
- Salicylates
- Minerals
- Vitamins
- Sterols
- Amino acids

Box 64-1 provides a partial listing of the remarkably diverse range of compounds isolated from *A. vera*.[2-5]

HISTORY AND FOLK USE

A. vera has a storied history of use. Mesopotamian clay tablets dated 1750 BC indicate that *A. vera* was used for medicinal purposes. Egyptian records from 550 BC also mentioned aloe for infections of the skin. The ancient Greeks were also aware of aloe's medicinal effects, since both Pliny (23-79 AD) and Dioscorides (first century AD) wrote of aloe's ability to treat wounds and heal infections of the skin. *A. vera* is still widely used in many traditional systems of medicine. In India, for example, in addition to external applications, aloe (whole leaves, the exudate, and the fresh gel) is used as a cathartic, stomachic, and anthelmintic. *A. vera* has been adopted into their materia medicas by many cultures of the world.[1]

In the United States, the history of aloe can be traced as far back as the *United States Pharmacopoeia* of 1820, where a number of aloe preparations were described. Most of these preparations were designed to take advantage of aloe's laxative effects. By the early 1900s, more than 27 different aloe preparations were in popular use. In 1920, aloe began being cultivated for pharmaceutic use.[4]

A major development in the modern use of aloe occurred in 1935, when a group of physicians successfully used the fresh juice to treat a patient with facial burns due to radiographs.[9] The relief offered by aloe in the topical treatment of burns, minor irritations, skin ulcers, and other skin disorders is a major reason why companies supplying dermatologic and cosmetic products have incorporated aloe into many of their formulations.

Although more and more of aloe's medicinal effects are being confirmed, it is still predominantly administered without direct medical supervision. Therefore, the history and folk use of aloe are continuing to evolve.

PHARMACOLOGY

The pharmacology of aloe is surprisingly diverse—its laxative, immune potentiation, antimicrobial, and wound-healing activities help explain its wide-ranging folk and clinical applications.

Gastrointestinal Effects

Laxative Effects

Although physicians have prescribed the whole aloe leaf as a cathartic for more than 2000 years, it was not until 1851 that the active principle aloin was discovered.[1] In small doses, aloin acts as a tonic to the digestive system, giving tone to the intestinal muscle. At higher doses, it becomes a strong purgative. Its actions are most obvious on the large intestine, where it increases colonic secretions and peristaltic contractions. In combination with strychnine and belladonna, aloin became one of the most popular laxatives for chronic constipation for many years. Because aloin often causes painful contractions, other anthraquinone laxatives like cascara and senna are now much more popular.[10,11]

A substantial amount of research activity continues in an effort to understand the laxative effects of aloe. Research using the rat large intestine showed that the increase in water content of the large intestine induced by barbaloin preceded the stimulation of peristalsis, attended by diarrhea. Therefore, it was suggested that the increase in water content was a more important factor than the stimulation of peristalsis in the diarrhea induced by barbaloin.[12] Further studies by the same researchers suggested that aloe-emodin-9-anthrone (AE-anthrone) produced from barbaloin in the rat large intestine might be the actual chemical mediator of this effect. AE-anthrone not only caused an increase in the intestinal water content but also stimulated mucus secretion.[13]

Bowel Detoxification

In 1985, Bland[14] reported the effect of orally consumed *A. vera* juice on urinary indican, gastrointestinal pH, stool culture, and stool specific gravity in a semi-controlled study of 10 (5 men and 5 women) healthy human subjects.[14] Urinary indican (see Chapter 30) is used as an indicator of the degree to which either dietary protein is malabsorbed or intestinal bacteria are engaged in putrefactive processes. After a full week of drinking 6 oz. of *A. vera* juice three times daily, urinary indican levels decreased one full unit. This suggests that regular *A. vera* juice consumption can lead to improved protein digestion and assimilation or reduced bacterial putrefaction, or both.

Inhibition of Gastric Acid Secretion

With Heidelberg gastric analysis, *A. vera* juice was shown to increase gastric pH by an average of 1.88 U. This supports the findings of other researchers that *A. vera* gel can inhibit the secretion of hydrochloric acid. The Heidelberg test also demonstrated that *A. vera* juice can slow down gastric emptying, possibly leading to improved digestion.

Six of the 10 subjects showed marked alterations in stool cultures after the week long study. This implies that *A. vera* juice may exert some bacteriostatic or fungistatic activity. In the four subjects with positive cultures for yeast, there was a reduction in the number of yeast colonies.

Stool specific gravity was reduced after the week of drinking *A. vera* juice. This implies improved water retention, yet none of the subjects complained of diarrhea or loose stools.

TABLE 64-1 **Antimicrobial Effects of *Aloe Vera* Extract in Cream Base Compared with Silver Sulfadiazine in Agar (AgSD) Well (6-mm) Diffusion**

ORGANISM	ALOE VERA	AgSD
Gram-negative		
Escherichia coli	16	12
Enterobacter cloacae	14	12
Klebsiella pneumoniae	14	6
Pseudomonas aeruginosa	17	12
Gram-positive		
Staphylococcus aureus	18	12
Streptococcus pyogenes	16	12
Streptococcus agalactiae	16	12
Streptococcus faecalis	6	11
Bacillus subtilis	19	14

Data from Robson MC, Heggers JP, Hagstrom WJ. J Burn Care Rehabil 1982;3:157-162.
Inhibition zones measured in millimeters.

IMMUNE-ENHANCING AND ANTIMICROBIAL ACTIVITY

Immunologic Effects

Antibacterial and Antifungal Activity

Aloe demonstrated activity against many common bacteria and fungi in several studies. In a detailed review of these studies, the researchers assayed the antimicrobial properties of an *A. vera* extract and reviewed the work of others.[15-17] Both mean inhibitory and mean lethal concentrations were determined and compared with silver sulfadiazine (SSD), a potent antiseptic used in the treatment of extensive burns. As shown in Table 64-1,[19] the antimicrobial effects of *A. vera* compare quite favorably with those of SSD. A 60% *A. vera* extract was found to be bactericidal against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Citrobacter* spp., *Enterobacter cloacae*, *Streptococcus pyogenes*, and *S. agalactiae*. Concentrations of 70% aloe were bactericidal for *Staphylococcus aureus*, 80% for *E. coli*, and 90% for *S. faecalis* and *Candida albicans*. Organisms inhibited in other studies include *Mycobacterium tuberculosis*, *Trichophyton* spp., and *Bacillus subtilis*.[2,4,5] The antimicrobial activity against common skin pathogens of *A. vera* gel in a cream base was shown to be slightly better than SSD in agar well diffusion studies.[19]

Antiviral Effects

Acemannan (acetylated mannose) in injectable form has been approved for veterinary use in fibrosarcomas and feline leukemia. Its action in feline leukemia is quite impressive. Feline leukemia, like AIDS, is caused by a retrovirus (feline leukemia virus). The virus is so lethal that once cats develop clinical symptoms, they are usually euthanized. Typically more than 70% of cats die within 8 weeks of the onset of clinical signs. In a study of 44 cats with clinically confirmed feline leukemia, acemannan was injected (2 mg/kg) weekly for 6 weeks and the cats were reexamined 6 weeks after termination of treatment.[18] At the end of the 12-week study, 71% of the cats were alive and in good health.

Acemannan demonstrated significant antiviral activity against several viruses, including feline AIDS, human immunodeficiency virus type 1 (HIV-1), influenza virus, and measles virus.[20-22]

Immune Enhancement

Acemannan is a potent immunostimulant.[18,23-25] Among the effects noted for acemannan are the enhancement of macrophage release of interleukin (IL)-1-α, cytokines, tumor necrosis factor, and nitric oxide release, as well as phagocytosis and nonspecific cytotoxicity. Acemannan also enhances T-cell function and interferon production, although these actions may also be due to enhanced macrophage function. Macrophage production of cytokines IL-6 and tumor necrosis factor-α were dependent on the dose of acemannan provided. These effects can be substantial. For example, in one study, acemannan was shown to enhance the macrophage respiratory burst (two-fold increase above the media controls), phagocytosis (45% compared with 25% in controls), and killing of *C. albicans* (38% killing of *C. albicans* compared with 0% to 5% killing in controls).[26]

Hematopoietic Effects

Several complex carbohydrates have been found to significantly stimulate hematopoiesis. CARN 750, a polydispersed β-(1,4)-linked acetylated mannan isolated from the *A. vera* plant, has been shown to have hemato-augmenting properties. Subcutaneous injections of 1 mg/mouse of CARN 750 optimally increased hematopoietic progenitors, measured as IL-3–supported colony forming units, culture (CFU-C) and high proliferative potential colony forming cell (HPP-CFC) assays in the spleen. Providing 2 mg/animal of CARN 750 optimally increased bone marrow cellularity, frequency, and absolute number of HPP-CFCs and CFU-Cs. The hematopoietic activity of CARN 750 increased with the frequency of administration. The greatest increase in activity occurred in mice myelosuppressed with radiation.[27]

Antiinflammatory Activity

A. vera has been shown to exert a number of antiinflammatory actions, including blocking of the generation of inflammatory mediators like thromboxanes and bradykinin, reducing neutrophil infiltration during inflammation and reducing edema.* Several compounds in aloe are responsible for these actions. The most important are glycoproteins, which inhibit and actually break down bradykinin, a major mediator of pain and inflammation; various anthraquinones; and salicylates. These antiinflammatory substances may be of significance in both topical and oral applications.

One comprehensive study evaluated the effects of aqueous, chloroform, and ethanol extracts of *A. vera* gel on carrageenan-induced edema in the rat paw and neutrophil migration into the peritoneal cavity stimulated by carrageenan. The capacity of the aqueous extract to inhibit cyclooxygenase activity was also evaluated. The aqueous and chloroform extracts decreased the edema induced in the hind paw and the number of neutrophils migrating into the peritoneal cavity, whereas the ethanol extract only decreased the number of neutrophils. The aqueous extract was also found to inhibit prostaglandin E_2 production from arachidonic acid, demonstrating an inhibitory action on cyclooxygenase. The aqueous extract contained anthraglycosides, reductor sugars, and cardiotonic glycosides, whereas the ethanol extract contained saponins, carbohydrates, naphthoquinone, sterols, triterpenoids, and anthraquinones. The chloroform extract contained sterols and anthraquinones.[32]

Another useful aspect of aloe is its ability to inhibit lipid peroxidation and scavenge free radicals. One study measured the activity of seven anthraquinones and four anthrones against nonenzymatic and enzymatic lipid peroxidation in vitro and their ability to scavenge free radicals. Using rat hepatocytes exposed to strong oxidizing agents, dithranol and anthrone provided the strongest inhibition of nonenzymatic peroxidation. Rhein anthrone and aloe-emodin showed the highest inhibitory activity against peroxidation of linoleic acid catalyzed by lipoxygenase. Anthrone, dithranol, and rhein anthrone were the most effective free radical scavengers.[33]

Other Effects

Wound Healing

The topical effects of *A. vera* appear to be due to a combination of enhancement of wound healing along with antiinflammatory, moisturizing, emollient, and antimicrobial actions.* *A. vera* contains a number of compounds necessary for wound healing, including vitamin C, vitamin E, and zinc. Unlike many other antiinflammatory substances, *A. vera* has been shown to stimulate fibroblast and connective tissue formation, thereby promoting wound repair. Finally, aloe appears to stimulate the epidermal growth and repair process, including increasing the manufacture of supportive glycosaminoglycans, presumably due to its polysaccharides.[41] Mannose-6-phosphate, the major sugar in the *A. vera* gel, may be its most active growth substance.[42]

Another interesting effect of aloe in wound healing is its ability to counteract the wound healing suppression effects of cortisone. In one study, *A. vera* at doses of 100 and 300 mg/kg daily for 4 days blocked the wound healing suppression of hydrocortisone acetate up to 100% using the wound tensile strength assay. The authors suggested this response was because of the growth factors present in *A. vera* masking the wound-healing inhibitors.[43]

Alcohol Detoxification

Oral administration of aloin (300 mg/kg) given 12 hours before administration of alcohol (3 g/kg) significantly decreases the blood alcohol area under the curve by a remarkable 40%. This suggests an increase in the rate of blood alcohol elimination from the body of 45% to 50%. Analysis of hepatic triglyceride levels revealed that both ethanol and aloin given alone significantly increased the triglyceride levels in a comparable manner. However, the level obtained by the combined treatment of aloin and ethanol was not statistically different from that produced by either treatment alone. The levels of serum L-aspartate:2-oxoglutarate aminotransferase and L-alanine:2-oxoglutarate aminotransferase activities were not increased by acute alcohol intoxication, aloin alone, or the combined treatment of alcohol and aloin.[44]

CLINICAL APPLICATIONS

Burns, Frostbite, and Other Tissue Damage

Despite growing consumer awareness of *A. vera*'s soothing effects on burns and wound healing during the past 40 years, few human studies have been conducted. Virtually all of the studies support the topical use of *A. vera* gel, especially in minor burns or skin inflammation.[6] Recent research has supported its use for even more severe tissue damage.

*References 2, 4, 5, 19, 28-31.

*References 2, 4, 5, 19, 34-40.

Although limited, the human research has been promising. For example, one study found *A. vera* gel quite successful in three patients with chronic leg ulcers of 5, 7, and 15 years' duration.[45] The gel was applied to the ulcers on gauze bandages. Rapid reduction in ulcer size was noted in all three subjects, and complete resolution occurred in two. Encouraging results were also reported for acne and seborrhea.

In a study of 27 patients with a partial-thickness burn wound, treatment with *A. vera* gel was compared with Vaseline gauze. The average time of healing in the aloe gel area was a statistically significant and dramatic 1 week shorter: 11.9 days compared with 18.2 days for the Vaseline gauze–treated wound. Histologic evaluation showed early epithelialization in the *A. vera* gel–treated area.[46]

In another double-blind study, the efficacy of *A. vera* cream for partial-thickness burn wounds was studied and compared with that of SSD. Thirty patients with similar types of second-degree burns at two sites on different parts of the body were included in this study. Each patient had one burn treated with topical SSD and one treated with aloe cream, randomly. The rate of reepithelialization and healing of the partial thickness burns was significantly faster in the site treated with aloe than in the site treated with SSD (15.9 vs 18.73 days, respectively; $P < 0.0001$).[47]

Another study compared the therapeutic effects of systemic pentoxifylline with topical *A. vera* cream in the treatment of frostbite. The frostbitten ears of 10 New Zealand white rabbits were assigned to one of four treatment groups: untreated controls, those treated with *A. vera* cream, those treated with pentoxifylline, and those treated with *A. vera* cream and pentoxifylline. The control group had a 6% tissue survival. Tissue survival was notably improved with pentoxifylline (20%), was better with *A. vera* cream (24%), and was best with the combination therapy (30%).[48]

Aloe appears to be effective even in particularly severe tissue injuries, such as those seen in necrotizing fasciitis. Necrotizing fasciitis usually manifests as a low-grade cellulitis that quickly deteriorates to a limb- and life-threatening soft tissue infection. Immediate surgical débridement is essential, followed by aggressive wound management. An interesting report described excellent results in two cases. Case 1 was a 72-year-old female who, upon presenting to the emergency department with a "sore bottom," was diagnosed with five problems:

- Anal-rectal abscess
- Fournier's gangrene
- Ulcerative enterocolitis
- Chronic blood loss/anemia
- Protein caloric malnutrition

After débridement, her anal-rectal wound extended from the labia to the left buttock. Care was multidisciplinary and included applying a water-based aloe gel and saline-soaked gauze twice a day. After 45 days, the wound exhibited a pink base with granulation tissue and contraction of the wound edges.

Case 2 was a 48-year-old male with seroma of the left leg secondary to a crush injury. Within 3 days he developed deep vein thrombosis in that leg, as well as two large seroma cavities on either side of the thigh. Care included packing with aloe gel and saline-soaked sponges. Two weeks after admission, the anterior wound was covered with a split-thickness skin graft, whereas partial closure of the lateral cavity was attempted unsuccessfully with retention sutures. After 5 weeks, healing was complete for the anterior wound and 95% complete for the posterior wound.[49]

A double-blind study showed that patients with pressure sores responded equally to an acemannan hydrogel wound dressing or a moist saline gauze wound dressing.[50]

Radiation Burns

Research into the topical applications of *A. vera* gel began in the 1930s for the treatment of radiation burns. During the 1930s, radiographs were used therapeutically for cancer, eczema, and other skin complaints, and as a depilatory agent. In 1935, Collins and Collins[9] reported the success of *A. vera* gel in a single case, a woman with a patch of severe x-ray dermatitis on her forehead. The woman had tried various medical treatments for 8 months, only to have her condition worsen. The Collinses were going to perform a skin graft, but as a temporary measure applied a preparation of fresh whole *A. vera* leaves to reduce the itching. The result was that "Twenty-four hours later she reported that the sensation of itching and burning had entirely subsided," and by 5 weeks "there was complete regeneration of the skin of the forehead and scalp, new hair growth, complete restoration of sensation, and absence of scar." Five months after treatment was started, there was complete healing. The following case reports, although not as positive as this initial study, clearly indicated that *A. vera* was effective in some cases.

Until the 1940s most of the studies on aloe were reported case histories.[4] To substantiate these case studies, animal studies began to appear in the literature. Rowe and colleagues[39] performed several studies in rats with radiation-induced ulcers and determined that fresh aloe pulp was effective, whereas dried aloe powder was not.[4,38]

In 1953 Lushbaugh and Hale,[40] working for the US Atomic Energy Commission, produced one of the most convincing studies of the efficacy of *A. vera* gel. Twenty albino rats were exposed to β-radiation, and different treatments were used on quadrants of the affected area of each animal. The treatments used were fresh *A. vera* leaf, a commercial *A. vera* ointment, application of a dry gauze bandage, and an untreated control. Both fresh *A. vera* and the *A. vera* ointment produced clear improvements. At the end of 2 months, the *A. vera*–treated areas were completely healed, whereas the other two areas had not yet healed at the end of 4 months.

A large, placebo-controlled, double-blind study cast doubt on the efficacy of aloe for severe radiation burns. Three Phase III randomized trials were reported in this study. The first one was double-blind, used a placebo gel, and involved 194 women receiving breast or chest wall irradiation. The second trial randomized 108 such patients to *A. vera* gel versus no treatment. Skin dermatitis was scored weekly during both trials both by patients and by health care providers. Skin dermatitis scores were virtually identical on both treatment arms during both trials.[51] The aim of the study was to see if topical *A. vera* gel would be beneficial in reducing the identified skin side effects of radiation therapy, including erythema, pain, itching, dry desquamation, and moist desquamation compared with aqueous cream. The secondary aim was to assess the effect of other factors known to predict severity of radiation skin reaction (i.e., breast size, smoking habit, and one or more drainages of lymphocele after surgery) on other skin side effects. The third study involved more than 225 patients with breast cancer after lumpectomy or partial mastectomy who required a course of radiation therapy using tangential fields. Like the other two studies, *A. vera* gel did not significantly reduce radiation-induced skin side effects.[52]

These surprising results might be explained by another study that compared the efficacy of commercially available gels with an acemannan-rich extract from aloe leaves in the treatment of irradiated mice. Male C3H mice received graded single doses of γ-radiation ranging from 30 to 47.5 Gy to the right leg. In most experiments,

the gel was applied daily, beginning immediately after irradiation. To determine the timing of application for the best effect, gel was applied beginning on days –7, 0, or +7 relative to the day of irradiation (day 0) and continuing for 1, 2, 3, 4, or 5 weeks. The right inner thigh of each mouse was scored on a scale of 0 to 3.5 for severity of radiation reaction from the seventh to thirty-fifth day after irradiation. Dose–response curves were obtained by plotting the percentage of mice that reached or exceeded a given peak skin reaction as a function of dose. The researchers found that although the acemannan-rich extract gel was highly effective, the commercially available gel showed no improvement over the control. They also found that the aloe gel had to be applied immediately after irradiation and continued for at least 2 weeks. There was no effect if the aloe gel was applied only before irradiation or beginning 1 week after irradiation. Clearly, the quality and concentration of aloe constituents are crucial if clinical results are to be obtained.[53]

Psoriasis

One double-blind, placebo-controlled study evaluating the clinical efficacy and tolerability of topical *A. vera* extract 0.5% in a hydrophilic cream obtained impressive results. Sixty patients (36 males and 24 females) aged 18 to 50 years (mean 25.6 years) with slight to moderate chronic plaque–type psoriasis and psoriasis area, and severity index (PASI) scores between 4.8 and 16.7 (mean 9.3) were enrolled and randomized to two groups. The mean duration of the disease before enrollment was 8.5 years (range 1 to 21 years). Patients self-administered trial medication topically at home three times daily for 5 consecutive days/week (maximum 4 weeks active treatment). Patients were examined on a weekly basis, and those showing a progressive reduction of lesions, desquamation followed by decreased erythema, infiltration, and lowered PASI score, were considered healed. The study was scheduled for 16 weeks with 12 months of follow-up on a monthly basis. The treatment was well tolerated by all the patients, with no adverse drug-related symptoms and no dropouts. By the end of the study, the *A. vera* extract cream had cured 25 of 30 patients (83.3%) compared with the placebo cure rate of only 2 of 30 patients (6.6%), resulting in significant clearing of the psoriatic plaques (328 of 396, or 82.8%) versus placebo (28 of 366, or 7.7%), and a decreased PASI score to a mean of 2.2.[54]

In another study, the efficacy of topical *A. vera* was compared with 0.1% triamcinolone acetonide (TA) in mild to moderate plaque psoriasis. After 8 weeks of treatment, the mean PASI score decreased from 11.6 to 3.9 in the *A. vera* group and from 10.9 to 4.3 in the TA group. The mean Dermatology Life Quality Index scores decreased from 8.6 to 2.5 in the *A. vera* group and from 8.1 to 2.3 in the TA group. These results indicated that both treatments had similar efficacy in improving the quality of life of patients with mild to moderate psoriasis.[55]

Gastric Ulcers and Ulcerative Colitis

Internal use of *A. vera* gel to treat peptic ulcers was studied in 1963.[56] Twelve patients with x-ray–confirmed duodenal ulcers were given 1 tablespoon of an emulsion of *A. vera* gel in mineral oil once daily. At the end of 1 year, all patients demonstrated complete recovery and no recurrence. On the basis of experimental evidence, the following factors were considered responsible for the effectiveness:

- *A. vera* gel inactivates pepsin in a reversible fashion. When the stomach is devoid of food, pepsin is inhibited by *A. vera* gel; however, in the presence of food, pepsin is released and allowed to digest the food.
- The gel inhibits the release of hydrochloric acid via interference with histamine binding to the parietal cells.
- *A. vera* gel is an extremely good demulcent that heals and prevents aggravating irritants from reaching the sensitive ulcer.

One double-blind study also found *A. vera* gel useful for ulcerative colitis. In the study, 44 patients were randomly given oral *A. vera* gel or placebo, 100 mL twice daily for 4 weeks. Clinical remission, improvement, and response occurred in 9 (30%), 11 (37%), and 14 (47%), respectively, of 30 patients given aloe vera, compared with 1 (7%), 1 (7%), and 2 (14%), respectively, of 14 patients taking placebo. The Simple Clinical Colitis Activity Index and histologic scores decreased significantly during treatment with *A. vera* ($P = 0.01$ and $P = 0.03$, respectively), but not with placebo.[57]

Acquired Immunodeficiency Syndrome

Although acemannan has demonstrated some direct antiviral activity against HIV-1 by inhibiting glycosylation of viral glycoproteins, its main promise in treating AIDS and HIV may be to enhance the action of azidothymidine (AZT), the antiviral drug used in the treatment of AIDS. In vitro studies have shown that acemannan combined with suboptimal noncytotoxic concentrations of AZT or acyclovir acts synergistically to inhibit the replication of HIV and herpes simplex type 1 (HSV-1).[22] On the basis of these studies, as well as preliminary human studies, researchers believe that the use of acemannan may reduce the amount of AZT required by as much as 90%,[58] which is significant. In addition to AZT's cost, its use is often associated with severe side effects, including anemia and granulocytopenia due to bone marrow suppression.

Preliminary clinical studies suggest that acemannan and *A. vera* may be beneficial when administered orally in HIV-positive individuals.[59,60] In one study, 14 HIV patients prescribed oral acemannan (800 mg/day) demonstrated significant increases in circulating monocytes/macrophages. In particular, there were significant increases in the number of large circulating monocytes, indicating improvement in phagocytizing, processing, and presenting cells in the blood.[60] In another study of 15 AIDS patients receiving an oral dose of acemannan (800 mg/day), the average scores of Modified Walter Reed (MWR) Clinical Evaluation scoring, absolute T-4, absolute T-8, and p24 core antigen levels all improved in those surviving (Table 64-2) at the end of 900 days. Two patients died of AIDS, and another committed suicide. From this study, as well as others, it has been suggested that prognostic criteria to determine the most responsive patients are those with an absolute T-4 count greater than 150/mm^3 and p24 levels less than 300.[59]

TABLE 64-2 **Acemannan in the Treatment of Acquired Immunodeficiency Syndrome**

TEST	PRETREATMENT	AFTER 900 DAYS
Modified Walter Reed Clinical Evaluation	65	2
Absolute T-4	322/mm^3	324/mm^3
Absolute T-8	469/mm^3	660/mm^3
p24 Core antigen	5/15	4/12

Data from McDaniel HR, Carpenter RH, Kemp M, et al. Antiviral Res 1990;13(suppl 1):117.

In another study *A. vera* juice (0.6 L/day) was used in conjunction with essential fatty acids and a multiple vitamin, mineral, and amino acid supplement to treat 30 patients. The 15 AIDS, 12 AIDS-related complex, and two HIV-seropositive patients continued with regular medication, including AZT. After 180 days, all patients showed clinical improvement according to modified Karnofsky Quality of Life Assessment scores and the MWR Clinical Evaluation; 25% of those positive for the p24 core antigen converted to nonreactive; and anemia induced by AZT showed improvement in all patients.

Unfortunately, a follow-up study did not reproduce these early, promising results. A comprehensive study assessed the safety and efficacy of acemannan as an adjunctive to antiretroviral therapy among 63 male patients (mean age, 39 years) with advanced HIV disease receiving zidovudine (ZDV) or didanosine (ddI).[61] The randomized, double-blind, placebo-controlled trial provided a large dose of acemannan (400 mg orally four times daily). Eligible patients had CD4 counts of 50 to 300/uL twice within 1 month of study entry and had received 26 months of antiretroviral treatment (ZDV or ddI) at a stable dose for the month before entry. CD4 counts were made every 4 weeks for 48 weeks. p24 antigen was measured at entry and every 12 weeks thereafter. Sequential quantitative lymphocyte cultures for HIV and ZDV pharmacokinetics were performed in a subset of patients.

The mean baseline CD4 counts were 165 and 147/uL in the placebo and acemannan groups, respectively; 90% of the patients were receiving ZDV at entry. Six patients in the acemannan group and five in the placebo group developed AIDS-defining illnesses. There was no statistically significant difference between the groups at 48 weeks with regard to the absolute change or rate of decline of the CD4 count. Among ZDV-treated patients, the median rates of CD4 change (ACD4) in the initial 16 weeks were −121 and −120 cells/year in the placebo and acemannan groups, respectively; ACD4 decline from week 16 to 48 was 0 and −61 cells/year in the acemannan and placebo groups, respectively ($P = 0.11$). No statistical difference between groups occurred with regard to adverse events, p24 antigen, quantitative virology, or pharmacokinetics. Twenty-four patients, 11 receiving placebo and 13 receiving acemannan, discontinued study therapy prematurely, none due to serious adverse reactions. The decreased, but not statistically significant, rate of loss of CD4 cells in the acemannan group from weeks 16 to 48 provides a possible ray of hope that long-term use, such as reported previously, may be of value and should be investigated.

Asthma

Oral administration of an extract of *A. vera* for 6 months was shown to produce good results in the treatment of asthma in some individuals of various ages.[62] The exception was the fact that the *A. vera* extract was not effective in patients dependent on corticosteroids. The mechanism of action is thought to be via restoration of protective mechanisms, followed by augmentation of the immune system.

The extract used in the study was produced from the supernatant of fresh leaves stored in the dark for 7 days at 4°C. The dosage was 5 mL of a 20% solution of the aloe extract in saline twice daily for 24 weeks. Eleven of 27 patients (40%) without corticosteroid dependence reported significant improvement at the study's conclusion.

Studies indicate that subjecting the leaves to dark and cold results in an increase in the polysaccharide fraction. One gram of the crude extract obtained from leaves stored in the cold and dark produced 400 mg of neutral polysaccharide, compared with only 30 mg produced from leaves not subjected to cold or dark.

Diabetes

A. vera also exhibits a hypoglycemic effect in both normal and alloxan-induced diabetic mice.[63] A small human study showed benefit in diabetics. Five patients with non–insulin-dependent diabetes ingested half a teaspoonful of aloe four times daily for 14 weeks. Fasting blood sugar in each patient fell from a mean of 273 to 151 mg/dL with no change in body weight. The authors concluded that aloe lowered blood glucose levels by an unknown mechanism.[64] A more recent and larger study (49 men and 23 women) provided more support for the efficacy of aloe in combination with glibenclamide in diabetes. Although there was no response to glibenclamide alone, the combination was effective.[65] The patients were provided with 1 tablespoon of aloe gel and 5 mg of glibenclamide twice daily, with 5 mg twice daily of glibenclamide serving as the control. After 2 weeks, fasting blood sugar decreased significantly in the treated group, and by day 42 had decreased from an average of 289 mg/dL to a remarkable 148 mg/dL. Although the drop in serum cholesterol was insignificant, serum triglycerides decreased from 223 mg/dL to (again remarkable) 128 mg/dL by day 42. No adverse effects were noted using standard blood chemistries.

Contraception

An interesting new application of aloe is as a spermicide. Twenty samples of fresh ejaculate from healthy human volunteers between 20 and 30 years of age were treated in vitro with a 1% concentration of zinc acetate combined with lyophilized *A. barbadensis* (at concentrations of 7.5% to 10%). The combination of zinc acetate with lyophilized *A. barbadensis* was shown to possess powerful spermicidal and antiviral effects. This was attributed to their concentration of minerals (boron, barium, calcium, chromium, copper, iron, potassium, magnesium, manganese, phosphorus, and zinc), which were toxic to the sperm tail, causing instant immobilization. Studies with rabbit vaginal epithelium showed no irritation. This is important because nonoxynol-9, the active spermicidal ingredient used in vaginal contraception for more than 30 years, appears to cause cell membrane damage in vaginal and cervical epithelium and may possibly have teratogenic effects.[66]

Cancer Prevention

The antigenotoxic and chemopreventive effect of *A. barbadensis* on benzo[*a*]pyrene (B[*a*]P)-DNA adducts was investigated in vitro and in vivo in an animal model. Aloe showed a time-course and dose-dependent inhibition of [3H]B[*a*]P-DNA adduct formation in primary rat hepatocytes, inhibited cellular uptake of [3H]B[*a*]P in a dose-dependent manner, and significantly inhibited adduct formation in various organs (liver, kidney, forestomach, and lung). When mice were pretreated with aloe for 16 days before B[*a*]P treatment, inhibition of BPDE-I-DNA adduct formation and persistence was enhanced. Phase II glutathione-*S*-transferase activity was slightly increased in the liver, but phase I cytochrome P450 activity was not affected.[67]

This translates into animal cancer studies as protection from Norman murine sarcoma in mice[68] and efficacy in treatment of spontaneous neoplasms in dogs and cats.[69]

A. vera may also play a role in cancer therapy. One clinical study sought to evaluate whether the concomitant administration of

aloe could enhance the therapeutic results of melatonin in patients with advanced solid tumors for whom no effective standard anticancer therapies were available. The study included 50 patients with lung cancer, gastrointestinal tract tumors, breast cancer, or brain glioblastoma who were treated with melatonin alone (20 mg/day orally in the dark period) or melatonin plus *A. vera* tincture (1 mL twice daily). A partial response was achieved in 2 of 24 patients treated with melatonin plus aloe and in none of the patients treated with melatonin alone. Stable disease was achieved in 12 of 24 and in 7 of 26 patients treated with melatonin plus aloe or melatonin alone, respectively. Therefore, the percentage of nonprogressing patients was significantly higher in the group treated with melatonin plus aloe than in the melatonin group (14 of 24 vs 7 of 26; $P < 0.05$). The percentage of 1-year survival was also significantly higher in patients treated with melatonin plus aloe (9 of 24 vs 4 of 26; $P < 0.05$).[70]

DOSAGE

A. vera gel can be applied liberally for topical applications. A wide range of products are available on the market; however, simple pure *A. vera* gel is sufficient.

A. vera juice can be consumed orally as a beverage or tonic. Although detailed information is currently lacking as to the optimal dose for these types of products, it is recommended that no more than 1 quart be consumed daily.

The dose of acemannan being used in HIV/AIDS patients is 800 to 1600 mg/day. This corresponds to a dose of approximately 0.5 to 1 L/day for most *A. vera* juice products. However, there may be great variation in the amount of acemannan in various products.

TOXICOLOGY

Although rare, hypersensitivity reactions manifesting as generalized, nummular, eczematous, and papular dermatitis have been reported as a result of topically applied *A. vera* preparations. *A. vera* gel has been shown to delay wound healing in cases of surgical wounds, such as those produced during laparotomy or cesarean delivery.[71] Therefore, topical aloe preparations are not useful for treating deep vertical wounds.

Oral aloe preparations are extremely well-tolerated. There are a few reports of aloe preparations inducing elevations in hepatic enzymes.[72] Thus, it may be appropriate to perform annual assessment of liver function enzymes. There is also a case report of aloe ingestion leading to thyroid dysfunction (reduced serum triiodothyronine).

DRUG INTERACTIONS

Excessive use of aloe dried juice/latex may interact with several drugs.[73-75] Large doses of aloe may increase the risk of toxicity of antiarrhythmic drugs. Theoretically, overuse of aloe dried juice/latex may increase the risk of cardiac glycoside toxicity. Potential for adverse effects exists when aloe dried juice/latex is used excessively along with herbs containing cardiac glycosides (e.g., black hellebore, Canadian hemp roots, digitalis leaf, pheasant's eye plant, pleurisy root, squill bulb leaf scales, Strophanthus seeds) or with cardiac glycoside drugs (e.g., digoxin). Overuse of aloe dried juice/latex can exacerbate the potassium loss caused by corticosteroids, diuretics, horsetail, and licorice root.

Due to the hypoglycemic effects of internally consumed *A. vera* gel, persons using glyburide drugs to control blood sugar (e.g., Diabeta, Micronase, Glynase) should monitor blood glucose levels closely.

Aloe dried juice/latex causes shorter gastrointestinal transit time, so it may reduce the absorption of some drugs.

Theoretically, concomitant use of aloe with other stimulant laxative herbs might increase the risk of potassium depletion. In addition to senna leaves and pods and cascara bark, the two herbs most widely used for this purpose, stimulant laxative herbs also include wild cucumber fruit *(Ecbolium elaterium)*, blue flag rhizome, alder buckthorn, European buckthorn, butternut bark, castor oil, colocynth fruit pulp, gamboge bark exudate, jalap root, black root, manna bark exudate, podophyllum root, rhubarb root, and yellow dock root.

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CHAPTER 65

Angelica Species

Michael T. Murray, ND

Angelica sinensis or *polymorpha* (family: Umbelliferae or Apiaceae)
Common names: Chinese angelica, tang-kuei (dong quai)
Angelica acutiloba (family: Umbelliferae or Apiaceae)
Common name: Japanese angelica
Angelica archangelica (family: Umbelliferae or Apiaceae)
Common name: European angelica
Angelica atropurpurea (family: Umbelliferae or Apiaceae)
Common name: American angelica
Angelica silvestris (family: Umbelliferae or Apiaceae)
Common name: wild angelica

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GENERAL DESCRIPTION

Angelica spp. are biennial or perennial plants with hollow fluted stems that rise to a height of 3 to 7 feet. The umbels, or clusters, of greenish-white flowers bloom from May to August. The plants are found in damp mountain ravines and meadows, on river banks, and in coastal areas; angelica is also a widely cultivated species. In Asia it is grown primarily for its medicinal action, whereas in the United States and Europe, it is cultivated for use as a flavoring agent in most major categories of food products, including alcohol (e.g., bitters, liqueurs, vermouths) and nonalcoholic beverages, ice cream, candy, gelatins, and puddings. With all species, the roots and rhizomes are the most extensively used portions of the plant.

Angelica sinensis and *Angelica acutiloba*

In Asia, the authentic and original medicinal angelica is *Angelica sinensis* (dong quai), native to China. Although at least nine other angelica species are used in China, dong quai is by far the most highly regarded. For several thousand years, dong quai has been cultivated for medicinal use in the treatment of a wide variety of disorders, particularly "female" disorders. Several hundred years ago, when the supply of Chinese angelica was scarce, the Japanese began to cultivate *A. acutiloba*, an angelica species indigenous to Japan, as a substitute.[1] The two species appear to have similar therapeutic effects despite the following opinions: in China the Japanese angelica is thought to have no therapeutic value, whereas in Japan, Chinese angelica is thought to have no effect. Experimentally, both species exhibit similar therapeutic effects, so each country's claim to produce a superior dong quai is apparently based more on emotion than scientific investigation.

Angelica archangelica and *Angelica atropurpurea*

Historical usage suggests that European angelica *(A. archangelica)* and American angelica *(A. atropurpurea)* have properties different from the Asian species. However, this difference has not been evaluated by chemical analysis.

CHEMICAL COMPOSITION

Angelica sinensis and *Angelica acutiloba*

Although it has been assumed that Chinese and Japanese angelica are similarly composed of various coumarins and flavonoids that are responsible for their medicinal actions, a recent analysis showed that *A. sinensis* contained approximately ten fold

higher levels of the key components ferulic acid and Z-ligustilide compared with roots of *A. acutiloba*.[2]

Many medicinal compounds are believed to be present in the essential oil, including the following[3]:

- 3*n*-Butylphthalide
- Cadinene
- Carvacrol
- *n*-Dodecanal
- Isosafrole
- Linoleic acid
- Palmitic acid
- Safrole
- Sequiterpene
- *n*-Tetradecanoyl

Angelica archangelica

A. archangelica is also rich in coumarins and is particularly phototoxic. Coumarins including osthole, angelicin, osthenol, umbelliferone, archangelicine, bergapten, and ostruthol are found in significant concentrations, with osthole composing nearly 0.2% of the root. The root is also a good source of flavonoids, including archan-gelenone and caffeic acids. The root contains 0.3% to 1% volatile oil composed mainly of β-phellandrene, α-pinene, borneol, limonene, and four macrocyclic lactones.[3,4]

HISTORY AND FOLK USE

Angelica sinensis and *Angelica acutiloba*

In Asia angelica's reputation is perhaps second only to ginseng. Predominantly regarded as a "female" remedy, angelica has been used to treat dysmenorrhea, amenorrhea, metrorrhagia, and menopausal symptoms, and to assure a healthy pregnancy and easy delivery. Angelica is also used in the treatment of abdominal pain, anemia, injuries, arthritis, migraine headache, and many other conditions.[3,5]

Angelica archangelica

One of the most highly praised herbs in old herbal texts, *A. archangelica* was used by all Northern European countries as a protection against contagion, for purifying the blood, and for curing every conceivable malady; it was considered a sovereign remedy for poisons, agues, and all infectious maladies. According to one legend, *A. archangelica* was revealed in a dream as a cure for the plague. One explanation for the name is related to its blooming near May 8, the feast day of Michael the Archangel. It was therefore seen as a "protector against evil spirits and witchcraft."[6]

A. archangelica has been used for a wide variety of conditions, including flatulent dyspepsia, pleurisy, respiratory catarrh, and bronchitis. The plant was believed to possess carminative, spasmolytic, diaphoretic, expectorant, and diuretic activity.[6]

Angelica atropurpurea

American angelica's therapeutic use mirrors that of European angelica. Its most common use is for heartburn and flatulent colic.[7]

PHARMACOLOGY

The pharmacology of *Angelica* spp. primarily relates to high coumarin content. However, unlike other scientific investigations of botanical medicines, most research on *Angelica* spp. has been done on plant extracts, rather than isolated constituents. The overwhelming majority of studies have been done on the Asian species. Some of the pharmacologic activities demonstrated include the following:

- Phytoestrogen activity
- Cardiovascular effects
- Smooth muscle–relaxing effects
- Analgesic activity
- Antiallergic, immunomodulating, and direct antitumor activity
- Antimicrobial activity

Phytoestrogen Effects

Plant estrogenic substances or phytoestrogens are components of many medicinal herbs with historic use in conditions that are now treated by synthetic estrogens. Chinese and Japanese angelica contain weakly active phytoestrogens much lower in activity than other phytoestrogens, and approximately no more than 1:400 are active as estrogen.[8] This helps to explain why angelica was used in both excessive and deficient estrogen conditions. Phytoestrogens demonstrate an alterative effect by competing with estrogen for binding sites. When estrogen levels are low, they can exert some weak estrogenic activity; when estrogen levels are high, they reduce overall estrogenic activity by occupying estrogen receptor sites. This apparent alterative action of angelica's phytoestrogens is probably the basis of much of the plant's use in amenorrhea and menopause.

Japanese angelica has demonstrated uterine tonic activity, causing an initial increase in uterine contraction followed by relaxation.[9,10] In addition, administration of Japanese angelica to mice resulted in an increase of uterine weight, increase of the DNA content of the uterus and liver, and increase of glucose use by the liver and uterus.[1,9] Because of these and other effects, angelica has been referred to as a uterine tonic.

Administration of a standardized ethanol extract in ovariectomized rats exhibited stimulation of the uterine histoarchitecture, a significant cornification in the vaginal epithelium, and a reduction of serum luteinizing hormone concentration, showing the estrogenic nature of the extract. Furthermore, the administration of the extract in intact female rats provoked a significant modification of the vaginal smear in 67% of treated rats.[3,11]

Cardiovascular Effects

Although not used historically for these purposes, angelica does possess significant hypotensive action.[1,9] This is largely due to its vasodilator activity. Dihydropyranocoumarins and dihydrofuranocoumarins from Umbelliferous plants have been shown to possess significant coronary vasodilatory, spasmolytic, and cyclic adenosine monophosphate phosphodiesterase inhibitory properties.[12] The mechanism of action appears to be largely a result of calcium channel antagonism. Agents that interact with calcium channels (calcium channel blockers) are quickly coming into prominence in the treatment of wide-ranging conditions, including hypertension and angina. Umbelliferous plants such as angelica may offer similar effects.

Other cardiovascular effects noted for angelica are negative inotropic and antiarrhythmic action.[1]

Smooth Muscle–Relaxing Activity

Calcium channel blocking compounds are also capable of relaxing the smooth muscles of visceral organs. Angelica (essential oil) has demonstrated relaxing action on the smooth muscles of the

intestines and uterus, whereas the water extract produces an initial contraction and then prolonged relaxation.[1,9,10] This confirms its historical use in the treatment of intestinal spasm and uterine cramps. Its action on other smooth muscles could explain its hypotensive action (vascular smooth muscle) and historic use in asthma (bronchial smooth muscle).

Analgesic Activity

Both Chinese and Japanese angelica have demonstrated pain-relieving and mild tranquilizing effects in experimental studies in animals.[1,9,13,14] Angelica's analgesic action was 1.7 times that of aspirin in one study.[14] Its analgesic activity, combined with its smooth muscle–relaxing activity, supports its historic use in such conditions as uterine cramps, trauma, headaches, and arthritis.

Antiallergic, Immunomodulating, and Direct Antitumor Activity

Angelica has a long history of use by Chinese and Japanese herbalists in the prevention and treatment of allergic symptoms in individuals who are sensitive to various substances (e.g., pollen, dust, animal dander, food).[1,15] Its action is related to its ability to inhibit the production of immunoglobulin-E in a selective manner. Because immunoglobulin-E levels in patients with atopic conditions are typically 3 to 10 times greater than the upper limit of normal, angelica may offer some benefit by reducing these elevated antibodies.

Coumarin compounds have demonstrated immune-enhancing activity in both healthy and cancer patients.[16,17] Coumarins have been shown to stimulate macrophages and increase phagocytosis.[16] Such activity is thought to offer significant protection against metastasis and growth of tumor cells. Upon coumarin administration, macrophages are said to be "activated" and thus capable of entering the tumor, where a specific destruction of the tumor cells may occur.[16,17]

Coumarin compounds of angelica and the polysaccharides of the water extract of Japanese angelica have demonstrated immune-modulating and antitumor activity. They have been shown to possess mitogenic activity to B-lymphocytes, interferon-producing activity, antitumor activity, and complement-activating (both the classic and alternative pathway) activity.[18-22] Chinese angelica has been shown to increase murine interleukin-2 production, stimulate the reticuloendothelial system, and increase tumor necrosis factor production.[23-25] The antitumor effects of angelica appear to be mainly due to the polysaccharide components, since these compounds have been shown to exert antitumor effects on experimental tumor models in vivo and inhibitory effects on invasion and metastasis of cancer cells in vitro.[26-28] The time-effect relation of cytokine response also suggests that macrophages and natural killer cells involved in nonspecific immunity were primarily activated, and helper T cells were secondarily affected by angelica polysaccharides.[29] Altogether these effects by coumarins, polysaccharides, and extracts of *Angelica* sp. would seem to support the historic use of angelica as an adjunct in cancer therapy.

Antimicrobial Activity

Extracts of Chinese angelica have been shown to possess antibacterial activity against both gram-negative and gram-positive bacteria, whereas extracts of Japanese angelica exhibited no antibacterial action.[8] The inconsistency could be due to different essential oil concentrations of the extracts used in the studies. The oil of *A. archangelica* has also exhibited significant antifungal and anthelmintic properties but virtually no antibacterial activity.[4,30,31] As other herbs have much greater antimicrobial activity, *Angelica* spp. would be considered a less than optimum agent if this effect is desired.

CLINICAL APPLICATION

Angelica spp. have been used worldwide to treat wide-ranging conditions. At present it appears that *A. archangelica* and *A. atropurpurea* are most indicated as expectorants, antispasmodics, and carminatives in the treatment of respiratory ailments, gas, and abdominal spasm. Chinese angelica (*A. sinensis* or *polymorpha*) and Japanese angelica *(A. acutiloba)* appear most useful in the treatment of disorders of menstruation, menopause (especially hot flashes), atopic conditions, smooth muscle spasm (e.g., uterine cramps, migraines, abdominal spasm), and possibly as an immunostimulatory adjunct in cancer therapy.

Menopause

By far the most popular use of *Angelica* spp. has been the use of *A. sinensis* in the treatment of menopausal complaints. Although a double-blind, placebo-controlled study in women showed no significant benefit, the traditional use of angelica has been in combination with other plants. The preparation used (a dried aqueous extract) was clearly lacking some of the important volatile compounds, though it was standardized for ferulic acid content.[32] A study conducted in China showed that a combination of *A. sinensis, Paeonia lactiflora, Ligusticum monnieri, Atractylodes chinensis, Sclerotium poriae,* and *Alisma orientalis* was effective in roughly 70% of women experiencing menopausal symptoms.[33] Although not double-blind, this study shows promise for using angelica in the management of menopausal symptoms. Interestingly, in an in vitro study with human bone, the aqueous extract of *A. sinensis* was found to directly stimulate proliferation, alkaline phosphatase activity, protein secretion, and type I collagen synthesis in a dose-dependent manner.[34]

Also, in a double-blind study, the combination of 100 mg angelica, 60 mg soy isoflavones, and 50 mg of black cohosh extract significantly reduced menstrual migraines.[35]

Recently, the estrogenic aspect of dong quai has been called into question for women with estrogen-dependent breast cancer. In vitro studies have shown the aqueous extract of dong quai stimulated the growth of breast cancer cells, resulting in the caution against its use in herbal preparations for the treatment of peri- or postmenopausal symptoms, especially in women with breast cancer, pending further study.[36]

DOSAGE

- Dried root or rhizome: 1 to 2 g orally, or by infusion, three times a day
- Tincture (1:5): 2.5 to 5 mL, three times a day
- Fluid extract (1:1): 0.5 to 2 mL, three times a day

TOXICOLOGY

Angelica is generally considered to be of low toxicity. However, it contains many photoreactive substances that may induce photosensitivity. This should be kept in mind when using any Umbelliferous plant. This photoreactive activity can be used therapeutically in the treatment of vitiligo and psoriasis.

Use of *Angelica* spp., particularly *A. sinensis,* in men may lead to gynecomastia.[37]

DRUG INTERACTIONS

Angelica species may interfere with anticoagulants. Although animal studies showed no significant variation in the pharmacokinetic parameters of warfarin after dong quai treatment for either single-dose administration or steady-state concentrations of warfarin, there was a single case report of dong quai possibly being responsible for raising the international normalized ratio in women on long-term coumadin therapy, indicating that caution is advised and monitoring is necessary in patients on anticoagulant therapy.[38]

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CHAPTER 66

Artemisia absinthium (Wormwood)

Eric L. Yarnell, ND, RH(AHG), and Kathy Abascal, BS, JD, RH(AHG)

Artemisia absinthium (family: Asteraceae)
Common names: wormwood

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GENERAL DESCRIPTION

Artemisia absinthium generally occurs as an aromatic, semi-woody, perennial subshrub reaching up to 1 m tall, particularly in its native Mediterranean habitat. The leaves and flowers are used as medicine.

CHEMICAL COMPOSITION

The aerial parts of wormwood contain two components considered most important to its medicinal activity: 0.15% to 0.4% volatile oil and 0.2% to 1.5% sesquiterpene lactones.[1] The volatile oil is most notorious for its content of the terpenoids α- and β-thujone, given the potential neurotoxicity of these compounds. Alpha-thujone is believed to be much more toxic and is present as 0.53% to 1.22% of the volatile oil compared with 17.5% to 42.3% of β-thujone.[2] Several chemotypes of wormwood depend on growing environment, and only certain ones contain thujone—others have trans-sabinyl acetate, cis-epoxyocimen, or chrysanthenyl acetate instead.[1] Major sesquiterpene lactones present are absinthin, artabsin, matricin, and anabsinthin (Figures 66-1 to 66-3).

HISTORY AND FOLK USE

Wormwood was used historically as a digestive bitter in traditional herbal systems of various societies around its native Mediterranean habitat. The Ebers papyrus, an Egyptian medical treatise and one of the oldest extant pieces of writing (circa 1550 BC), mentions wormwood. Pliny the Elder discussed the use of wormwood to expel parasites, as reflected in the common name of the plant, in the first century AD.

The medicinal aspects of most of the history of wormwood are unfortunately overshadowed by development in the late eighteenth century of absinthe. The standard account of the rise of absinthe, a liqueur derived in part from wormwood, begins with French expatriate Pierre Ordinaire, who allegedly developed the first absinthe recipe in 1792 in Switzerland.[3] Absinthe schnapps, absinthe-infused ale (known as "purl"), absinthe-infused wine, and other absinthe-containing beverages had been in use since Dioscorides' time and probably before. Absinthe was apparently made by infusing wormwood, garden angelica root, anise fruit, and marjoram herb in ethanol; distilling them; and adding other flavorings, including volatile oils.[3] The resulting product was bright green and intensely bitter, formed a white precipitate, and had a high alcohol content (50% to 80%).[4]

Henri Dubied and his son-in-law Henri Louis Pernod purchased Ordinaire's formula and began producing large quantities of absinthe at the Pernod Fils distillery.[4] One client for their product was the French military, which invaded Algeria from 1844 to 1847 and issued absinthe regularly to the troops to help prevent and treat dysentery. These troops apparently returned to France with a taste for absinthe and increased the popularity of the beverage.

Although originally absinthe was most popular with people in the lower classes, it caught on among the intelligentsia in the 1860s and 1870s, a time of cultural ferment, particularly in Paris. Parisians would gather in cafes to sip absinthe, often diluted by pouring cold water over a sugar cube held in a perforated spoon into a glass

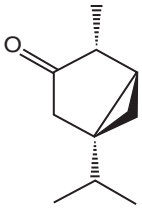


FIGURE 66-1 Alpha-thujone.

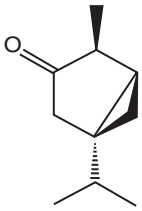


FIGURE 66-2 Beta-thujone.

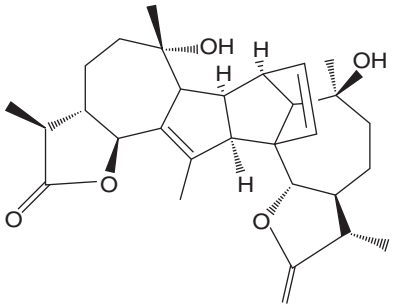


FIGURE 66-3 Absinthin.

containing a shot of absinthe.[5] Numerous famous artists of the time drank absinthe regularly, including Vincent van Gogh, whose insanity has been blamed (without proof) on his absinthe habit.

The growing popularity of absinthe, combined with a fire at the Pernod Fils distillery in 1901, led to a surge of absinthe-like products on the market. Unfortunately, these imitation products were often made as cheaply as possibly by simply mixing volatile oils with alcohol, adding various coloring agents to give the appropriate green hue (including copper sulfate), and antimony chloride to create the appearance of the white precipitate formed in true absinthe.[3] At the same time, a new phenomenon termed absinthism was becoming widely known. This syndrome was a result of chronic absinthe overindulgence and included bursts of violent aggressiveness followed by prolonged depression, trembling, hallucinations, seizures, and death.[5] However, the presence of adulterated, low-quality, high-ethanol absinthe products on the market and the inability to distinguish the effects of ethanol abuse from those of other compounds in the mixture made it difficult to be certain exactly what was causing absinthism. The levels of the purported neurotoxin thujone in true absinthe were 2 to 4 mg per drink, far below the 10 mg/kg levels needed to induce neurologic damage in numerous animal experiments.[6] In the early twentieth century, absinthe was banned in most of Europe and the United States. Absinthe, usually with limits on thujone content, is now legal again in many places, including Europe and the United States.

The Eclectics regarded wormwood as a digestive tonic useful in atonic dyspepsia, as a potential treatment for roundworms, and for topical application to sprains and bruises.[7] The dangers of absinthism were well known to these turn-of-the-century American natural physicians, but they did not seem clear on the various problematic elements in the history of absinthe discussed previously.

PHARMACOLOGY

Wormwood's actions have been studied in three major realms: digestive effects, antiparasitic effects, and effects on the central nervous system. Growing evidence suggests it is also a potent tumor necrosis factor-α inhibitor. Various reported effects of isolated α- and β-thujone may also be relevant to wormwood's effects.

Digestive Effects

In a controlled clinical trial, wormwood tincture and thujone-free wormwood tincture were both shown to significantly increase bile and pancreatic enzyme secretion in humans compared with water.[8] The levels of secretion were assessed intraduodenally. These effects seem to be common to many bitter herbs that contain sesquiterpene lactones. Wormwood extract had a modest antidiarrheal effect in one rat model unrelated to infection.[8a]

Hepatic Effects

Pretreatment of mice with 500 mg/kg of wormwood extract decreased the 100% lethality of 1 g/kg acetaminophen to 20%.[9] The toxicity of carbon tetrachloride was also reduced by pretreatment of rats with wormwood. Administering 500 mg/kg wormwood extract to rats 6 hours after toxic but sublethal doses of acetaminophen (but not carbon tetrachloride) significantly reduced hepatic damage. An aqueous extract of wormwood protected mice against carbon tetrachloride- and immune-mediated liver damage, partly by reducing oxidation and partly by inhibiting tumor necrosis factor-α and interleukin-1.[9a]

Antiparasitic Effects

Wormwood does not appear to contain the same active constituents as sweet Annie, notably artemisinin, yet aqueous extracts of wormwood showed antimalarial effects in vitro.[10] In mice, oral administration of extracts using 95% ethanol of wormwood was shown to have a potent schizonticidal effect against *Plasmodium berghei*, although not as potent as chloroquine.[11,11a] Activity of wormwood against multidrug resistant *P. falciparum* has been demonstrated in vitro.[11a]

Crude extracts of wormwood have been reported to inhibit other organisms in vitro or in animals, including *Trypanosoma brucei*, *Trichinella spiralis*, and nematodes.[11b] However, crude extract of wormwood was ineffective at treating infection with the nematode *Haemonchus contortus*.[11c-11e]

In vitro, aqueous, and ethanolic extracts of wormwood strongly inhibited the growth of the ameba *Naegleria fowleri*.[12] The lowest concentration of a sesquiterpene lactone extract from wormwood that inhibited growth of the amebae to 50% or less than that of controls was 31.9 mg/mL compared with 0.025 mg/mL for amphotericin B. Apparently, research in India has shown an effect for wormwood against *Entamoeba histolytica*, but details of this publication could not be obtained.[13]

Neurologic Effects

Structural and biosynthetic similarities have long been noted among α- and β-thujone and tetrahydrocannabinol from *Cannabis sativa* (marijuana).[14] Although thujone does weakly bind cannabinoid receptors in animals and human receptors in vitro, it does not appear to activate them.[15] Wormwood oil also failed to have significant cannabinomimetic activity in this assay. Thujone's

purported hallucinogenic and epileptogenic effects have been disproven.[15a] An 80% ethanol extract of wormwood was a strong muscarinic and nicotinic cholinergic receptor agonist in vitro.[16] Methanol extracts of wormwood at concentrations of 100 to 200 mg/kg significantly reduced memory loss and motor incoordination after middle cerebral artery occlusion in rats.[16a]

CLINICAL APPLICATIONS

Wormwood was officially approved by the German Commission E for treatment of patients with dyspepsia, loss of appetite, and biliary dyskinesia.[17] The article[8] discussed in the "Pharmacology" section showing that wormwood could increase digestive secretions supports the use of wormwood for loss of appetite, although much more specific work is necessary for definitive proof of efficacy.

A randomized, double-blind clinical trial in Crohn's disease found that wormwood extract, standardized to 0.2% to 0.38% absinthin and 0.25% to 0.52% total volatile oil (without thujone), in a base of rose petal, cardamom, and mastic gum or ginger (500 mg 3 times per day) was more effective than placebo at preventing relapse at 20 weeks.[17a] All patients were tapered off corticosteroids after 2 weeks on the medication. At a dose of 750 mg 3 times per day, this same extract has been shown to lower TNF-α levels in patients with Crohn's disease over 6 weeks.[17b]

In an uncontrolled trial, the same extract mentioned earlier, at a dose of 600 mg 3 times per day in 10 patients with immunoglobulin-A nephropathy not responding to immunosuppressive medications, was effective at decreasing proteinuria and blood pressure over 6 months.[17c] Glomerular filtration rate remained stable, and there were no adverse effects.

DOSAGE

Wormwood is primarily used in three forms—tea, tincture, and capsule. Volatile oil should not be used. A typical dose of tea is 1 g (1 to 2 tsp) dried leaf and flower per cup of water, steeped for 10 to 15 minutes.[18] The tea should be covered during steeping to retain as many volatile constituents as possible. A cup of tea is sipped before meals three times daily. Thujone is not water soluble, so aqueous extracts of the plant are generally low in thujone. A typical dose of tincture is 0.5 to 1 mL 3 times daily mixed with 2 to 4 oz water, sipped before meals. A typical capsule dose is 2 to 3 g/day in divided doses.[19]

TOXICITY

Although much toxicity is ascribed to wormwood, it now appears that this is largely the result of poor research methodology in the early twentieth century and improperly conflating wormwood volatile oil and absinthe.[15a] Any toxicity attributed to the use of various forms of the beverage absinthe must not be confused with use of teas or tinctures in medicinal doses. Alpha-thujone is considered a neurotoxin and convulsant compound.[20] Beta-thujone, present in much higher levels in wormwood, is generally considered much less toxic.[21] In mice, α- and β-thujone both antagonized γ-aminobutyric acid-A receptors and induced seizures.[22] Alpha-thujone was a much stronger convulsant than β-thujone in this study. This study confirmed previous findings that thujone is rapidly metabolized by the liver and removed from the body in animals.[23]

A 31-year-old man who drank 10 mL of wormwood volatile oil, mistakenly believing it was identical to absinthe, became agitated, belligerent, and incoherent, and developed tonic-clonic seizures.[24] Haloperidol improved his mental function, but acute renal failure and rhabdomyolysis were discovered, becoming worse a day later. Congestive heart failure developed, in part due to aggressive alkalinization. Seventeen days after discharge from the hospital he had recovered completely.

These effects have never been documented to occur in patients being treated with reasonable doses of medicinal extracts of or crude wormwood. In one naturopathic medical practice, nine patients over a 3-year period were identified who had been treated with a bitters formula including 11% tincture of wormwood, generally as a treatment for dyspepsia or malabsorption.[25] Administered at a dose of 1 teaspoon (5 mL) 3 times daily, patients would have been exposed to approximately 500 mL wormwood tincture 3 times daily for weeks to months. For the eight patients with available laboratory data, there was no evidence of renal, hepatic, or other damage. One patient showed improvement in serum liver enzyme levels while taking the bitters formula. None of the patients developed seizures or other signs or symptoms of neurotoxicity. Although retrospective, this study did support the notion that wormwood in this form and at this dose is safe for use in adults as a digestive aid.

Thujone stimulates 5-aminolevulinate synthase in vitro, leading to large increases in porphyrin levels.[26] Although it seems likely that porphyrogenic levels of thujone could be achieved by drinking large volumes of absinthe, levels of intake of tincture of wormwood are far lower and unlikely to lead to such high levels. Porphyrogenic effects have not been clearly documented to be induced by wormwood in humans, although thujone and thujone-containing herbs such as wormwood should be avoided by people with porphyria until more information is available.

DRUG INTERACTIONS

No confirmed drug interactions exist for wormwood. It should be avoided in combination with chronic ethanol abuse due to historic reports pertaining to absinthe. Given the low doses of tinctures used, this should not represent any health threat related to ethanol ingestion. Wormwood may have synergistic porphyrogenic effects with other drugs that can induce porphyric attacks, including barbiturates, hydantoins, and carbamazepine.

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CHAPTER 67

Artemisia annua (Sweet Wormwood)

Eric L. Yarnell, ND, RH(AHG), and Kathy Abascal, BS, JD, RH(AHG)

Artemisia annua (family: Asteraceae)
Common names: sweet wormwood, sweet Annie, qing hao

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GENERAL DESCRIPTION

The genus *Artemisia* is named after the Greek goddess Artemis, who apparently used a plant in the genus and gave her name to it.

CHEMICAL COMPOSITION

Sweet wormwood contains several sesquiterpene trioxane lactones, most notably artemisinin (also known as qinghaosu) but also deoxyartemisinin, artemisinic acid, and arteannuin-B.[1] These compounds give the plant a distinctive bitter taste. A peroxide bridge in artemisinin is vital in the antimalarial effects of the compound (Figure 67-1).[2] Artemisinin is rapidly and readily reduced to dihydroartemisinin in the body. Dihydroartemisinin appears to be the active metabolite of artemisinin and all synthetic artemisinin derivatives developed to date (Figure 67-2).[3]

Sweet wormwood also contains a number of flavonoids.[1] In vitro research suggests these flavonoids potentiate the antimalarial activity of the sesquiterpene lactones.[4]

Three semisynthetic derivatives of artemisinin are widely available for use: artemether, artesunate, and arteether.[3] Artemether is a lipophilic β-epimer of dihydroartemisinin and is administered intramuscularly. Artesunate is a hydrophilic hemisuccinate compound administered orally or by injection. Arteether is an ethyl ether derivative of dihydroartemisinin and is lipophilic (Figure 67-3).

HISTORY AND FOLK USE

The herb, known to the ancient Chinese as qing hao, was recommended for treatment of fever as early as 341 AD, as written in the handbook for prescription for emergencies, *Zhou Hou Bei Ji Fang* by Ge Heng.[3] Qing hao had been prescribed in traditional Chinese medicine for other problems for at least 500 years beforehand on the basis of extant written records.

Qinghaosu, known as artemisinin in the West, was isolated and identified in qing hao in the 1970s in China.[5] It was thoroughly investigated and determined to have excellent antimalarial activity.

PHARMACOLOGY

Antimalarial Effects

Dihydroartemisinin preferentially accumulates in erythrocytes, and malaria-infected erythrocytes accumulate 300 times as much as uninfected erythrocytes.[6] Because active artemisinin compounds all appear to be converted to dihydroartemisinin in vitro and then act as mentioned previously, all these compounds ultimately end up in erythrocytes.

Artemisinin and related molecules appear to act in part by generation of free radicals, leading to damaging the membranes of several parasitic organisms.[7] This leads to rapid death of all stages of malaria parasites.[8] Because the presence of an oxidizing peroxide bridge appears essential to the activity of artemisinin compounds,

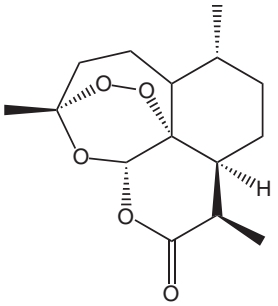


FIGURE 67-1 Artemisinin.

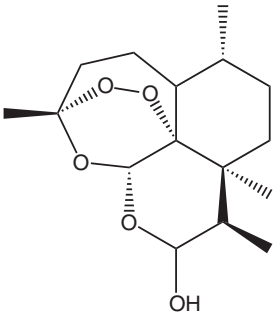
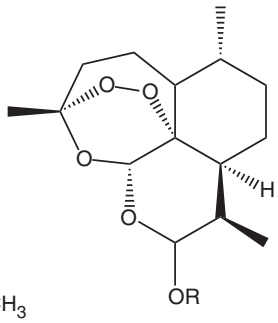


FIGURE 67-2 Dihydroartemisinin.



Artemether: R=CH_3

Arteether: R=C_2H_5

Artesunate sodium: R=$COCH_2CH_2CO_2Na$

FIGURE 67-3 Artemisinin derivatives (artesunate, artemether, and arteether).

the oxidative hypothesis is further supported. The importance of iron to this process is unclear. Some investigators suggest that iron chelators such as desferrioxamine actually increase the activity of artemisinin in vitro.[9]

Artemisinin compounds are synergistic with many other, but not all, antimalarial drugs. Low doses of mefloquine and artemisinin showed definite synergism in vitro against *Plasmodium falciparum*, whereas higher doses showed additive effects.[10] Mefloquine, chloroquine, primaquine, and tetracycline were all potentiated by artemisinin in mice with malaria; the effects of pyrimethamine, cycloguanil, and sulphonamide antibiotics were all decreased.[11]

Antiparasitic Effects

Besides killing *Plasmodium* spp., artemisinin compounds have shown activity against *Schistosoma* spp. and *Clonorchis sinensis*. Numerous animal studies show that artemether and artesunate can prevent and cure infections by *Schistosoma japonicum*, *Schistosoma mansoni*, and *Schistosoma haematobium*.[12-15] It is not clear if artemisinin or dihydroartemisinin is effective. However, artemisinin and the various available semisynthetic variants were all effective at treating *Clonorchis* infections in rats with no sign of toxicity.[16]

Antineoplastic Effects

Mounting evidence suggests that artemisinin compounds have potent anticancer activity. Artemisinin and quercetagetin 6,7,3',4'-tetramethyl ether, a flavonoid found in sweet wormwood, both showed activity against several tumor types in vitro.[17] Dihydroartemisinin and artesunate have also been investigated and found to inhibit cancer cells significantly in vitro.[18,19] The presence of ferrous iron appears to be essential for this activity, and sufficient quantities of iron may be necessary to prevent cancer cells from becoming resistant to artemisinin compounds.[18,20]

A combination of ferrous sulfate and dihydroartemisinin proved effective at limiting the growth of implanted fibrosarcomas in rats.[21] The combination did not appear to cause adverse effects. Ferrous sulfate or dihydroartemisinin administered alone were not effective in this model.

CLINICAL APPLICATIONS

Malaria

A meta-analysis confirmed that artemisinin, dihydroartemisinin, artemether, artesunate, and arteether are potent, effective, and safe in patients with uncomplicated malaria compared with other antimalarial agents.[22] In cases of severe or cerebral malaria, these agents appeared to be at least as effective as quinine.[23] No artemisinin compound has been shown to work better than any other, although there is a relative dearth of studies examining this question. It should be noted that most trials have been conducted in Southeast Asia, an area with a high incidence of multidrug-resistant malaria. Profligate use of artemisinin and derivatives by itself (instead of coupled with other drugs and measures as should be) is associated with rising resistance to these agents.[24]

Two uncontrolled trials investigated the efficacy of an infusion of sweet wormwood leaves in patients against *P. falciparum* or *P. malariae* malaria at two centers in the Democratic Republic of Congo.[25] The sweet wormwood was grown locally in both instances to try to determine the efficacy and cost effectiveness of this approach in Africa. In the first trial, 22 nonpregnant volunteers more than 11 years of age with fevers higher than 38°C, evidence of parasitemia, and symptoms of malaria participated. Each received 1 L of an infusion of 5 g of sweet wormwood leaves in four divided doses for 5 days. Chromatography showed that this provided 12 mg of artemisinin total per day. Artemisinin has low water solubility, and this high degree of extraction can perhaps best be explained by the presence of nonartemisinin compounds improving artemisinin's water solubility or enhancing its efficacy. All but two patients reported complete elimination of symptoms. Five of these patients agreed to have blood smears checked daily during the trial. All five showed rapid decreases in parasite counts in the blood, and by day four all five patients showed complete elimination of parasitemia.

In the second trial, 48 nonpregnant patients more than 11 years of age, all with *P. falciparum* and symptoms of malaria, volunteered for the study. The tea was prepared by boiling 5 g of sweet wormwood leaves in 1 L water for 5 minutes, resulting in a total of 7.2 mg of artemisinin being delivered daily for 4 days. In this group, 92% had complete clearance of parasitemia by the end of the trial, and 77% were symptom free. Of the 11 patients (23%)

who still had parasites, only 2 showed evidence of parasitemia. Twelve patients complained of nausea or vomiting, or both, during the trial. The dose of artemisinin delivered in this study was substantially lower than the typical daily dose of artemisinin, which is 500 to 1,000 mg. This strongly suggests that compounds in sweet wormwood besides artemisinin have synergistic antimalarial activity, enhance absorption of artemisinin, or in other ways increase the effectiveness of artemisinin.

It is unknown if artemisinin would work the same way in people not chronically exposed to malaria. There is no logical reason why artemisinin would prevent malaria infection because it attacks a form of the parasite that forms after infection occurs, although this does not appear to have been studied.

Schistosomiasis

Several double-blind trials conducted in China and in the Ivory Coast proved that artemether is effective at reducing the risk of developing schistosomiasis compared with placebo.[26,27] It is unclear if artemisinin or whole sweet wormwood would also be effective for this purpose, but trials are warranted.

DOSAGE

The historical dosage of sweet wormwood tea is 5 g/1 L water in three to four divided doses.[20] The dose of a 1:5 tincture of dried leaf is difficult to extrapolate because a higher ethanol concentration (60% to 70%) could be used, which would greatly improve the ability of the solvent to draw artemisinin into the final product. A rough estimate would be 1 to 3 mL three times a day for a healthy adult. The usual dose of isolated artemisinin as a prescription drug for uncomplicated malaria is 500 to 1000 mg/day for 5 days.[20,28] Food does not appear to significantly affect the absorption of artemisinin.[29] Artemisinin and sweet wormwood should not be used for more than 5 to 7 days continuously, because it stops being absorbed and stops working at that point.

TOXICITY

The only common adverse effects from use of sweet wormwood are nausea, loss of appetite, and dizziness.[28] Vomiting is rare. Neurotoxic effects have been observed in experimental animals treated with artemisinin derivatives and in a small handful of humans.[30] These effects have not been observed during use of whole sweet wormwood or its extracts. Sweet wormwood should be avoided in pregnancy and lactation until more data are available regarding its safety in these situations. Artemisinin derivatives have frequently been used safely in children, particularly when administered by suppository.[31]

DRUG INTERACTIONS

Artemisinin compounds generally show more rapid parasite clearance and fever reduction when combined with mefloquine than either drug given by itself, according to a meta-analysis of clinical trials.[18] Mefloquine's neurologic toxicity does not appear to be altered by combination with artemisinin compounds, although the tendency to induce severe vomiting may be slightly lessened.

Artemisinin compounds can be combined safely with doxycycline and tetracycline according to the results of two clinical trials, although at least one of these trials suggested the combination was less effective than artemether combined with mefloquine.[32,33] Another double-blind trial found that the combination of artesunate and tetracycline was equally effective and much safer than quinine and tetracycline.[34]

Artemisinin may interfere slightly with sulfadoxine-pyrimethamine. In one trial, artemisinin by itself led to insignificantly more rapid parasite clearance than artemisinin combined with sulfadoxine-pyrimethamine.[35] Fever relief was achieved equally rapidly, and adverse effects were absent in both groups. Further research is necessary to determine for certain if there is any negative effect from combining these two agents.

Grapefruit juice initially increases bioavailability of oral artemether, although it does not stop the inevitable decline in bioavailability of this compound that occurs with repeated dosing over a few days.[36]

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CHAPTER 68

Bee Products—Pollen, Propolis, and Royal Jelly

Michael T. Murray, ND

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GENERAL DESCRIPTION

Historically, one of the most valued groups of natural medicines is that of bee pollen, propolis, and royal jelly.

Bee pollen comes from the male germ cell of flowering plants. As the honeybee travels from flower to flower, it fertilizes the female germ cell. Honeybees enable the reproduction of more than 80% of the world's grains, fruits, vegetables, and legumes. The pollen is collected and brought to the hive, where the bees add enzymes and nectar to the pollen.

Propolis is the resinous substance collected by bees from the leaf buds and barks of trees, especially poplar and conifer trees. The bees use the propolis, along with beeswax, to construct the hive. Propolis has antimicrobial activities that help the hive block out viruses, bacteria, and other organisms.

Royal jelly is a thick, milky substance produced by worker bees to feed the queen bee. The worker bees mix honey and bee pollen with enzymes in the glands of their throats to produce royal jelly. Royal jelly is believed to be a useful nutritional supplement because of the queen bee's superior size, strength, stamina, and longevity compared with other bees.

CHEMICAL COMPOSITION

Honey is composed primarily (roughly 70%) of simple sugars (mainly fructose, glucose, and maltose), but it also contains minerals including manganese, calcium, iron, and sodium; organic acids; amino acids; vitamins; and enzymes.

Bee pollen is often referred to as "nature's most perfect food" because it is a complete protein (typically containing 10% to 35% total protein), meaning it contains all eight essential amino acids, and also provides B vitamins, vitamin C, carotenes, minerals, DNA, RNA, numerous flavonoid molecules, and plant hormones.

Propolis and royal jelly have similar nutritional qualities to pollen but considerably higher levels of different biologically active compounds.[1,2] Royal jelly contains approximately 12% protein, 5% to 6% lipids, and 12% to 15% carbohydrates.

HISTORY AND FOLK USE

The use of bee products for medicinal purposes is as old as beekeeping itself. Chinese texts more than 2000 years old include many mentions of bee products. Hippocrates also wrote about them. Honey was so valued during Roman times that it was often used instead of gold to pay taxes.

Of the bee products, propolis was the most valued as a medicinal agent. Hippocrates prescribed propolis to help heal sores, as well as external and internal ulcers. Propolis-making bees were also depicted on vases from ancient Egypt, where the sign of the bee was often interwoven with the titles of the kings and used as the motif on ornaments presented as rewards for valor. The ancient Egyptians looked upon bees and their propolis as the source of eternal health and life. In the seventeenth century, propolis was a major ingredient of healing ointments in the European pharmacopoeia.

PHARMACOLOGY AND CLINICAL APPLICATIONS

The health benefits of bee products are much heralded but insufficiently researched. Some overlap exists in the clinical uses of pollen, propolis, and royal

jelly. Following is a list of the principal uses for each of these bee products as shown in Box 68-1. This list is likely to grow with continued research.

Bee Pollen

Little research has been done on bee pollen, probably because financial rewards to justify such an investment are lacking. The research that does exist is limited but impressive. For example, studies in animals show that pollen can promote growth and development; protect against free radical and oxidative damage; and protect against the effects of harmful radiation, as well as toxic exposure to chemical solvents.[3-5] A pollen extract has also been shown to produce significant improvement in menopausal symptoms (headache, urinary incontinence, vaginal dryness decreasing vitality) in double-blind studies.[6] The improvements were achieved although the pollen extract produces no estrogenic effect, an important consideration for women who cannot take estrogens of any kind.[7]

Propolis

The primary use of propolis has been in immune system enhancement and infections. Propolis has inherent antimicrobial activity that protects the hive block from viruses, bacteria, and other organisms. Propolis has shown considerable antimicrobial activity in in vitro studies.[8-10] Propolis also stimulates the immune system, according to preliminary human studies.[11,12] In vitro and animal studies have also shown that propolis exerts some antioxidant, liver protecting, anti-inflammatory, and anticancer properties.[13-17]

A key use of propolis is protection against and shortening the duration of the common cold. A preliminary human study reported that propolis extract (PE) reduced upper respiratory infections in children.[11] In a double-blind study of 50 patients with the common cold, the group taking PE became symptom free far more quickly than the placebo group.[18]

Another possible application of propolis is in the treatment of inflammatory bowel diseases like Crohn's disease and ulcerative colitis. An anecdotal article described an interesting case of ulcerative colitis that responded to propolis therapy.[19] The author suggested that the antimicrobial and anti-inflammatory properties of propolis might be of value in the treatment of inflammatory bowel diseases.

The antimicrobial properties of propolis may also help protect against parasitic infections in the gastrointestinal tract. One preliminary study of children and adults with giardiasis showed a 52% rate of successful parasite elimination in children and a 60% rate in adults in those given PE (amount not stated).[20] However, these results are not as impressive as those achieved with conventional drugs used against giardiasis, so propolis should not be used alone for this condition without first consulting a physician about available medical treatment.

Propolis may also have an effect in vaginal infections. In one study, 97 vaginal yeast strains were evaluated for susceptibility to nystatin and PEs. All the yeasts tested were inhibited by low concentrations of PE (maximum of 393.19 mcg/mL of the total flavonoid content), including an isolate resistant to nystatin, regardless of the clinical conditions of the women and the species of yeast isolated.[21]

Finally, one of the key components of propolis, caffeic acid phenethyl ester has been shown to exert selective estrogen receptor modulation.[22] This action, along with inhibition of receptor activator nuclear factor-κB ligand (RANKL)-activated signaling, implied that it might be an effective agent against osteoporosis. RANKL is essential for osteoclast differentiation, activation and survival. Low concentrations of caffeic acid phenethyl ester (<1 mcM) dose dependently inhibited RANKL-induced osteoclastogenesis in cell and bone marrow macrophage cultures, as well as decreasing the capacity of human osteoclasts to resorb bone.[23]

Royal Jelly

Some research on royal jelly found a cholesterol-lowering effect. Specifically, 11 human studies have been published, 8 of which were double blind.[24,25] Of the seven double-blind studies, only three used an oral preparation. An injectable form was used in the other four studies. Results of a detailed analysis of the double-blind studies indicated that with oral preparations, despite shortcomings in the design of the studies and lack of standardization with commercial preparations used, royal jelly decreased total cholesterol levels by about 14% in patients with moderate to severe elevations in blood cholesterol levels (initial values ranging from 210 to 325 mg/dL). Even better results may be noted when using higher quality royal jelly products.

BOX 68-1 Clinical Applications for Bee Products

Bee pollen
- Allergies
- Antioxidant support
- Energy enhancement
- Menopausal symptoms
- Support for chemotherapy and radiation therapy

Propolis
- Common cold
- Gastrointestinal infections
- Immune enhancement
- Topical anti-inflammatory
- Upper respiratory tract infections
- Vaginitis

Royal jelly
- Elevated cholesterol levels
- Energy enhancement

DOSAGE

- Bee pollen: usually 1 to 3 tablespoons a day
- Propolis: 100 to 500 mg three times a day
- Royal jelly: 50 to 250 mg of royal jelly one to two times a day

TOXICITY

Allergic reactions are the most common side effects. If there is a known allergy to conifer and poplar trees, use of bee products should be avoided. Allergic reactions can range from mild (e.g., mild gastrointestinal upset) to severe (e.g., asthma, anaphylaxis [shock], intestinal bleeding, even death in people who are extremely allergic to bee products).[26]

DRUG INTERACTIONS

No drug interactions are known.

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CHAPTER 69

Beta-Carotene and Other Carotenoids

Michael T. Murray, ND

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INTRODUCTION

The carotenoids represent the most widespread group of naturally occurring pigments in nature. They are a highly colored (red and yellow) group of fat-soluble compounds, composed of hydrocarbons (carotenes) and their oxygenated derivatives (oxycarotenoids or xanthophylls). The basic carotenoid structure consists of eight isoprenoid units with a series of conjugated double bonds. All photosynthetic organisms, whether bacteria or plants, contain carotenoid pigments. These compounds not only function as auxiliary pigments in photosynthesis but also play a crucial role in protecting the organism or plant against photosensitization by its own chlorophyll.

More than 600 carotenoids have been characterized, but only about 30 to 50 are believed to have vitamin A activity, and some 20 are found in human plasma and tissues. Biological activity of a carotenoid has historically been considered synonymous with its corresponding vitamin A activity. Beta-carotene has been termed the most active of the carotenoids due to its higher provitamin A activity (Figure 69-1). However, recent research suggests that this function of carotenoids has been overemphasized, since they have been found to exhibit many other important physiologic activities. For a carotenoid to have vitamin A activity, it must have an unaltered β-ionone ring with an attached polyene side chain containing 11 carbon atoms. In contrast, apocarotenoids are compounds that have been shortened by the removal of at least one end of the molecule beyond a designated location (e.g., β-Apo-8′-carotenal has been cleaved at the 8' carbon). Apocarotenes and xanthophylls have reduced or no vitamin A activity, but many have been shown to have significant antioxidant and physiologic benefits.[1-3] Also, approximately 25% of whites do not convert β-carotene to vitamin A.

DIETARY SOURCES

Among the richest sources of carotenes are green leafy vegetables. The carotenoids in green plants are found in the chloroplasts with chlorophyll, usually in complexes with a protein or lipid. Beta-carotene is the predominant form in most green leaves. In general, the greater the intensity of the green color, the greater the concentration of β-carotene. Orange-colored fruits and vegetables (e.g., carrots, apricots, mangoes, yams, squash) typically have higher concentrations of provitamin A carotenoids, the provitamin A content again paralleling the intensity of the color. Yellow vegetables have higher concentrations of xanthophylls and, hence, lower provitamin A activity. In orange and yellow fruits and vegetables, β-carotene concentrations are high, but other provitamin A carotenoids typically predominate. Red and purple vegetables and fruits such as tomatoes, red cabbage, berries, and plums contain large portions of non–vitamin A–active pigments, including flavonoids. Legumes, grains, and seeds are also significant sources of carotenoids. Carotenoids are also found in various animal foods such as salmon and other fish, egg yolks, shellfish, milk, and poultry. Carotenoids are also frequently added to foods as colorants. Table 69-1 lists carotenoids with provitamin A activity found in common food sources, whereas Table 69-2 lists some important carotenoids that have no vitamin A activity. The structures of two of these, lycopene and zeaxanthin, are illustrated in Figures 69-2 and 69-3.

According to a detailed analysis of the levels of carotenoids in 120 fruits and vegetables, lycopene is found in few.[4] Table 69-3 lists the foods that contained lycopene. These values indicate that lycopene levels are retained in food processing.

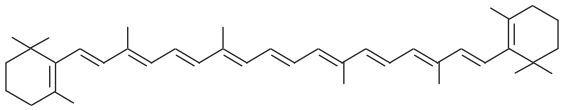


FIGURE 69-1 Beta-carotene.

TABLE 69-1 **Provitamin A Carotenoids and Food Sources**

CAROTENOID	VITAMIN A ACTIVITY (%)	FOOD SOURCES
Beta-carotene	100	Green plants, carrots, sweet potatoes, squash, spinach, apricots, green peppers
Alpha-carotene	50-54	Green plants, carrots, squash, corn, watermelons, green peppers, potatoes, apples, peaches
Gamma-carotene	42-50	Carrots, sweet potatoes, corn, tomatoes, watermelons, apricots
Beta-zeacarotene	20-40	Corn, tomatoes, yeast, cherries
Cryptoxanthin	50-60	Corn, green peppers, persimmons, papayas, lemons, oranges prunes, apples, apricots, paprika, poultry
Beta-apo-8'-carotenal	72	Citrus fruit, green plants
Beta-apo-12'-carotenal	120	Alfalfa meal

TABLE 69-2 **Non–Provitamin A Carotenoids and Food Sources**

CAROTENE	VITAMIN A ACTIVITY (%)	FOOD SOURCES
Lycopene	0	Tomatoes, carrots, green peppers, apricots, pink grapefruit
Zeaxanthin	0	Spinach, paprika, corn, fruits
Lutein	0	Green plants, corn, potatoes, spinach, carrots, tomatoes, fruits
Canthaxanthin	0	Mushrooms, trout, crustaceans
Crocetin	0	Saffron
Capsanthin	0	Red peppers, paprika

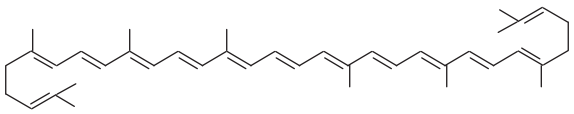


FIGURE 69-2 Lycopene.

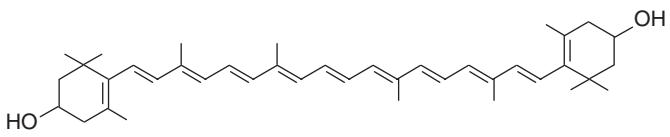


FIGURE 69-3 Zeaxanthin.

TABLE 69-3 **Lycopene Content of Common Foods**

FOOD	LYCOPENE (mg/100 g)
Apricot, canned	0.06
Apricot, dried	0.8
Grapefruit (pink and raw)	3.4
Guava juice	3.3
Tomato, raw	3.1
Tomato juice, canned	8.6
Tomato paste, canned	6.5
Tomato sauce, canned	6.3
Watermelon, raw	4.1

METABOLISM

Absorption

Various factors are known to influence the absorption efficacy of vitamin A and carotenoids. Although retinol does not require bile acids to assist absorption, carotenoids do. Other factors that affect vitamin A and carotenoid absorption include the following:

- The presence of fat, protein, and antioxidants in the food
- The presence of bile and a normal complement of pancreatic enzymes in the intestinal lumen
- The integrity of the mucosal cells

The absorption efficiency of dietary vitamin A is usually quite high (80% to 90%), with only a slight reduction in efficiency at high doses. In contrast, β-carotene's absorption efficiency is much lower (40% to 60%), and it decreases rapidly with increasing dosage.[1-3] Carotene supplements are better absorbed than the carotenes from foods.[5] Supplying only β-carotene, whether natural or synthetic, may be exerting a detrimental effect to the absorption of other carotenes. For example, β-carotene supplementation has been shown to inhibit the absorption of lutein.[6] Studies in humans have shown that with β-carotene supplementation, the absorption of lutein can drop by more than 50%.[7] Interestingly, the absorption of lutein from vegetables is five times greater than that of β-carotene.[8]

Transformation in the Intestinal Mucosa

As stated earlier, of the more than 600 carotenoids that have been reasonably well characterized, only about 30 to 50 are believed to have provitamin A activity. However, carotenoids provide the majority of dietary vitamin A. Provitamin A carotene conversion to vitamin A depends on diverse factors[9]:

- Protein status
- Thyroid hormones
- Zinc
- Vitamin C

The conversion diminishes as carotene intake increases and when serum retinol levels are adequate.[10] Beta-carotene and other provitamin A carotenes were originally believed to be cleaved by carotene dioxygenase at the 15,15' double bond, which would yield two molecules of all-*trans* retinal. Current belief, however, is that the dioxygenase enzyme nonspecifically attacks any one of the double bonds of the β-carotene, resulting in the formation of a

TABLE 69-4 **Distribution of Carotenoids in Some Human Tissues (milligrams per kilogram)**

TISSUE	CAROTENOIDS	BETA-CAROTENE
Adrenal	20.1 ± 11.9	10.8 ± 5.5
Liver	8.3 ± 21.3	—
Testis	5 ± 7.7	4.7 ± 2
Fat	3.9 ± 6	1.3 ± 1.1
Pancreas	2.3 ± 1.2	1.1 ± 1
Spleen	1.6 ± 2.2	1.2 ± 0.5
Lung	0.6 ± 1.0	—
Thyroid	0.6 ± 0.4	—

corresponding apo-β-carotenal or retinal.[11] The apocarotenal formed can either be degraded to retinal or absorbed. The retinal formed is then converted to retinol by retinaldehyde reductase.

Uncleaved provitamin A carotenoids, apocarotenoids, and non–provitamin A carotenoids, like retinol, are transported in the chylomicra.

Transport, Storage, and Excretion

No specific carrier protein exists in the plasma for carotenoids. These compounds are typically transported in human plasma in association with the plasma lipoproteins, particularly by low-density lipoprotein (LDL). As a consequence, patients with high serum cholesterol or LDL levels tend to have high serum carotene levels. The concentrations found in the plasma usually reflect the dietary concentration, with β-carotene typically comprising only 20% to 25% of the total serum carotene level.[12]

Lycopene is the most predominant carotenoid in human plasma, accounting for more than 50% of the carotenoids in human serum. Owing to its lipophilic nature, lycopene is found to concentrate in LDL and very-low-density lipoprotein fractions and not in high-density lipoprotein (HDL) fractions of the serum cholesterol. Interestingly, although *trans*-lycopene constitutes the predominant isomer in food sources, in human plasma 50% of the total lycopene has been found as *cis* isomers. Whether this is due to in vivo isomerization or preferential absorption of *cis*-lycopene is still unclear. Little is known about in vivo metabolism of lycopene.

Carotenes may be stored in adipose tissue, the liver, other organs (the adrenals, testes, and ovaries have the highest concentrations), and the skin (Table 69-4). Deposition in the skin results in carotenodermia. This is a benign (and probably beneficial) state. Carotenodermia not directly attributable to dietary intake or supplementation, however, may indicate a deficiency in a necessary conversion factor (e.g., zinc, thyroid hormone, vitamin C, or protein).

PHYSIOLOGIC ROLES

Antioxidant Activity

In general, carotenes exert significant antioxidant activity, whereas the antioxidant activity of vitamin A is relatively minor.[13] However, its antioxidant actions are specific in that they are involved primarily in scavenging singlet molecular oxygen and to a much lesser extent peroxyl radicals. The efficacy of the various carotenoids for physical quenching is related to the number of conjugated double bonds present in the molecule determining their lowest triplet energy level. The most efficient singlet oxygen quenching carotenoid is the open-ring carotenoid lycopene.

The antioxidant activity of carotenes is thought to be responsible for their anticancer effects. Because aging is associated with free radical damage, a hypothesis developed that carotenes may also protect against aging as well. Evidence seems to support this hypothesis. It appears that tissue carotenoid content is the most significant factor in determining maximal life span potential (MLSP) of mammalian species ($r = 0.835$ for 12 mammalian species, and for primates alone, $r = 0.939$).[14] For example, human MLSP of approximately 90 years correlates with a serum carotene level of 50 to 300 mg/dL, whereas other primates, such as the rhesus monkey, have an MLSP of approximately 34 years, correlating with a serum carotene level of 6 to 12 mg/dL.

Although β-carotene has received most of the attention, many carotenes that have either low or no vitamin A activity exert much greater protection compared with β-carotene. For example, β-carotene generates vitamin A much more efficiently than α-carotene, but α-carotene is approximately 38% stronger as an antioxidant and 10 times more effective in suppressing liver, skin, and lung cancer in animals compared with β-carotene.[15] Even more powerful are lycopene, lutein, and astaxanthin.[16-21] Studies have shown lycopene to exhibit the highest overall singlet oxygen quenching of the carotenoids thus far studied.[22] Its activity is roughly double that of β-carotene. Furthermore, lycopene exerts even more impressive anticancer effects.[17,18]

To evaluate the role of lycopene as a protective factor in digestive tract cancers, a case-control study was conducted in northern Italy, where tomato intake is high but also heterogenous in that some people eat a lot of tomatoes, whereas others eat few, if any. Tomatoes are a perfect food to study since they are quite high in lycopene but low in carotene.

The data were obtained from a series of hospital-based studies on various cancers of the digestive tract from 1985 to 1991.[23] Frequency of consumption of raw tomatoes was divided into four levels: fewer than two; three to four; four; five to six; and more than seven servings per week. Results showed a consistent pattern of protection by high intake of raw tomatoes in all examined cancer sites of the digestive tract. The degree of protection was similar to, but somewhat more marked than, those afforded by green vegetables and fruit studies carried on in the same areas. The results supported the findings of other researchers who found, for example, a 40% reduction in the risk of esophageal cancer by simply consuming one serving of raw tomatoes per week and a 50% reduced rate for cancers of all sites among elderly Americans reporting a high tomato intake. These results suggest that increasing dietary lycopene levels may be a significant protector against cancer.[17,18]

Immune System

Carotenes have demonstrated significant effects in enhancing immune function. Some of these effects are probably related to an ability to prevent stress-induced thymic involution, as well as promote thymus growth and function and increase interferon's stimulatory action on the immune system.[24] Interferon is a powerful immune-enhancing compound that plays a central role in protection against viral infections.

Reproduction

Beta-carotene reportedly has a specific effect in fertility distinct from its role as a precursor to vitamin A.[25-27] In bovine nutritional studies, cows fed β-carotene–deficient diets exhibited delayed

ovulation and an increase in the number of follicular and luteal cysts.[25,26] The corpus luteum has the highest concentration of β-carotene of any organ measured.[27] The carotene cleavage activity changes with the ovulation cycle, with the highest activity occurring during the midovulation stage. It has been speculated that a proper ratio of carotene to retinol must be maintained to ensure proper corpus luteum function.

As the corpus luteum produces progesterone, inadequate corpus luteum function could have significant deleterious effects. Inadequate corpus luteum secretory function is one of the characteristic features of infertile or irregular menstrual cycles, or both.[28] Furthermore, an increased estrogen-to-progesterone ratio has been implicated in various clinical conditions, including ovarian cysts, premenstrual tension syndrome, fibrocystic breast disease, and breast cancer.[29] Because supplemental β-carotene given to cows significantly reduced the incidence of ovarian cysts (42% in control group vs 3% in the β-carotene group), it may have a similar effect in humans.[26,27] Another bovine condition that benefited from increased dietary β-carotene levels was cystic mastitis.[28] Apparently dairy farmers have a greater appreciation of β-carotene than do many nutritionists. Of course, there are significant financial reasons, because the annual monetary loss from bovine mastitis in the United States has been estimated at 1.5 to 2 billion dollars, and ovarian cysts represent the major cause of infertility in cattle.

Photoprotection

Photo-oxidative processes play a role in the pathology of light-exposed tissues, including the eye and skin. Age-related macular degeneration affects the macula lutea of the retina, the area of maximal visual acuity. It is a major cause of irreversible blindness among the elderly in the United States. Macular pigments protect against the photo-oxidative processes, which may be related to the antioxidant activities of the macular carotenoids or their light-filtering effects. Although lutein and zeaxanthin are responsible for coloration of the macula lutea, neither lycopene, α-carotene, or β-carotene are found in this tissue. Lutein supplementation has proven particularly beneficial in offering protection against macular degeneration, as well as improving visual acuity in the early stages of the disease.[18,19] In regard to protecting the skin against oxidative damage, although clinical applications have focused on β-carotene, lycopene seems particularly well suited for this application.[17]

Commercial Forms

Six primary sources of carotenes are on the market:
- Synthetic all-*trans* β-carotene
- Beta- and α-carotene from the algae *Dunaliella*
- Mixed carotenes from palm oil
- Lutein
- Lycopene
- Astaxanthin

Of the three sources of β-carotene, mixed carotenes from palm oil carotenes seem to be the best form (Table 69-5).

Palm oil carotenes appear to give much better antioxidant protection. The carotene complex of palm oil closely mirrors the pattern in high-carotene foods. In particular, unlike the synthetic version, which only provides the *trans* configuration of β-carotene, natural carotene sources provide β-carotene in both a *trans* and *cis* configuration:
- 60% β-carotene (both *trans* and *cis* isomers)
- 34% α-carotene
- 3% γ-carotene
- 3% lycopene

Palm oil carotenes are absorbed about 4 to 10 times better than synthetic all-*trans* β-carotenes.[30-33] Carotenes from *Dunaliella* have also been shown to be well absorbed.[34] The widespread health concerns over the use of "tropical oils" like palm and coconut do not apply to carotene products extracted from palm oil, because the fat content is minimal. In addition, the real problem with palm oil occurs when it is processed (i.e., partially hydrogenated).

Lutein is used primarily for macular degeneration[19,20] (see Chapter 187), whereas lycopene is emerging as a valued carotene for protection against cancer and cardiovascular disease. Astaxanthin is promoted for its ability to prevent oxidative damage to the cardiovascular system as well as for its ability to transfer across the blood–brain barrier to help protect against neurodegeneration and macular degeneration.[21,35]

CLINICAL APPLICATIONS

Prevention of Cancer

Most epidemiologic studies have demonstrated a strong inverse correlation between dietary carotene intake and various cancers, especially those involving epithelial tissues (e.g., lung, skin, uterine cervix, gastrointestinal tract).[1-3,36-38] The epidemiologic association is much stronger for carotene than for vitamin A. This may

TABLE 69-5 **Antioxidant Potential of Different Carotene Products (Per 25,000 IU of Vitamin A Activity)**

SOURCE	CAROTENOID	QUENCHING RATE	% IN SOURCE	mg/25,000 IU	ANTIOXIDANT POTENTIAL
Antioxidant potential	Alpha-carotene	1.9	33	7.36	2.6
	Beta-carotene	1.4	63	14.04	3.66
	Gamma-carotene	2.5	2.5	0.56	0.26
	Lycopene	3.1	0.1	0.02	0.01
	TOTAL				6.53
Algal	Alpha-carotene	1.9	4	0.61	0.22
	Beta-carotene	1.4	96	14.69	3.83
	TOTAL				4.05
Synthetic	Beta-carotene	1.4	100	14.97	3.9
	TOTAL				3.9

reflect carotene's superior antioxidant, immune-potentiating, and anticarcinogenic activity.[39]

Although there is no argument that a diet high in carotenes protects against cancer, the big question is: "Can β-carotene supplementation reduce the risk of cancer?" The answer appears to be that synthetic β-carotene supplementation does not. Three highly publicized reports on cancer prevention trials featuring synthetic all-*trans* β-carotene in high-risk groups produced negative results. Taking a close look at each of these studies is important to help put things into perspective.

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group

This study's population was 29,000 men in Finland who smoked and drank alcohol.[40] The men were given β-carotene (20 mg/day) or vitamin E, or both. The results of this study indicated an 18% increase in lung cancer in the β-carotene group. This result was not totally unexpected, as studies in primates demonstrated that when animals were fed alcohol and β-carotene, they experienced an increase in liver damage as a result of oxidative damage.[41] Other researchers have pointed out that β-carotene is susceptible to oxidative damage.[42] The protection against oxidative damage of β-carotene is the presence of other antioxidant nutrients.[43] Absence of these protective nutrients could result in formation of cancer-causing compounds, stressing the importance of relying on foods and broader spectrum nutritional antioxidant support. Adding support to this statement is the fact that the group receiving both β-carotene and vitamin E did not show an increase in cancer. In the group not receiving β-carotene supplements, there was a strong protective effect of high dietary β-carotene and blood carotene levels against lung cancer. Altogether, these data strongly suggest that the protection offered by β-carotene is only apparent when other important antioxidant nutrients are provided and may not be provided by the synthetic forms.

Carotene and Retinol Efficacy Trial

The second trial reporting on the role of β-carotene in a high-risk group is the Carotene and Retinol Efficacy Trial (CARET).[44] This study comprised more than 18,000 U.S. men and women smokers and asbestos workers. It was halted 21 months prematurely in January 1996 after 4 years of intervention indicated that β-carotene supplementation (30 mg/day) increased lung cancer by 28% and overall deaths by 17%. Although this appears dramatic, a closer look at the numbers and percentages puts them into proper perspective. Among active smokers, the risk of lung cancer during the CARET study was 5 per 1000. The 28% increase found with β-carotene supplementation increased this number to roughly 6 per 1000.[44]

Interestingly, once again in the group not taking β-carotene, the lowest rate of cancer was found among individuals with the highest blood β-carotene levels, and in former smokers, β-carotene supplementation actually reduced cancer risk by 20%.

The Physician's Health Study

The Physician's Health Study was composed of 22,071 U.S. male physicians who took either 50 mg of β-carotene or a placebo every other day for 12 years. Results demonstrated no significant effect—positive or negative—on cancer or cardiovascular disease, even in the group (11%) that smoked.[45]

General Comments on the "Negative" Studies

Although scientific research is clear that diets high in antioxidants are protective against many cancers, the data are not as solid with antioxidant supplements. Three main points should be kept in mind when discussing research with antioxidants:

- The antioxidant system of the body relies on a complex interplay of many different dietary antioxidants.
- Taking any single antioxidant nutrient is not enough. Total protection requires a strategic comprehensive dietary and supplement program.
- Although dietary supplements are important, they cannot replace the importance of consuming a diet rich in antioxidants.

A shortcoming of many dietary studies is that researchers often focus on the effects of just one factor. In a way this is like judging an entire symphony by listening to a single trombone. Such research has its value, but it is not complete and often raises more questions than it answers.

Another issue is that not all antioxidants are created equal. When it comes to quenching free radicals, each may have a somewhat different (and usually narrow) range of activity. For example, β-carotene is an effective quencher of a free radical known as singlet oxygen, but is virtually powerless against the dozens of other types of free radicals. As a result, it has a narrow range of benefit and is susceptible to being damaged itself and forming a free radical without additional antioxidant support. Most antioxidants require some sort of "partner" antioxidant that allow them to work more efficiently. Additionally, research has shown that β-carotene itself can become damaged if used alone (i.e., without its partner antioxidants vitamin C, vitamin E, and selenium). For example, although studies showed that synthetic β-carotene supplements given alone actually increased the risk of cancer in smokers, when β-carotene was given along with vitamin E and selenium, it reduced cancer deaths by a significant 13%.[40] Damaged β-carotene is extremely toxic to the liver, the lining of the arteries, and the lungs. This fact alone may explain some of the disappointing results from recent β-carotene studies.

The results of these three studies indicate that synthetic β-carotene supplementation may have adverse effects in high-risk groups for cancer and cardiovascular disease. These studies do not invalidate the hundreds of studies showing the preventive effect of a diet rich in carotenes and nutritional antioxidants against cancer and cardiovascular disease. These results seem to indicate the need for a diet high in carotenes and, if carotene supplementation is desired, people should not smoke, natural forms should be used, and the β-carotene needs to be protected against the formation of toxic derivatives by taking extra vitamins C and E and selenium. That said, even studies with β-carotene supplementation that also used additional vitamins C and E failed to show a protective effect against either cancer or cardiovascular disease.[46,47]

Other Prospective Studies

In addition to these three highly publicized studies, several prospective and double-blind studies have shown promising results. In particular, β-carotene supplementation is especially effective in the treatment of early cancerous lesions of the oral cavity and esophagus.[48,49] Although β-carotene has been shown to exert these benefits on its own (in dosages ranging from 15 to 180 mg/day), one of the most positive studies showing a reduction in cancer risk with supplemental β-carotene to date is one that featured a broader supplement program. The Linxian Cancer Chemoprevention Study was a prospective study of 30,000 rural Chinese adults. In one substudy, subjects received one of four supplement programs:

- Retinol and zinc
- Riboflavin and niacin
- Vitamin C and molybdenum
- Beta-carotene, vitamin E, and selenium (dosages one to three times greater than the US recommended daily allowance)

The latter group demonstrated 13% less cancer deaths and a reduction of 9% in overall deaths.[50,51] These results again support

the notion that a combination of antioxidants is superior to high levels of any single antioxidant.

Lycopene in the Treatment of Prostate Cancer

In one of the first detailed studies of lycopene protection against cancer, Harvard researchers discovered that men who consumed the highest levels of lycopene (6.5 mg/day) in their diet showed a 21% decreased risk of prostate cancer compared with those eating the lowest levels.[52] Men who ate two or more servings of tomato sauce each week were 23% less likely to develop prostate cancer during the 22 years of the study than men who ate less than one serving of tomato sauce each month. In addition to a protective effect, lycopene may exert a therapeutic effect as well. In a study of patients with existing prostate cancer, lycopene supplementation (15 mg/day) was shown to slow tumor growth, shrink the tumor, and lower the level of prostate specific antigen (PSA), a marker of cancer activity, by 18%.[53]

In another study, the efficacy of lycopene (4 mg/day) plus orchidectomy was compared with orchidectomy alone in the management of advanced prostate cancer.[54] Fifty-four patients with histologically confirmed metastatic prostatic cancer and a performance status of 0 to 2 (World Health Organization) were entered into the trial. At 6 months there was a significant reduction in PSA level in both treatments, but it was more marked in the lycopene group (mean 9.1 and 26.4 ng/mL). After 2 years, these changes were more consistent in the lycopene group (mean 3.01 and 9.02 ng/mL). Eleven (40%) patients in the orchidectomy alone group and 21 (78%) in the lycopene group had a complete PSA response, with a partial response in 9 (33%) and 4 (15%) and progression in 7 (25%) and 2 (7%), respectively. Bone scans showed that in the orchidectomy arm only 4 (15%) patients had a complete response versus 8 (30%) in the lycopene group, with a partial response in 19 (70%) and 17 (63%) and progression in 4 (15%) and 2 (7%), respectively. Of the 54 patients who entered the trial, 19 (35%) died: 12 (22%) in the orchidectomy group and 7 (13%) in the lycopene group. Researchers concluded that adding lycopene to orchidectomy produced a more reliable and consistent decrease in serum PSA level; it not only shrunk the primary tumor but also diminished the secondary tumors, providing better relief from bone pain and lower urinary tract symptoms and improving survival compared with orchidectomy alone. Lycopene appears to be most useful in early stages of prostate cancer as no clinically relevant benefits were shown for patients with advanced stages of the disease in one clinical trial. Lycopene also does not appear to be effective for androgen-independent prostate cancer.[55] Lycopene does, however, appear to helpful in benign prostate hyperplasia (BPH). In one double-blind, placebo-controlled trial total of 40 patients with histologically proven BPH free of prostate cancer were randomized to receive either lycopene at a dose of 15 mg/day or placebo for 6 months. The primary end point of the study was the inhibition or reduction of increased serum PSA levels. Symptoms of the disease, as assessed via the International Prostate Symptom Score questionnaire, were improved in both groups with a significantly greater effect in men taking lycopene supplements.

Prevention of Cardiovascular Disease

Just as in the case of cancer prevention, although a high intake of carotene-rich foods appears to be protective, the same may not be true for supplementation with synthetic β-carotene. Double-blind trials wherein people were supplemented with β-carotene alone or placebo have not found benefit for synthetic β-carotene supplementation.[56] Three of four trials reported a higher risk of cardiovascular disease in the β-carotene groups compared with those receiving placebo. The research implied that a full-spectrum of carotenes or more significant carotenes like lycopene or lutein would offer the greatest degree of protection.[1-3,19,20,56-59]

Just as in cancer, a potential problem with much research on carotenes in cardiovascular disease protection has been the focus on β-carotene. It may not be the most important marker of protection. A large clinical study evaluating the relationship between carotene status and heart attack (acute myocardial infarction) found that lycopene, but not β-carotene, was protective.[59] Lycopene and astaxanthin exert greater antioxidant activity compared with β-carotene in general but specifically against LDL oxidation.[21,35,57-60]

Beta-carotene is likely of less importance compared with many other carotenes, especially lycopene, astaxanthin, and lutein, because it does not get incorporated into LDL effectively, although it may help protect the endothelium.[50] Lutein may turn out to be the most significant carotene in the battle against atherosclerosis. On the basis of analysis of the different subtypes of LDL, it was found that lycopene, β-carotene, and cryptoxanthin were mainly located in the larger, less dense LDL particles, whereas lutein and zeaxanthin were found preferentially in the smaller, denser LDL particles.[61] Because the smaller, denser LDL subtype is most easily oxidized, lutein and zeaxanthin are particularly important in protecting against damage to LDL cholesterol.

Despite the focus on protecting LDL cholesterol from damage, it appears that the protective effect of carotenes against the development of atherosclerosis does not occur early in the progression (i.e., they exert little effect on protecting against oxidative damage to LDL cholesterol), but rather later on by some undetermined mechanism. This conclusion is based on studies indicating that carotenoid-enriched diets are associated with less atherosclerotic plaque formation.

Immune Enhancement

Carotenes demonstrated a number of immune-enhancing effects in recent studies.[24] However, these effects were demonstrated as far back as 1931, when it was found that a diet rich in carotenes, as determined by blood carotene levels, was inversely related to the number of school days missed by children.[62] Originally, it was thought that the immune-enhancing properties of carotenes were due to their conversion to vitamin A. Now it is known that carotenes exert many immune system–enhancing effects independent of any vitamin A activity.[24]

In a recent study, the relationship of plasma concentrations of six major carotenoids (β-carotene, α-carotene, β-cryptoxanthin, lycopene, lutein, and zeaxanthin) with the incidence and severity of acute respiratory infections was determined.[63] The incidence rate ratio of acute respiratory infections at high β-carotene status was 0.71 (95% confidence interval [CI] 0.54 to 0.92) compared with the low β-carotene concentration group. Interestingly, α-carotene, β-cryptoxanthin, lycopene, lutein, and zeaxanthin were not related to incidence or severity of infections, indicating that β-carotene may exert the most significant immune-enhancing effects.[52]

One of the most impressive studies with supplemental β-carotene was conducted on normal human volunteers.[64] Results demonstrated that oral β-carotene (180 mg/day, approximately 300,000 international unit [IU]) significantly increased the frequency of OKT4+ (helper/inducer T cells) by approximately 30% after 7 days, and of OKT3+ (all T cells) after 14 days.[44] Because T4+ lymphocytes play a critical role in determining host immune status, this study indicates that oral β-carotene may be effective in

increasing the immunologic competence of the host in conditions characterized by a selective diminution of the T4 subset of T cells, such as the acquired immunodeficiency syndrome and cancer.

However, rather than supplementing the diet with synthetic β-carotene, it may be more advantageous to use natural carotene sources or to increase the intake of carotene-rich foods. In another study, 126 healthy college students were randomly assigned to one of the following groups:

- Group A, the control group
- Group B, a group that used a 15-mg (25,000 IU) β-carotene supplement daily
- Group C, a group that consumed approximately 15 mg β-carotene per day from carrots

Better results (i.e., increase in white blood cell number and function) were achieved in the group eating the carrots.[65]

Since the absorption studies have shown supplemental β-carotene to be much better absorbed than the carotenes from carrots and other vegetables, the differences are likely the result of form (i.e., natural is better than synthetic).[5]

Vaginal Candidiasis

It is a well-established fact that women are more susceptible to vaginal candidiasis when the immune system is depressed, which may be due to low carotene levels. Beta-carotene levels were determined in exfoliated vaginal cells in 22 women with vaginal candidiasis and compared with vaginal cells from 20 controls. The β-carotene level per 1 million cells in the women with vaginal candidiasis was 1.46 ng compared with 8.99 ng in the control group (i.e., one-sixth that of normal).[66]

These results, coupled with β-carotene's known effects on enhancing the immune system, suggest that a low tissue level of β-carotene is associated with vaginal candidiasis, and a high dietary or supplemental intake of β-carotene may be protective against vaginal candidiasis.

Photosensitivity Disorders

Beta-carotene has become the treatment of choice for photosensitivity disorders. It is most effective in the treatment of erythropoietic protoporphyria (EPP). Its effectiveness in other photosensitivity disorders such as polymorphous light eruption, solar urticaria, and discoid lupus erythematosus is significant but not as great.[67-76] Beta-carotene also has a small but significant effect in increasing the exposure at which manifestations of sunburn begin, thus allowing some subjects the opportunity to stay in the sun long enough to get a "tan" for the first time.[76]

Patients with EPP are characterized by elevated levels of porphyrins in blood, feces, and skin and by sensitivity to visible light. This sensitivity manifests after exposure to sunlight as a burning sensation followed by swelling and redness. Topical sunscreens are of no value. The photosensitivity is due to excitation of the porphyrin molecule by ultraviolet radiation, resulting in the production of free radicals that are deleterious to the skin. Direct cell damage results in the release of chemical mediators, which in turn damage other cells, resulting in the manifestations of itching, burning, redness, and swelling.

In EPP, it appears that carotene levels must be maintained in the blood at 600 to 800 mg/dL for optimum effects and that the protective effect is not usually observed until after 4 to 6 weeks of therapy. The actions of β-carotene and other carotenes in human tissue are similar to their action in plant cells (i.e., they function as a cellular screen against sunlight-induced free radical damage).

DOSAGE

For carotenes, a daily dosage of 25,000 IU (15 mg of β-carotene) appears to be reasonable for general health. Mixed carotene preparations are preferred to isolated β-carotene supplements to provide the full range of carotenes in a natural form. For the treatment of precancerous lesions and immune enhancement, the dosage range is 25,000 to 300,000 IU. In the treatment of EPP, the dosage is based on maintaining blood carotene levels between 600 and 800 mg/dL. Again, for the best clinical impact, it appears that natural mixed forms of carotene should be used in conjunction with a broad range of other natural antioxidants (see Chapter 108).

TOXICITY

Supplementing the diet with β-carotene has not been shown to possess any significant toxicity despite its use in high doses in the treatment of numerous photosensitivity disorders (see discussion on "Photosensitivity Disorders"). Occasionally patients complain of loose stools, which usually clears spontaneously and does not necessitate stopping treatment. Elevated carotene levels in the blood do not lead to vitamin A toxicity, nor do they lead to any other significant disturbance besides yellowing of the skin (carotenodermia).

The ingestion of large amounts of carrots or carrot juice (0.45 to 1 kg/day of fresh carrots for several years) has, however, been shown to cause neutropenia, as well as menstrual disorders.[77,78] Although the blood carotene levels of these patients did reach levels (221 to 1007 mg/dL) similar to those of patients taking high doses of β-carotene (typically 800 mg/dL), the disturbances are due to some other factor in carrots, as neither of these effects nor any others have been observed in subjects consuming high doses of pure β-carotene (e.g., 300,000 to 600,000 IU/day [180 to 360 mg β-carotene], which is equivalent to 4 to 8 lb of raw carrots) over long periods of time.[79-83] Doses up to 1000 mg/kg have been given to rats and rabbits for long periods of time with no signs of embryotoxicity, toxicity, tumorigenicity, or interference in reproductive functions.[84]

DRUG INTERACTIONS

One study showed that β-carotene in combination with selenium, vitamin C, and vitamin E appeared to decrease the effectiveness of the combination of simvastatin (Zocor) and niacin. The researchers proposed that this inhibition of hydroxymethylglutaryl coenzyme-A reductase inhibitors could reduce the effectiveness of similar drugs such as atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor), and pravastatin (Pravachol).[85]

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CHAPTER 70

Boron*

Joseph E. Pizzorno, ND

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INTRODUCTION

Boron is a ubiquitous constituent of the environment, typically occurring in nature as inorganic borates. In human tissues, boron is found as the borate anion and boric acid, predominantly the latter form, with a concentration primarily reflecting dietary intake.[1,2] In trace amounts boron is essential for the growth of many plants, and although it has yet to be recognized as an essential nutrient for humans, data from animal and human studies continue to suggest that boron is important for many life processes. This includes embryogenesis; bone growth and maintenance; immune function; regulation of inflammation; psychomotor skill; mineral metabolism; brain function and performance; and prevention of osteoporosis, osteoarthritis, and prostate, lung, and cervical cancer.[3] It also has been shown to affect the metabolism or action of many biological compounds, including glucose, S-adenosylmethionine, amino acids, triglycerides, macrominerals, and a number of hormones, including vitamin D, insulin, testosterone, and estrogen.[4,5]

SOURCES

Because boron in plants depends on the availability of boron in the soil, the same food crop can vary greatly in boron content depending on where and how it is grown. In general, soils exposed to high degrees of precipitation have decreased levels of boron.[6] Heavy rainfall leaches the highly soluble boric acid from the soil, whereas in more arid regions, evaporation of groundwater results in higher concentrations of boron solutes. Food processing results in additional loss of boron, and the use of superphosphate and potash fertilizers reduces its uptake by plants.[7,8] Foods of plant origin, such as leafy vegetables, noncitrus fruits (apples), nuts, legumes (peanut butter), avocados, and sea vegetables are considered the best sources of boron.[1,9] Wine has also been shown to contribute appreciable amounts of boron to the diet, and water intake may also be a significant source of total intake.[10] A diet containing an abundance of these items would provide 2 to 6 mg/day of boron.[9,11]

Daily intake of boron depends on several variables. Concentration of boron in water varies considerably according to geographic source. In some areas boron in drinking water and water-based beverages may account for most of the total dietary boron intake. Individual food preference greatly influences daily intake of boron. Fruits, vegetables, tubers, and legumes have higher concentrations of boron than do cereal grains or animal tissues. For adults and seniors, though, the largest source of boron turns out to be instant regular coffee.[12] Given the poor dietary intake of produce in the United States, the top two boron contributors to adult boron intake, coffee and milk, are actually deficient in this nutrient (Table 70-1)[13] compared with other more nutritious foods. Nevertheless, these make up 12% of the total boron intake by virtue of the volume consumed.[13] Boron has also been determined to be a notable contaminant or major ingredient of many personal care products, and it (boric acid) is occasionally used as a food preservative.[14]

In Sydney, Australia, 32 subjects aged 20 to 53 years old were assessed over a 7-day period for their dietary intake of boron. The average boron intake in male

*The original version of this chapter in a previous edition was reprinted with permission from Alternative Medicine Review 1997;2:48-56.

TABLE 70-1 **Top Contributors of Dietary Boron in the American Diet**

FOOD	BORON (mg/mL)
Coffee, from ground beans	0.029
Milk, whole	0.018
Apples, raw	0.36
Beans, refried	0.4
Potatoes, from French fries	0.11
Orange juice	0.072
Peanut butter	1.145
Wine	0.61
Apple juice	0.18
Cola	0.013

Data from Rainey CJ, Nyquist LA, Christensen RE, et al. Daily boron intake from the American diet. J Am Diet Assoc. 1999;99:335-340.

and female subjects was found to be 2.28 ± 1.3 and 2.16 ± 1.1 mg/day, respectively.[10] The boron content of selected Australian foods has been found to correlate with values in Finnish and U.S. Food and Drug Administration tables and is presented in Table 70-2 (note, however, the large variations between countries and even regions of a country).[10] Regional differences are certainly important. An analysis of nearly 300 foods that are commonly consumed in Korea found considerable discrepancies with values reported elsewhere. For example, the boron content in Korean apples was found to be one-twelfth that found in German apples. The foods found to be richest in boron (in micrograms/100 g) included buckwheat flour (828), soybeans (1642), mung beans (818), almonds (917), cocoa (2026), coffee powder (approximately 1530), and oolong and green tea powder (1274 and 1316, respectively).[15]

METABOLISM

Chemical Properties

Elemental boron was first isolated in 1808. It is the first member (atomic number 5) of the metalloid or semiconductor family of elements, including silicon and germanium, and is the only nonmetal of the group IIIA elements. Like carbon, boron has a tendency to form double bonds and macromolecules.[16] Boron, as boric acid, acts as a Lewis acid, accepting hydroxyl (OH^-) ions and leaving an excess of protons.[17] Because boron complexes with organic compounds containing hydroxyl groups, it interacts with sugars and polysaccharides, adenosine-5-phosphate, pyridoxine, riboflavin, dehydroascorbic acid, and pyridine nucleotides.[18] Given boron's affinity for hydroxyl groups, it is possible that it interacts with glycoproteins and glycolipids found in cellular membranes. Animal studies have supported a role for boron in maintaining cellular membrane structure and function, with boron deprivation causing pathologic changes in both zebrafish and frogs.[19] Dietary magnesium and essential fatty acids, both of which are involved in cell membrane function, also influence the response to boron deprivation, lending further support for a role for boron. For example, in an animal-based study, boron deprivation was found to alter animal behavior in ways that were modifiable by varying the composition of dietary fatty acids, and vice versa, possibly by altering the fluidity of cellular membranes.[20]

TABLE 70-2 **Concentration of Boron in Selected Australian* Foods**

FOOD	BORON (mg/100 g)
Almonds	2.82
Apples (red)	0.32
Apricots (dried)	2.11
Avocados	2.06
Bananas	0.16
Beans (red kidney)	1.4
Bran (wheat)	0.32
Brazil nuts	1.72
Broccoli	0.31
Carrots	0.3
Cashews (raw)	1.15
Celery	0.5
Chickpeas	0.71
Dates	1.08
Grapes (red)	0.5
Hazelnuts	2.77
Honey	0.5
Lentils	0.74
Olives	0.35
Onions	0.2
Oranges	0.25
Peaches	0.52
Peanut butter	1.92
Pears	0.32
Potatoes	0.18
Prunes	1.18
Raisins	4.51
Walnuts	1.63
Wine (Shiraz Cabernet)	0.86

*Note that there is a large variation between countries.

Biochemistry

Boron in food, sodium borate, and boric acid are well absorbed from the digestive tract.[21] However, homeostatic mechanisms for maintaining serum levels of boron exist, with urinary levels mirroring intake.[8] A boron transporter has been identified *(NaBC1),* and dietary supplementation of boron has been shown to alter its genetic expression.[4,22] Compounds of boron are also absorbed through damaged skin and mucous membranes; however, they do not readily penetrate intact skin.[23]

No accumulation of boron has been observed in soft tissues of animals fed long-term low doses of boron; however, in acute poisoning incidents, the amount of boric acid in brain and liver tissue has been reported to be as high as 2000 ppm. Within a few days of consumption of large amounts of boron, levels in blood and most soft tissues quickly reach a plateau.[24] Tissue homeostasis is maintained by the rapid elimination of excess boron, primarily in the urine, with bile, sweat, and breath also contributing as routes of elimination.[18]

Evidence suggests that supplemental boron does accumulate in bone; however, cessation of exposure to dietary boron results in a rapid drop in bone boron levels. The half-life of boric acid in animals is estimated at about 1 day.[24]

Biological Functions

Boron contributes to living systems by acting indirectly as a proton donor and exerting an influence on cell membrane structure and function.[25] Although the absolute essentiality of boron for plants as well as two animal species (zebrafish and frogs) is well documented, studies to date have not shown it to be unequivocally essential for other species or humans. However, boron supplementation has been shown to affect certain aspects of animal physiologic function. In general, supplemental dietary boron has its most marked effects when the diet is deficient in known nutrients.[26]

Recent animal-based data suggests boron may in some way affect the utilization or production of S-adenosylmethionine, which in turn influences homocysteine metabolism, as well as other molecules involved in cellular signaling and differentiation. Rats deprived of boron had increases in plasma cysteine and homocysteine as well as decreases in hepatic S-adenosylmethionine and the related compounds S-adenosylhomocysteine and spermidine. It is possible that many of boron's biological effects are mediated through this mechanism, because S-adenosylmethionione is involved in many methylation reactions, including DNA methylation, as well as methylation of other neurotransmitters, phospholipids, and signaling molecules, and is also used frequently as an enzyme substrate.[27]

Evidence suggests that boron might also have an effect on decreasing fasting serum glucose concentrations in postmenopausal women.[28]

Embryo Maturation

Research has shown that boron is an important player in the early stages of life.[3] Boron deficiency negatively affects reproductive ability, as well as embryo development in both the African clawed frog *(Xenopus laevis)* and the zebrafish. Experimentation with *Xenopus* noted that dietary boron deprivation elicited necrotic egg increases combined with a high frequency of abnormal gastrulation, causing adverse effects during gametogenesis, gamete maturation, embryonic development, and larval maturation.[19] In the zebrafish model, 45% of boron-deprived embryos died during the early postfertilization period. Conversely, only 2% of boron-supplemented embryos died. Other studies with rats and mice corroborated that low boron status might affect reproduction in mammals, although conclusions from these studies were not as clear.

Life Span

Boron in an animal model has been shown to affect life span, although the process is undefined. Extremes in dietary boron, both a deficiency and an excess, appear to affect the median life span of *Drosophila.* Adding excess during the adult stage decreased life span by as much as 69%, whereas supplementing the diet with low levels of boron increased life span by 9.5%.[29] No research exists for other species.

Brain Function and Performance

Although limited data exist for boron's influence on brain function, existing research is "among the most supportive in demonstrating that boron is a beneficial bioactive element for humans."[30] Brain electrophysiology and cognitive performance were assessed in response to dietary manipulation of boron (approximately 0.25 versus approximately 3.25 mg boron/2000 kcal/day) in three studies with healthy older men and women. A low boron intake was shown to result in a decrease in the proportion of power in the α-band and an increase in the proportion of power in the δ-band, effects similar to those induced by heavy metals and nonspecific malnutrition, as well as mental drowsiness and reduced alertness. Other changes in left–right symmetry and brain wave coherence were noted in various sites, indicating an influence on brain function. When contrasted with the high boron intake, low dietary boron resulted in significantly poorer performance (P <0.05) on tasks emphasizing manual dexterity, eye–hand coordination, attention, perception, encoding, and short- and long-term memory. Collectively, the data from these studies indicate that boron may play a role in human brain function, alertness, and cognitive performance.[31]

Interestingly, as mentioned previously, essential fatty acid composition may interact with boron status to influence brain function. A number of biomarkers for low activity were observed in boron-deficient rats when given safflower oil, but fish oil negated these deficits.[20]

Hematologic

Boron supplementation to human subjects who had previously followed a dietary regimen deficient in boron increased blood hemoglobin concentrations, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. It lowered hematocrit, red cell count, and platelet count.[32] As discussed in the "Toxicology" section, boron may inhibit the enzyme δ-aminolevulinic acid dehydratase.

Hepatoprotection

Studies of fulminate hepatic failure in Wistar rat models showed boron pretreatment significantly reduced lipid peroxidation, as well as decreased serum liver enzymes in these animals. Boron pretreatment also increased the peroxide-metabolizing enzymes' levels of glutathione peroxidase and catalase, as well as glutathione itself.[33,34]

Mineral Metabolism

Boron also affects mineral metabolism as well as related hormones in human subjects. In the first nutritional study with humans involving boron,[23] postmenopausal women first were fed a diet that provided 0.25 mg boron/2000 kcal for 119 days and then were fed the same diet with a boron supplement of 3 mg boron/day for 48 days. The boron supplementation reduced the urinary excretion of calcium and magnesium and elevated the serum concentrations of 17 β-estradiol and testosterone.[9]

In a study designed to determine the effects of boron supplementation on blood and urinary minerals in athletic subjects on Western diets, findings suggested that boron supplementation modestly affected mineral status.[35]

DEFICIENCY SIGNS AND SYMPTOMS

Information on boron deficiency is limited, especially in humans. It is thought that insufficient intake of boron becomes obvious only when the body is stressed in a manner that enhances the need for it. When the diets of animals and humans are manipulated to cause functional deficiencies in nutrients such as calcium, magnesium, vitamin D, essential fatty acids, and methionine, a large number of responses to dietary boron occur.[36] Evidence suggests that more than 21 days on a boron-deficient diet are required to demonstrate detectable effects in humans.[37] The variables that are changed due to a boron-deficient diet abruptly improve about 8 days after boron supplementation is introduced.[9] Evidence indicates that hemodialysis results in an excessive decrease in serum boron compared with controls.[38] Although blood urea is by no

means nitrogen pathognomonic for a boron deficiency, it has been found to be slightly elevated during boron depletion.[39]

NUTRIENT INTERACTIONS

Vitamin D

Considerable evidence indicates that dietary boron alleviates perturbations in mineral metabolism that are characteristic of vitamin D_3 deficiency.[40] In one study, chicks fed a diet inadequate in vitamin D exhibited decreased food consumption and plasma calcium concentrations and increased plasma concentrations of glucose, β-hydroxybutyrate, triglycerides, triiodothyronine, cholesterol, and alkaline phosphatase activity after 26 days. Supplemental boron returned plasma glucose and triglycerides to concentrations exhibited by chicks fed a diet adequate in vitamin D.[41]

In rachitic chicks, boron elevated the numbers of osteoclasts and alleviated distortion of the marrow sprouts of the proximal tibial epiphysial plate, a distortion characteristic of vitamin D_3 deficiency.[40,42] Higher apparent balance values of calcium, magnesium, and phosphorus have been observed for rats fed a vitamin D-deprived diet if the diet was supplemented with boron.[26]

After supplementation with 3.25 mg boron daily, plasma levels of vitamin D_2 increased in men older than age 45 and postmenopausal women on low magnesium and copper diets.[43] In a very small human study (n = 8), healthy male volunteers were given 10 mg boron per day for 1 week, resulting in a nonsignificant 7% rise in vitamin D levels.[5] Inhibition of 24-hydroxylase, the enzyme that catabolizes vitamin D, has been speculated to be the possible mechanism of action, although this has not been demonstrated.[44]

Calcium

Boron supplementation may have a favorable impact on calcium metabolism. A boron supplement of 3 mg/day affected several indexes of mineral metabolism of seven women consuming a low-magnesium diet and five women consuming a diet adequate in magnesium; the women had consumed a conventional diet supplying about 0.25 mg boron per day for 119 days. Boron supplementation modestly reduced the urinary excretion of calcium when dietary magnesium was low.[9]

In men older than age 45 and postmenopausal women, changes caused by boron supplementation included increased concentration of ionized plasma and total calcium, as well as reduced serum calcitonin concentration and urinary excretion of calcium.[43] A 1993 study demonstrated that a low boron diet elevated urinary calcium excretion. The high level of calcium excretion was maintained throughout the 6-week study; however, it remained elevated even after boron supplementation began.[45]

Animal studies suggest that boron deprivation does not markedly affect the concentration of calcium (and phosphorus) in bone, but rather it does affect the concentration of other nutrients associated with osteoblast and osteoclast function, such as magnesium, potassium, copper, and zinc.[30]

Copper

Supplemental boron acts to increase serum levels of both copper and copper-dependent enzymes in humans. Boron supplementation (3 mg/day) to five men older than age 45, four postmenopausal women, and five postmenopausal women on estrogen therapy who had been fed a low boron diet (0.23 mg/2000 kcal) for 63 days resulted in higher erythrocyte superoxide dismutase, serum enzymatic ceruloplasmin, and plasma copper.[43] In a subsequent study, these same variables were again found to be higher during boron repletion than while subjects were fed a diet low in boron.[46]

Magnesium

When magnesium deprivation is severe enough to cause typical signs of deficiency, a significant interaction between boron and magnesium is found.[16] A combined deficiency of boron and magnesium causes detrimental changes in the bones of animals. Supplemental boron elevates plasma magnesium concentrations and enhances growth.[42]

Boron supplementation resulted in increased serum magnesium concentrations in human female subjects.[24] Boron supplementation increased red blood cell magnesium concentrations.[47] It has been shown that serum magnesium concentrations are greater in sedentary females whose diets are supplemented with boron than in exercising female athletes who are supplemented with boron.[48] This finding, although unexplained to date, may indicate an increased loss of boron through urine and perspiration during exercise.

Phosphorous

Supplemental boron seemed to lower serum phosphorus concentrations in female subjects 20 to 27 years old.[48] However, exercise training diminished these changes,[24] again possibly indicating increased losses or an increased need for boron as a result of exercise. A low magnesium status, along with supplementation of boron, may depress the urinary excretion of phosphorus. This does not occur in women with an adequate magnesium intake.[9]

Methionine and Arginine

In experimental animals, a beneficial impact is consistently observed after boron supplementation when the diet contains marginal methionine and excessive arginine. Among the signs exhibited by rats fed on a diet marginal in methionine and magnesium are depressed growth and bone magnesium concentration and elevated spleen weight/body weight and kidney weight/body weight ratios. Findings indicate that the severity of these symptoms is alleviated with boron supplementation.[49]

Essential Fatty Acids

Several studies have emerged that suggest some interaction between essential fatty acids and boron. As previously mentioned, boron deprivation was shown to decrease the activity of rats and alter their brain composition, yet supplementation with fish oil (vs safflower oil) minimized these effects.[20] Similarly, boron deprivation in rats was shown to impair both bone trabecular microarchitecture and cortical bone strength. Interestingly, the use of fish oil instead of safflower oil was also shown to benefit both of these structural markers through a distinct mechanism, yet the benefit of fish oil was limited only to the group receiving adequate boron. In other words, a boron deficiency prevented the normal benefit of fish oil to bone.[50] Lastly, as mentioned previously, boron deprivation was shown to decrease S-adenosylmethionine levels in rats. Feeding them corn oil instead of fish oil had similar effects, although they were likely mediated by a different mechanism.[50]

HORMONE INTERACTIONS

In rats, supplemental dietary boron substantially depressed plasma insulin, plasma pyruvate concentrations, and creatine kinase activity and increased plasma thyroxine (T4) concentrations. Boron supplementation also decreased plasma aspartate transaminase activity.[51] In animal experiments, boron supplementation offset the elevation in plasma alkaline phosphatase caused by vitamin D deficiency.[39] Boron supplementation in rats has also been shown to reduce plasma insulin levels, likely by increasing insulin sensitivity.[52]

An increase in dietary intake of boron from 0.25 to 3.25 mg/day has been reported to increase plasma 17 β-estradiol by more than 50% and to more than double plasma testosterone levels in postmenopausal women. The elevation seemed more marked when dietary magnesium was low.[9] In a subsequent study of healthy men, boron supplementation resulted in an increase in the concentrations of both plasma estrogen and testosterone; however, not all published trials support these observations.[10]

Ten male bodybuilders, 20 to 26 years old, were given a 2.5 mg boron supplement, whereas nine male bodybuilders, 21 to 27 years old, were given a placebo for 7 weeks. Because both groups demonstrated significant increases in total testosterone (P <0.01), lean body mass (P <0.01), one repetition maximum squat (P <0.001), and bench pressing (P <0.01), the authors concluded that the gains were a result of 7 weeks of bodybuilding, not of boron supplementation.[53] However, in a small study of male volunteers, 10 mg supplemental boron per day was associated with an increase in plasma free testosterone and a decrease in mean plasma estradiol levels. A decrease in the inflammatory markers C-reactive protein, tumor necrosis factor-α, and sex hormone binding globulin was also seen.[5]

One researcher hypothesized that boron might be required for the synthesis of steroid hormones, as well as vitamin D. Because the biosynthesis of steroids such as vitamin D, testosterone, and 17 β-estradiol involves one or more hydroxylation steps, and because of boron's ability as a Lewis acid to complex with hydroxyl groups, boron may assist the addition of hydroxyl groups to the steroid structures.[9] It has also been suggested that boron may act in an unspecified manner to protect hormones from rapid inactivation.[9] The current hypothesis suggests that boron can inhibit a range of microsomal enzymes that insert hydroxyl groups near existing hydroxyls in steroids. These enzymes include those that catabolize 25-hydroxyvitamin D.[54]

Table 70-3 lists boron's impact on selected hormones in either animals or humans. Some of these interactions have only been demonstrated in animal models, whereas others have not been demonstrated unequivocally to date in all age and gender segments of a human population.

TABLE 70-3 **Boron's Observed Impact on Selected Hormones**

HORMONE	INCREASES	DECREASES
Alkaline phosphatase		X
Aspartate transaminase*		X
Calcitonin		X
Cholecalciferol		X
Creatine kinase*	X	
17 Beta-estradiol†	X	
Insulin*		X
Superoxide dismutase		X
Testosterone†	X	
Thyroxine*		X

*These interactions have only been demonstrated in animal models.
†These interactions have not been demonstrated unequivocally to date in all age and gender segments of a human population.

CLINICAL APPLICATIONS

Osteoporosis

A considerable body of evidence has shown that both compositional and functional properties of bone are affected by boron status.[55] In experimental animals, histologic findings suggest that supplemental boron enhances maturation of the growth plate.[39] Boron has also been found at the highest concentrations in growing and calcifying areas of long bones.[9] In two human studies, boron deprivation caused changes in indexes associated with calcium metabolism in a manner that could be construed as being detrimental to bone formation and maintenance; these changes were enhanced by a diet low in magnesium.[9,39] The author concluded that boron and magnesium are apparently necessary for optimal calcium metabolism and are thus necessary to prevent the excessive bone loss that often occurs in postmenopausal women and older men.[39]

At the cellular level, in vitro studies have shown that boron may play a role in regulation of proteins in the morphogenesis of bone, including BMP-4, -6 and -7, as well as the mRNA expression of several extracellular matrix proteins.[56] This is consistent with animal-based studies that suggest boron deprivation causes deficits in bone modeling and remodeling by inhibiting bone formation.[57,58]

Osteoarthritis, Rheumatoid Arthritis, and Regulation of Inflammation

A dietary boron deficiency may be a contributing factor in some cases of arthritis.[59] In areas of the world where boron intake is routinely 1 mg/day or less, the estimated incidence of arthritis ranges from 20% to 70%, whereas in areas where boron intake ranges from 3 to 10 mg/day, the estimated incidence of arthritis ranges from 0% to 10%.[59]

Analytic evidence indicates that persons with arthritis have lower boron concentrations in femur heads, bones, and synovial fluid compared with persons without this disorder.[7]

In 1961, the first anecdotal evidence suggesting that boron may be beneficial for osteoarthritis was presented when one patient had reduced swelling and stiffness and remained symptom free for 1 year after supplementation with 3 mg of elemental boron twice daily for 3 weeks. A human study also offered evidence that boron supplementation might be beneficial in the treatment of this condition. In a double-blind, placebo-controlled trial of 20 subjects with osteoarthritis, 50% of subjects receiving a daily supplement containing 6 mg of boron noted a subjective improvement in their condition. Only 10% of those receiving placebo improved during the same time interval. Greater improvement was noted in the condition of all joints (P <0.01), as well as less pain on movement (P <0.001) in subjects receiving the boron supplementation.[60]

Clinical observations indicate that children with juvenile arthritis (Still's disease) improve with boron supplementation (6 to 9 mg/day) in 2 to 3 weeks, whereas adults with osteoarthritis may require 2 to 4 months of supplementation before benefits are

detected. Persons with rheumatoid arthritis may experience an aggravation of symptoms (Herxheimer response) for 1 to 3 weeks but generally notice improvement within 4 weeks of beginning boron supplementation.[7]

Boron also has been implicated as a potential regulator of inflammatory and immune responses, possibly explaining its benefit for arthritic conditions. For example, boric acid has been shown to inhibit lipopolysaccharide-induced tumor necrosis factor-α formation.[61] Other animal based studies support an anti-inflammatory role for boron.[62,63]

Prostate, Lung, and Cervical Cancer

Given that boron may act as a possible modifier of the hormones testosterone and estrogen, some studies have looked into its possible role in prostate cancer. One controlled case study compared the boron intake of 95 prostate cancer cases with that of 8720 male controls. After controlling for age, race, education, smoking, body mass index, dietary caloric intake, and alcohol consumption, this epidemiologic screening found the risk of prostate cancer to be inversely proportional to dietary intake of boron in a dose-responsive manner.[64] A more recent study compared the prevalence of prostate cancer among those with high exposure to boron to control populations, and although no significant difference in prevalence was found, they did find a lower prevalence of elevated prostate specific antigens (PSAs). The authors concluded that boron may interfere with processes related to hyperplasia and carcinogenesis.[65] This is consistent with previous research that purported that boron may act as an inhibitor of PSA. It is thought that uninhibited PSA cleaves insulin-like growth factor binding protein-3, providing increased local levels of insulin-like growth factor 1, which then leads to tumor growth. Most epidemiologic studies support a preventative effect of higher dietary boron, although not all do (the only exception used a different database for the boron content of foods).[66–68]

Some in vitro research observed that boric acid inhibited the proliferation of both the hormone-dependent and -independent human prostate cancer cell lines in a dose-dependent manner.[69] A study of 3 groups of 10 mice were implanted subcutaneously with human prostate adenocarcinoma cells. Two of the murine groups were given boric acid solutions (at 1.7 or 9 mg/kg of boron per day) by gavage, whereas the control group received only water. After 8 weeks, tumor sizes in the boric acid groups decreased by 38% and 25%, respectively, and serum PSA levels decreased by 88.6% and 86.4%, respectively, compared with the control group. Additionally, significantly less mitotic figures were seen in the boric acid groups. Immunohistochemical studies demonstrated significantly less expression of insulin-like growth factor 1 levels, although circulating levels were unchanged among the groups.[70]

Multiple mechanisms in addition to PSA inhibition have been suggested for boron's chemopreventative properties, including inhibition of stored calcium release from ryanodine receptor agonist sites and induction of apoptosis.[71,72]

This may explain its reported benefit for other cancers as well, for in addition to prostate cancer, diets with greater amounts of boron have been associated with reduced risks of cervical cancer (cytopathologic findings) and lung cancer among women.[73] A dose-dependent risk for lung cancer was seen among women, with those consuming the lowest amounts of boron having a nearly two-fold greater risk compared with those in the highest quintile. Additionally, a diet low in boron heightened the risk for lung cancer among those using hormone replacement therapy.[74]

For this reason, boron-containing compounds are increasingly being used for specific chemotherapy, based on a variety of mechanisms.[75]

DOSAGE

The optimal dose of boron for prevention of osteoporosis and proper physiologic function appears to be between 1 and 6 mg/day. It is best to obtain boron by means of a diet abundant in fruits, vegetables, legumes, and nuts, but persons whose diets are limited may need a supplement containing 1 to 3 mg of elemental boron. In patients with either osteoarthritis or rheumatoid arthritis, a trial period of 2 to 4 months with a dose of 3 mg of boron two to three times daily seems to be indicated.

TOXICOLOGY

Although boron is potentially toxic to all organisms and, as boric acid and borax, has been used as a pesticide and food preservative, higher animals usually do not accumulate boron because of their ability to rapidly excrete it.[17] Authenticated cases of poisoning in humans have been few and have primarily been the result of accidental ingestion of insecticides and household products containing borates or use of large amounts of boric acid in the treatment of burns.[76]

Improper use of boric acid–containing antiseptics is still one of the most common causes of toxic accidents in newborns and infants. Because boric acid is readily absorbed through damaged skin, it should not be applied topically to extensive wounds.[21]

In animals, long-term low-level boron exposure has been shown to cause reduced growth, cutaneous disorders, and suppression of male reproductive system function.[77] Studies indicated that male rodents developed testicular atrophy with dietary exposure to boric acid above 4500 ppm and had decreased sperm motility at all exposure levels above 1000 ppm.[78]

Humans given 100 mg of boron intravenously or 270 mg of boric acid orally reported no discomfort and showed no obvious signs of toxicity.[79,80] Drinking water with high boron concentrations in Turkey has not been shown to cause untoward effects in humans exposed over multiple generations.[81] Airborne exposures to boron oxide and its hydration product, boric acid, have been reported to cause respiratory and eye irritation.[82] A fatal outcome was reported after ingestion of 1 g of boric acid by a child; however, adults survived acute intakes of nearly 300 g.[83] The Food and Nutrition Board of the Institute of Medicine has established a Tolerable Upper Intake Level for boron of 20 mg/day for adults over 18 years of age, and as low as 6 mg for children between 1 and 3 years of age.[84] One author suggested that plasma or serum concentrations greater 300 ng/mL indicate an intake in excess of what is needed to prevent deficiency, whereas levels more than 1 mcg/mL indicate toxicity.[50]

Boron may also have the potential for toxicity during pregnancy. A study in a population of newborns exposed to normal environmental boron levels through pregnancy found a negative relationship between whole blood δ-aminolevulinic acid dehydratase activity and placental boron levels. This is certainly concerning given the neurotoxic effects caused by lead's inhibition of this same enzyme.[85]

Common signs and symptoms of acute boron toxicity (largely based upon animal data) include nausea as well as vomiting and diarrhea that are blue–green in color.[8,83] Other symptoms seen with acute exposure are abdominal pain, an erythematous rash involving both the skin and mucous membranes, stimulation or

depression of the central nervous system, convulsions, hyperpyrexia, renal tubular damage, abnormal liver function, and jaundice.[21] Increased urinary riboflavin excretion has also been reported subsequent to acute boric acid ingestion.[86] Symptoms of long-term intoxication include anorexia, gastrointestinal disturbances, debility, confusion, dermatitis, menstrual disorders, anemia, convulsions, and alopecia.[21] In three cases of work-related exposure, alopecia signs were reversed when boric acid exposure was reduced or eliminated.[87] Because it is excreted primarily in urine, caution should be used for those with impaired renal function.

Because of its ability to increase the excretion of boron, in cases of toxicity, *N*-acetylcysteine is the preferred intervention.[88]

DRUG INTERACTIONS

Boron supplementation may increase serum magnesium, testosterone, and estrogen levels. However, no adverse clinical effects have been reported.

SUMMARY

Although the skeletal response to boron is modified by other nutritional variables such as calcium, magnesium, vitamin D, methionine, essential fatty acid intake, and arginine, considerable evidence indicates that both compositional and functional properties of bone are affected by boron status at least somewhat independently of other variables.

Findings suggest that boron is an important nutrient not only for mineral metabolism but also for varied aspects of optimal health in humans, including influences on lipid membrane integrity and cellular signaling pathways. Although all published trials are not in agreement on the impact of boron supplementation on levels of 17 β-estradiol and testosterone, evidence strongly suggests that boron deficiency results in decreased levels in postmenopausal women, whereas supplementation tends to normalize levels in these same women. Boron's impact on sex hormones in other segments of the population is still equivocal, although recent evidence suggests it may increase free testosterone levels at least in men. Topically it has shown clinical benefit for treating some forms of vaginitis (see Chapter 213, Vaginitis and Vulvovaginitis). As the mechanisms for its action are more thoroughly understood, which now include influencing *S*-adenosylmethionine metabolism and regulation of osteogenesis and cellular signaling pathways, therapy with boron may become more targeted and specific.

On the basis of available information, boron appears to offer benefits in the prevention of osteoporosis and arthritis, as well as cancer prevention. It is also a safe and potentially effective mineral to consider in any treatment regimen for both rheumatoid and osteoarthritis, as well as several cancers.

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CHAPTER 71

Bromelain*

Anthony J. Cichoke, Jr. MA, DC, DACBN, PhD

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Proteolytic enzyme of *Ananas comosus* (family: Bromeliaceae)
Synonyms: bromelin, plant protease concentrate

INTRODUCTION

The pineapple plant (*Ananas comosus*) yields several proteolytic enzymes, including bromelain (from the stem and the fruit), ananain, and comosain,[1] as well as several nonproteolytic enzymes such as amylase, peroxidase, and acid phosphatase.[2] Most bromelain on the market is stem bromelain (which itself is composed of perhaps up to six different types of enzymes, including bromelain A and B).[3] Bromelain is widely utilized in food processing to prepare precooked cereals, produce protein hydrolysates, chillproof beer, tenderize meat, etc.; in cosmetics; in diagnostic laboratories; and in pharmaceuticals.

Bromelain is a sulfur-containing enzyme, with an optimum pH activity between 3.0 and 8.0.[4] Bromelain has endoproteolytic and catalytic activity and predominantly splits peptides, amides, as well as ester bonds involving lysine, alanine, tyrosine, glycine, and other basic amino acids.[4]

The extraction of bromelain is usually accomplished by fractionated ultrafiltration and subsequent lyophilization of the juice pressed from the stem of ripe pineapples (frequently from *Ananas comosus* of the cayenne variety). The molecular weight varies between 17,800 and 33,000 kDa.

Bromelain activity within the stem of the pineapple can vary widely depending on the age of the plant, as well as on the storage duration and conditions. A Thai study found that 3-year-old peeled pineapple stems contained substantially more activity than second and first year stems as measured in casein digesting units (CDU)—48.76% compared with 32.0% and 19.3%, respectively.[5] In addition, storage duration before considerable loss of activity occurred was limited to 3 days at room temperature or 2 weeks in a room cooled to 5°C (41°F).[5]

BROMELAIN SUPPLEMENTS

Over 200 medical articles on bromelain's therapeutic applications have been published since it was introduced as a therapeutic agent in 1957.[6,7] Initially, many studies employed Ananase (Rorer), an enteric-coated bromelain tablet.

Bromelain is currently available in tablets, chewable tablets, capsules, powder, and ointment. Although available in individual enzyme form, supplemental bromelain is often combined with other enzymes, as well as various vitamins, minerals, and herbs, for wider application.

Bromelain activity is measured in "units"—and there are several types of units currently in use. The Food Chemicals Codex recognizes milk-clotting units (MCUs), although gelatin dissolving units (GDU), Federation Internationale du

*This chapter is dedicated to the memory of Dr. Max Wolf, the father of systemic enzyme therapy, as well as Dr. Karl Ransberger, who validated and marketed systemic enzyme therapy, making it a highly accepted worldwide treatment for a wide variety of systemic diseases and injuries.

The author wishes to express his deep appreciation in writing these two Enzyme chapters, for the cooperation of the following researchers from the United States, Germany, The Czech Republic and other Eastern European Countries: Dr. Barry Ritz, Dr. Winfried Miller, Dr. Claudia Loyall, Dr. Zinovij Masinovsky, Dr. Michaela Lysikova, Dr. Joseph Pizzorno, Dr. Michael Murray, and Ms. Karen Hood.

Pharmaceutiques units, and CDUs are also widely utilized. However, these measurement methods are neither interchangeable nor comparable. On the basis of their respective enzyme units, different grades of bromelain are available. Therefore, when purchasing bromelain, be aware of this fact.

ENTERAL ABSORPTION (OR RESORPTION)

For enzymes to be used systemically, they must reach the circulatory system and be conveyed to needy cells and organs. This means that oral enzymes must pass through the digestive system, into the small intestine, and pass through the brush border into the circulatory system. Further, this is a rationale for enterically coating the enzyme tablets so that they will not be broken down in the digestive tract before they reach the small intestine to pass into the bloodstream. This is also the rationale for consuming enzymes between meals. These enzymes can pass easily through the gut without involvement in food digestion, allowing more enzyme molecules to reach the small intestine, pass through the brush border and into the circulatory system, and be used systemically by needy organs and cells in the body.

In the past, it was widely assumed that large protein molecules—such as enzymes—could not survive the digestive process and be reabsorbed intact. However, numerous studies have demonstrated that bromelain—and other proteolytic enzymes—can be absorbed by the small intestine through a number of routes, pass into the bloodstream, and ultimately circulate throughout the body. Oral administration is effective, as is parenteral administration.[8-11]

Research on dogs indicated that levels of bromelain (after oral administration) peaked at 10 hours, and were still detectable after 48 hours, whereas intravenous infusion peaked in 50 minutes and was detectable for 5 hours.[10]

A randomized, controlled, double-blind study on humans demonstrated that the highest plasma concentration of bromelain was achieved at approximately 48 hours.[12,13] A study of 19 men given 3 grams of oral bromelain daily indicated that the enzyme had a plasma half-life of 6 to 9 hours. Researchers estimated that within the 3- to 50-hour period, an average of 10.8 mcg of bromelain was present in plasma.[13] In both animals and humans, studies indicated that up to 40% of the absorbed orally administered bromelain was absorbed intact.[9-11] For an in-depth discussion of enzyme absorption, please refer to Chapter 111 on Pancreatic Enzymes in this book.

FACTORS AFFECTING BROMELAIN ACTIVITY

Bromelain, papain (from papaya), and ficin (from figs) are all sulfhydryl proteases and act similarly. Bromelain (from both stem and fruit) is inhibited by metallic ions (including cadmium, copper, iron, lead, and mercury), oxidizing agents (such as iodoacetate, methyl bromide, and hydrogen peroxide), and human serum (both in vivo and in vitro). Cysteine and magnesium activate commercial bromelain.[8]

As with all enzymes, bromelain's activity can be inhibited by cold or increased by heat. Bromelain is a hydrolytic enzyme, so supplements should be taken with plenty of water to place the enzyme into solution.

CLINICAL APPLICATIONS

Bromelain exerts a wide variety of therapeutic effects[6-8]:

- Antiinflammatory activity
- Appetite reduction
- Burn debridement
- Cancer remission and prevention
- Digestion assistance
- Immune stimulation
- Improved wound healing
- Induced pulmonary edema prevention
- Improved antibiotic absorption
- Inhibition of blood platelet aggregation
- Pain reduction
- Shortening of labor
- Sinusitis relief
- Smooth muscle relaxation
- Reduced swelling
- Ulcer prevention

During the process of aging, illness, or injury, the body's production of pancreatic enzymes decreases in amount, concentration, and potency, thus allowing the growth of pathogenic cells (such as cancer cells). Pathogenic cells are constantly produced by the body; however, the enzymes manufactured by and circulating in the blood lyse the abnormal pathogenic cells, breaking them up and flushing them out of the body. Unfortunately, when weakened through aging, illness, or injury, the body's capacity to overcome pathogens is diminished, resulting in illness.

Bromelain has long been used to improve digestion. However, when taken systemically, bromelain can also effectively speed healing from inflammatory diseases and conditions; inhibit cancer growth and metastasis; prevent the aggregation of blood platelets, and thereby help to prevent heart attacks, strokes, and other cardiovascular conditions; prevent intestinal attachment of *Escherichia coli*; improve the symptoms of dysmenorrhea; fight sinusitis; improve burn eschars and speed healing; improve skin appearance; and improve antibiotic and vitamin absorption.

Therefore, systemic enzyme therapy is essential for normal recovery of a sick or injured individual, to augment the body's own production of pancreatic enzymes, and to stimulate the production of proteolytic enzymes in the pancreas.

Systemic Enzyme Therapy

When taken between meals, enzymes—such as bromelain—move through the digestive system and directly into the small intestine, passing through the brush border into the circulatory system and traveling to the damaged areas. In this way, the enzyme acts systemically. To be most effective, systemically, it is essential to take enzymes on an empty stomach (approximately 1-1/2 hours before or after a meal). However, when used for digestive therapy, enzymes should be ingested before meals (approximately 30 minutes before). See the section on "Dosage" in this chapter.

Aging

Unfortunately, the process of aging is accompanied by an increasingly wide variety of health problems, such as chronic disorders, cancer, cardiovascular disease, and arthritis. Further, the numbers of those over 65 are escalating. According to the U.S. Census Bureau, over 20% of the American population will be age 65 or older by the year 2050. That figure was only 12% in 2008.[14]

Most commonly, as it ages, the body loses resiliency and various degenerative diseases manifest, particularly after the age of 50. This is accompanied by a decline in hormone secretion, immune system function, and enzyme production, thus reducing the body's effectiveness at fighting off foreign invaders. With aging, the body's enzyme supply also diminishes in activity. The symptoms of

aging could be, at least partially, the consequence of these enzymatic reductions. For example, the graying of hair has been attributed to a lack of tyrosinase or a loss of its activity level.

Unlike the known serious side effects of most prescription drugs, bromelain has been shown to effectively fight arthritis, high blood pressure, cancer, and many other disorders associated with aging, but without the serious and long-term side-effects of many drugs.

Bromelain is also effective in fighting the visual signs of aging, including wrinkles. Bromelain is widely incorporated into lotions, creams, scrubs, facial masks, and other skin care products, where it is believed to improve the skin's appearance by removing dead skin cells.

Cancer

Bromelain delays metastases considerably, delays skin cancer, and is effectively used in adjunctive tumor therapy. There is also some indication that it has a direct effect on cancer cells.[15]

The increased understanding of immunology makes it evident that the solution to cancer is not to be found in chemotherapy or radiation therapy, but in the use of immunotherapy (such as systemic enzyme therapy). Pharmacologic and preclinical studies indicate that bromelain acts as an immunomodulator by inducing the production of distinct cytokines (such as interleukin-1β [IL-1β], IL-6, and IL-8, as well as tumor necrosis factor-γ), and by raising the impaired immunocytotoxicity of monocytes against tumor cells.[8,15-19] These findings were recently partially confirmed in mammary tumor patients.[16] Particularly encouraging are animal studies suggesting antimetastatic properties and inhibition of platelet aggregation associated with metastasis, as well as inhibition of invasiveness and growth of tumor cells. It is interesting to note that the antiinvasive activity might not depend on bromelain's proteolytic activity.[8,15,16]

An in vitro study on bromelain and glioma (primary brain tumor) cells found that bromelain significantly and reversibly reduced the adhesion, migration, and invasion of glioma cells. Moreover, cell viability was not affected, even after treatment up to 3 months.[20]

In the United States, skin cancer is the most common form of cancer.[21] It is generally agreed that exposure to ultraviolet rays increases an individual's risk of skin cancer. To determine if bromelain could prevent skin cancer, researchers gave hairless mice 20 mg of bromelain per kilogram of body weight per day for 1 year and then subjected them to ultraviolet light for 15 minutes three times per week for the same period.[22] After 1 year, only 40% of the bromelain group developed skin cancer (as opposed to 100% of the control group). In addition, it took the bromelain group twice as long to develop lesions. An earlier, 6-month study found that mice receiving 80 mg of bromelain per kilogram of body weight did not develop any abrasions after 2 months.[23]

Bromelain (and other proteolytic enzymes) appears useful in the treatment of cancer. A number of mechanisms seem to be responsible. Bromelain had a significant impact on monocytes, natural killer cells, and lymphocytes in a clinical study of 16 women with breast cancer.[16] Regarding monocytic cytotoxicity, some 40% of the patients responded to bromelain with an increase of cytotoxicity from 7.8% to 54% (bMAK-cell activity).

Circulatory Disorders

Platelet aggregation is a major factor in atherogenesis and can result in heart attack, stroke, acute thrombophlebitis, transient ischemic attack, nightly leg cramps, edema, deep venous thrombosis, ecchymosis, and cellulitis. Research shows that bromelain is a potent inhibitor of platelet aggregation, both in vivo and in vitro.[23-30] This could be due to its plasmin-increasing effects (plasmin is a proteolytic enzyme produced by the body whose job is to dissolve fibrin, a protein involved in blood clot formation).[31] Further, research demonstrates that bromelain (in conjunction with potassium and magnesium) can be effective in treating angina pectoris.[27]

Researchers employed bromelain as an adjunct to analgesics in a double-blind study involving 73 patients with acute thrombophlebitis. All symptoms of inflammation, including pain, swelling, tenderness, redness, disability, and elevated skin temperature decreased.[26] The common daily dose of bromelain (in this study and others) was 60 to 160 mg of 1200 MCU bromelain. Several researchers believe that doses of 400 to 800 mg are necessary in treating patients with thrombophlebitis (and many other conditions, as well).[27] Researchers commented that poor study outcome was usually the result of inadequate dose strength and/or frequency of application.

Digestive Disorders

Bromelain can regulate digestion, alleviate symptoms of gastric and duodenal ulcers and ileitis, and can be used as enzyme substitution therapy after pancreatectomy.

Bromelain has a long history as a digestive aid. By the time Columbus and his men had "discovered" America, natives of Central and South America were already using bromelain-rich pineapple juice to cure bellyaches and improve digestion. As a proteolytic enzyme, bromelain aids in the digestion of protein foods. Because of bromelain's wide pH activity, it is effective on substrates in the acidic stomach as well as the alkaline small intestine. Although bromelain alone is effective in treating pancreatic insufficiency (and is a proven substitute for trypsin or pepsin in cases of pancreatic insufficiency and postpancreatectomy),[6] double-blind studies determined that it is particularly effective when combined with ox bile and pancreatin.[32,33]

Dysmenorrhea

Bromelain in combination with papain is an effective treatment for dysmenorrhea.[34] Because bromelain decreases the spasms of a contracted cervix in tested patients, it is believed to be a smooth muscle relaxant. As yet unidentified substances in bromelain may be more beneficial in this regard than the bromelain protease, because when isolated and purified, the protease failed to produce a similar effect. Bromelain increases levels of prostaglandin-E (PGE_1)-like compounds, while decreasing prostaglandins of the 2-series (such as PGE_2 and PGF_{2a}); this is hypothesized to be the basis for bromelain's muscle relaxing ability.[7]

Immune Disorders

The understanding and treatment of immune disorders is becoming increasingly important in today's society. Further, the immune and inflammatory systems are the two major factors in chronic disorders.

The lymphoid organs of the immune system are located throughout the body and are concerned with growth, development, and distribution of lymphocytes (white cells, which are key operatives of the immune system). These organs include the thymus, bone marrow, tonsils, lymph nodes, spleen, the appendix, adenoids, and Peyer's patches.

Circulating immune complexes seem a major factor in all immune and autoimmune disorders. Various factors inhibit cellular immunity, but the most important elements seem to be these "blocking factors" (i.e., immune complexes) that cause immune suppression.

Autoimmune disorders occur when the body's immune system mistakenly attacks healthy cells. There are dozens of such conditions, including rheumatoid arthritis and other rheumatic disorders, myasthenia gravis, type 1 diabetes mellitus, asthma, systemic lupus erythematosus, glomerulonephritis, and multiple sclerosis. Fortunately, an increasing number of studies have indicated that systemic enzyme therapy can reduce the severity of symptoms, more quickly resolving the condition because they stimulate the body's own defenses, accelerate the inflammatory process, and break down pathogenic immune complexes from the tissues, bringing them into the bloodstream for elimination. Immune complexes are created when antigens and antibodies bind, forming a cluster that can lodge in tissues or circulate throughout the body, leading to inflammation and tissue damage. It is important to note that as systemic enzyme use liberates immune complexes from the tissues, increasing their presence in the bloodstream, symptoms may actually increase in severity; however, this is only temporary. When used in sufficient quantities, the enzymes can then degrade the immune complexes in the bloodstream (sometimes within a few hours), and the disease symptoms should subside.

Infections

Infections caused by bacteria, viruses, fungi, and parasites can frequently be the most challenging conditions to treat. Bromelain has proven effective in fighting numerous infections ranging from *E. coli* to bronchitis (see the section on "Respiratory Tract Diseases" later in this chapter).

The O157:H7 strain of *E. coli* is a particularly severe and potentially life-threatening bacterial infection that causes bloody diarrhea in humans. The *E. coli* enterotoxins gain a foothold by adhering to receptors on the intestinal mucosa. Preventing the attachment could also prevent the resulting diarrhea. Researchers administered a single dose of enterically coated protease granules (containing bromelain) to rabbits and then inoculated the animals with different strains of *E. coli*. Of those rabbits given the enzyme mixture and strain H10407, only one animal died, and none of the remaining rabbits developed diarrhea. In the group not inoculated with the enzyme mixture, 87% either developed severe diarrhea or died.[35] Comparable results were obtained with other strains of *E. coli*.

Similar studies with bromelain have been conducted on piglets inoculated with K88 positive *E. coli*.[36] An in vitro study on rabbit ileum found that bromelain was also 51% effective against cholera toxin.[37]

Bromelain is of particular benefit if treatment with antibiotics becomes necessary. Numerous clinical studies show that bromelain can increase serum levels of several antibiotics (including tetracycline, amoxicillin, and penicillin) in different body fluids (including blood, cerebral spinal fluid, mucus, sputum, and urine) and tissues (including appendix, gallbladder, ovary, epithelium, and uterus).[38-40] In addition, researchers believe that bromelain itself possesses significant therapeutic effects. Studies tend to indicate that bromelain is as effective as antibiotics in treating bronchitis, perirectal abscess, pyelonephritis, cutaneous staphylococcus infection, and various infectious processes.[8,38]

Inflammatory Diseases and Conditions

Inflammatory conditions such as edema, rheumatoid arthritis, strains, sprains, bruises, fractures, and surgeries (oral, cosmetic, and general) all respond favorably to orally administered bromelain. Numerous studies have also noted bromelain's ability to reduce pain, swelling, and bruising and improve rate of healing after various surgical procedures.[8,41-44] Unlike the majority of nonsteroidal antiinflammatory drugs, there seems to be no indication that bromelain promotes bleeding.

Some of the earliest studies on bromelain involved athletic injuries. A 1960 study of boxers highlighted bromelain's rehabilitative effects.[43] Within 4 days of initiating bromelain treatment, 58 of 74 boxers experienced complete resolution of all signs of bruising. Complete clearance of bruising occurred in 8 to 10 days in the remaining 16 boxers receiving bromelain. At the end of 4 days, only 10 boxers in the control group demonstrated complete clearance of bruising, whereas clearance in the remaining 62 in the control group required 7 to 14 days. It is important to note that bromelain's effect on pain reduction is probably not due to any direct analgesic effect, but rather to its ability to reduce tissue edema and inflammation.

Fifty-nine patients with muscle strains, contusions, ligament tears, and other injuries to the musculoskeletal system received 500 mg of bromelain three times daily, 30 minutes before meals.[45] Results from this study and others indicated that the use of bromelain led to a rapid improvement of pain at rest and during motion, swelling, inflammation, and tenderness on palpation.[46,47]

Seventy-seven otherwise healthy subjects completed a study investigating bromelain's effect on mild acute knee pain of less than 3 months' duration.[48] Two validated questionnaires (the Psychological Well-Being Index and the Western Ontario and McMaster Universities [WOMAC] Knee Health Index) were completed as a baseline and after 1 month of bromelain treatment (200 or 400 mg/day, allocated randomly to volunteers). In both bromelain groups, all WOMAC symptom scores decreased significantly compared with baseline. Reductions in the total symptom score were 41% for the low-dose group of bromelain recipients and 59% in the high-dose group. Additionally, those receiving 400 mg/day of bromelain experienced significantly greater improvement in total symptom score plus stiffness and physical function dimensions compared with those receiving low-dose (200 mg/day) bromelain. Both bromelain groups experienced a significant improvement in overall psychological well-being compared with baseline (researchers noted a dose-dependent relationship).

Surgery

Numerous studies indicate bromelain's effectiveness at reducing postsurgical inflammation. In studies of patients who underwent oral surgery, Tassman et al[41,42] concluded that, although postsurgical medication alone was effective, a regimen of presurgical and postsurgical bromelain was recommended to enhance the healing process.

A double-blind study of patients who underwent oral surgery found that bromelain was significantly superior to placebo in reduction of swelling (3.8 days compared with 7 days for the placebo). In addition, the duration of pain decreased to 5.1 days in the bromelain group compared with 8.1 days for the placebo group.[42] Similar observations were made in studies of episiotomy cases. Bromelain reduced inflammation, pain, and edema. Further, preoperative administration of bromelain improved the potential positive effects.[44,49]

Antiinflammatory Action of Bromelain

Bromelain may function as an antiinflammatory by (1) activating proteolytic activity at the inflammation site; (2) lysing fibrin at the site; (3) depleting kininogen; and (4) inhibiting the biosynthesis of prostaglandins and the induction of PGE_1 accumulation.[7,17,50]

As a proteolytic enzyme, bromelain demonstrates a delayed analgesic effect that involves the action of two mechanisms. Bromelain cleaves such inflammatory mediators as the kinins and prostaglandins, which directly stimulate the pain receptors. Further, bromelain supports the breakdown of plasmin protein and immune complexes that stem from the tissues by cleaving them directly and by stimulating their phagocytosis. The reduction of edema that subsequently follows leads to a relief of pressure and, secondarily, a reduction in pain, thus inhibiting bradykinin formation (a chemical mediator of inflammation) at the inflammation site.

Of these processes, the primary pharmacologic effects of bromelain are most likely plasmin activation and the decrease in kinin levels. The ability of bromelain to decrease inflammation has been documented in various clinical studies and experimental models.[8,41-45,48,50-56] The inflammatory process is involved in numerous conditions, including infections and respiratory tract diseases. These conditions are covered separately within this chapter.

As mentioned in the "Cancer" section, bromelain functions as an immunomodulator and is able to increase levels of some cytokines, while reducing levels of others, thus leading to cytokine homeostasis and a reduction in inflammation.

Respiratory Tract Diseases

Bromelain's efficacy in treating respiratory tract diseases seems to be due to its mucolytic activity.[57] Bromelain appears to reduce sputum viscosity and possesses an antitussive effect in chronic bronchitis patients. Spirometric examination of patients before and after bromelain treatment indicated increased FEV_1 (a measurement of the amount of air exhaled in a forced exhalation) and vital capacity, whereas residual volume was reduced. These favorable results were believed to be due to bromelain's ability to function as a mucolytic and decrease bronchial secretions, thereby reducing respiratory congestion.

A double-blind study on patients with acute sinusitis found that 87% of those receiving bromelain experienced good to excellent results compared with 68% of the placebo group.[58] Treatment with bromelain also appears to lead to a significantly faster recovery time.[59]

Bromelain has been found to exert antiinflammatory effects in allergic airway disease in murine models.[60,61] Researchers hypothesize that it may be beneficial in treating human asthma.[60,61]

Skin Debridement

Severe burns leave dead and damaged tissue that can interfere with healing and potentially contaminate the wound. Removing the damaged or dead tissue ("debriding" the wound) exposes healthy tissue, promotes healing, and provides a clear foundation for skin grafting. Debridement can be accomplished surgically, chemically, or by using enzymes, which function without destroying the underlying, healthy tissue. Studies on a novel bromelain gel confirm its safety and efficacy in burn debridement.[62,63]

Bromelain is also effective in debriding contaminated tissue, as well as devitalized tissue from scars, wounds, and ulcers.

DOSAGE

When used as a digestive aid, bromelain should be taken just before a meal (no more than 30 minutes before eating). When used systemically, bromelain should be taken between meals, on an empty stomach (about 1-1/2 hours before or after a meal). The preparation's potency will dictate dosage. Most bromelain currently marketed in the United States is between 600 and 2400 GDUs. A good dosage with which to begin might be 230 to 250 mg taken three to four times daily.

SIDE EFFECTS AND CONTRAINDICATIONS

High doses (nearly 2 g) of bromelain have been administered with no apparent side effects.[64] No lethal dose 50 (LD_{50}) exists up to 10 g/kg, so it is deemed to be virtually nontoxic. Long-term use seems to be well-tolerated. As with most therapeutic agents, allergic reactions may occur with prolonged occupational exposure or in sensitive individuals; however, no significant side effects have been noted.[65,66]

No teratogenic studies have been conducted in humans, so bromelain should not be used by pregnant women. In addition, studies have not been conducted on the safety of using bromelain in nursing mothers.

Although no anaphylactic reactions have been reported, bromelain can induce gastrointestinal allergic and immunoglobulin-E–mediated respiratory reactions, as well as cross-react with papain, rye flour, wheat flour, birch pollen, and grass pollen.[65,66] Although side effects are infrequently observed, bromelain sensitivity as manifested by skin rash or urticaria has occurred. Other possible but unconfirmed reactions include vomiting, nausea, metrorrhagia, menorrhagia, and diarrhea. Researchers hypothesize that bromelain's ability to inhibit platelet aggregation may increase the risk of bleeding[67]; however, there are no studies to support this assertion.

DRUG INTERACTIONS

There are few known interactions between bromelain and other medications. However, because bromelain is a potent inhibitor of platelet aggregation (both in vivo and in vitro),[23-30] caution should be exercised when used with anticoagulants (blood thinners), including Jantoven, Lovenox, and warfarin, as well as over-the-counter nonsteroidal antiinflammatory drugs, including aspirin and ibuprofen. In addition, certain botanicals, including garlic, ginkgo biloba, and ginseng, may increase bleeding risk, so patients should be monitored when these are used in conjunction with bromelain.

Clinical studies show that bromelain can increase serum levels of several antibiotics (including tetracycline, amoxicillin, and penicillin) in body fluids and tissues.[38-40] This can be helpful when attempting to improve an antibiotic's efficacy; however, it is possible that there could be instances where elevated serum levels of antibiotics would be deleterious.

Any foods that contain protease inhibitors have the potential to decrease the proteolytic activity of bromelain. However, most of these foods (such as potatoes and soybeans) are rarely eaten raw (heat inactivates the protease inhibitors). In addition, many of the protease inhibitors found in these (and other) foods are trypsin inhibitors; however, bromelain contains no trypsin.

CONCLUSION

The future of oral enzyme therapy is already here; however, the rate at which this knowledge is utilized in restoring health to

millions is deplorably slow. This concerns those scientists, doctors, biochemists, and pharmacists who recognize the potential of enzyme therapy. This chapter on bromelain and Chapter 111 on Pancreatic Enzymes have been written in the hope of hastening the day when enzyme therapy will be employed as a matter of course for every disorder in which it can be of assistance.

Bromelain has proven to be effective in treating the following diseases and conditions:

- Angina
- Arthritis
- Athletic injuries
- Bronchitis
- Burn debridement
- Cancer
- Cellulitis
- Circulatory disorders
- Dermatologic conditions
- Digestive disorders
- Dysmenorrhea
- Ecchymosis
- Edema
- Infections
- Pancreatic insufficiency
- Phytobezoar
- Pneumonia
- Scleroderma
- Sinusitis
- Staphlococcal infection
- Surgical trauma
- Thrombophlebitis

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CHAPTER 72

Camellia sinensis (Green Tea)

Michael T. Murray, ND

Camellia sinensis (family: Theaceae)
Common name: green tea

CHAPTER CONTENTS

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GENERAL DESCRIPTION

Both green tea and black tea are derived from the same plant, the tea plant (*Camellia sinensis*). The tea plant originated in China but is now grown and consumed worldwide. The tea plant, an evergreen shrub or tree that can grow up to a height of 30 feet, is usually maintained at a height of 2 to 3 feet by regular pruning. The shrub is heavily branched with young hairy leaves. Parts used are the leaf bud and the two adjacent young leaves together with the stem, broken between the second and third leaves. Older leaves are considered of inferior quality.

Green tea is produced by lightly steaming the freshly cut leaf, whereas black tea is produced by allowing the leaves to oxidize. During oxidation, enzymes present in the tea convert many polyphenolic therapeutic substances to compounds with much less activity. With green tea, oxidation is not allowed to take place because the steaming process inactivates these enzymes. Green tea is high in polyphenols with potent antioxidant and anticancer properties. Oolong tea is a partially oxidized tea.

Of the nearly 2.5 million tons of dried tea produced each year, only 20% is green tea. India and Sri Lanka are the major producers of black tea. Green tea is produced and consumed primarily in China, Japan, and a few countries in North Africa and the Middle East (Table 72-1). Consumption is increasing in the United States.

CHEMICAL COMPOSITION

The chemical composition of green tea varies with climate, season, horticultural practices, and age of the leaf (position of the leaf on the harvested shoot). The major components of interest are the polyphenols.[1,2] The major polyphenols (Figure 72-1) in green tea are the following flavonoids:

- Catechin
- Epicatechin
- Epicatechin gallate
- Epigallocatechin gallate (EGCG)
- Proanthocyanidins

EGCG is viewed as the most significant active component. The leaf bud and the first leaves are richest in EGCG. The usual concentration of total polyphenols in dried green tea leaf is around 8% to 12%.

Other compounds of interest in dried green tea leaf include the following:

- Caffeine (3.5%)
- An unusual amino acid known as theanine (one half of the total amino acid content, which is usually 4%)
- Lignin (6.5%)
- Organic acids (1.5%)
- Protein (15%)
- Chlorophyll (0.5%)

One cup of green tea usually contains about 300 to 400 mg of polyphenols and between 50 and 100 mg of caffeine.

Commercial preparations that have been decaffeinated and concentrated for polyphenols to between 60% and 80% total polyphenols are available.

PHARMACOLOGY

The primary pharmacologic actions center around the antioxidant effects of the green tea polyphenols.[3] The degree of antioxidant protection produced by green tea is clearly dose-dependent and requires a threshold dose. In a randomized crossover study, 15 healthy volunteers consumed 500 mL of green tea with different solid contents (1.4, 1.6, 1.8, and 2.0 g/L). Ingestion of the lowest dose produced no change in plasma antioxidant capacity. At the highest dose, the effects increased the plasma antioxidant capacity the greatest at 1 and 4 hours after ingestion.[4] This study is extremely significant because it indicates that some of the studies failing to show green tea increasing in vivo antioxidant activity may have been due to insufficient dose.[5,6]

In addition to exerting antioxidant activity on its own, green tea may increase the activity of antioxidant enzymes. In mice, oral feeding of a polyphenolic fraction isolated from green tea in drinking water for 30 days resulted in significantly increased activities of antioxidant and detoxifying enzymes (glutathione peroxidase, glutathione reductase, glutathione-S-transferase, catalase, and quinone reductase) in the small intestine, liver, lungs, and small bowel.[7]

With regard to cancer, a number of in vitro and experimental models of cancer have shown that green tea polyphenols may offer significant protection.[8,9] Specifically, green tea polyphenols inhibit cancer via many mechanisms, including inhibition of metalloproteinases, various protein kinases, proteins that regulate DNA replication and transformation, tumor proteasomal activity, and the formation of cancer-causing compounds, like nitrosamines. They also upregulate or maintain intercellular gap junction communication and increase apoptosis.

TABLE 72-1 **World Tea Production by Type**

TYPE	DRY WEIGHT (×1000 TONS)
Black	1940
Green	515
Oolong	60
Total	2515

L-Theanine

L-theanine (*N*-ethyl-L-glutamine) or theanine is a major amino acid uniquely found in green tea. In animal models, L-theanine increases brain serotonin, dopamine, and γ-aminobutyric acid levels, and has micromolar affinities for various brain receptor sites, including α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate, kainate, and *N*-methyl-D-aspartic acid. It has been shown to exert neuroprotective effects in animal models, possibly through its antagonistic effects on group 1 metabotrophic glutamate receptors. Behavioral studies in animals suggest improvement in learning and memory. Clinical studies demonstrated that L-theanine reduces stress, improves the quality of sleep, diminishes the symptoms of premenstrual syndrome, heightens mental acuity, and reduces the negative side effects of caffeine. These clinical effects are directly related to L-theanine's ability to stimulate the production of α-brain waves (a state often achieved by meditation and characterized by being relaxed with greater mental focus and mental alertness) as well as reduce β-waves (associated with nervousness, scattered thoughts, and hyperactivity).[10,11]

L-theanine is a very popular ingredient in functional foods and beverages as well as dietary supplements designed to produce mental and physical relaxation, without inducing drowsiness. L-theanine is fast-acting. Generally, the effects are felt within the first 30 minutes, and have been shown to last up to 8 to 12 hours. Based on the results of clinical studies, it has been established that L-theanine is effective in the range of 50 to 200 mg.

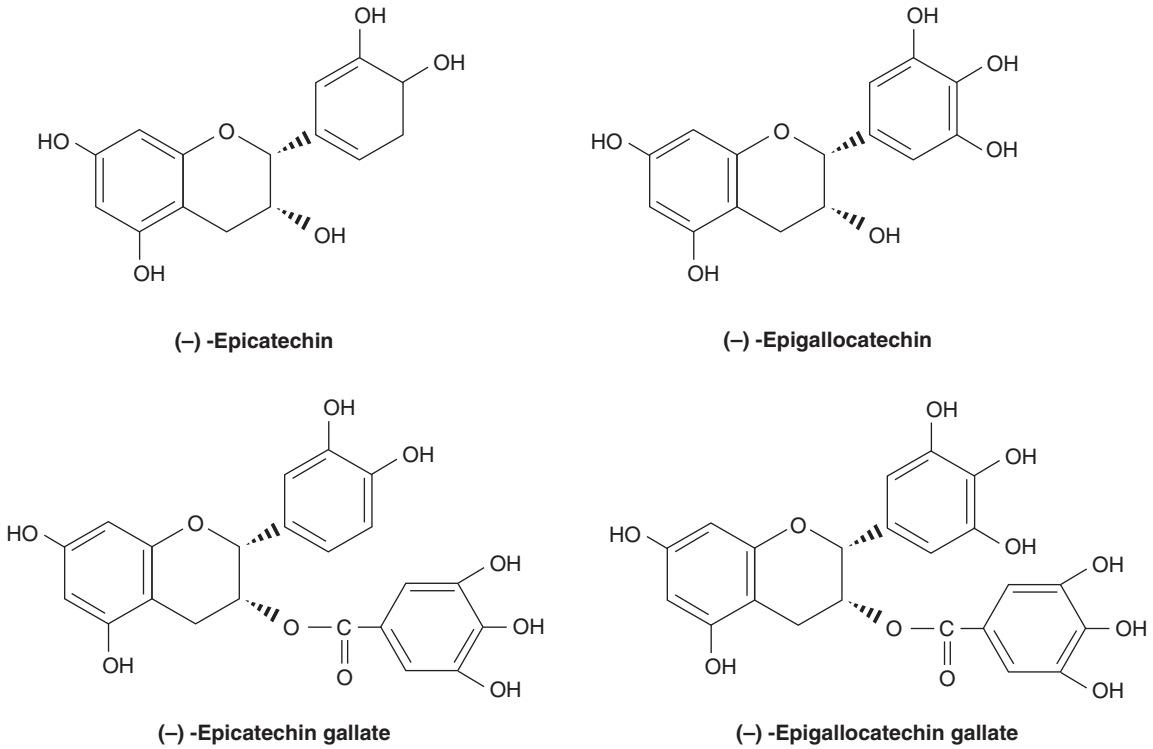


FIGURE 72-1 Primary green tea catechins.

CLINICAL APPLICATION

The primary clinical applications for green tea are in the prevention of cancer and heart disease, as well as aiding weight loss. It may also offer benefit to bone health and may protect the skin from sun damage.

Cancer

Epidemiologic studies demonstrated that green tea consumption might offer significant protection against many forms of cancer. However, epidemiologic correlations regarding the relationship between tea consumption and human cancer are confounded by numerous variables. The forms of cancer that appear to be best prevented by green tea are those of the gastrointestinal tract, including cancers of the stomach, small intestine, pancreas, and colon; the lung; and estrogen-related cancers, including most breast cancers, skin cancer, and prostate cancer.[12-17] It is generally held that a desirable green tea intake is 3 to 5 cups/day, providing a minimum of 250 mg/day catechins. However, based upon emerging clinical data, this dosage level may not be sufficient once neoplasia develops or in high-risk individuals.

It should be pointed out that although a population-based study of women in Shanghai found that among nonsmokers, the consumption of green tea was associated with a clearly reduced risk of lung cancer, in a dose-dependent manner, 17 studies showed that little benefit in antioxidant effects were found in smokers even at significant dosage levels (e.g., more than 3 grams green tea polyphenols per day).[18]

In preventing breast cancer, the main anticancer actions may be inhibition of the interaction of estrogen with its receptors in breast tissue. Polyphenol compounds in green tea extracts also block the interaction of tumor promoters, hormones, and growth factors with their receptors—a kind of sealing-off effect—in breast tissue. Experimental and epidemiologic studies demonstrated a protective effect against breast cancer, and clinical results confirmed that green tea might be helpful for early-stage breast cancer. An observational study of 1160 surgical cases of invasive breast cancers were followed for 9 years. During a review of 5264 person-years follow-up, 133 subjects (12%) had a documented recurrence of breast cancer. A decreased hazard ratio for recurrence adjusted for stage was observed with consumption of three or more cups a day of green tea. Particularly in Stage I, the hazard ratio was decreased quite significantly. A similar tendency was observed for Stage II subjects, but was not present among more advanced stages.[19]

Green tea components such as epigallocatechin-3-gallate have also been shown to have antiproliferative properties through the induction of apoptosis and cell cycle arrest in cervical cancer cell lines.[20] Topical and oral treatments of green tea flavonoid components have also been explored to treat human papillomavirus (HPV)-related cervical cancer. A randomized, controlled clinical trial of 51 patients with cervical lesions, including chronic cervicitis, mild dysplasia, moderate dysplasia, and severe dysplasia, were divided into four treatment groups, whereas 39 untreated patients served as controls.

A second trial used a polyphenol ointment made with epigallocatechin-3-gallate applied locally to 27 patients twice a week for 12 weeks. For oral delivery, 200 mg of the ointment or an epigallocatechin-3-gallate capsule was taken orally every day for 8 to 12 weeks. Overall, a 69% response rate (35 of 51 patients) was noted for treatment with green tea extracts, with each treatment showing a similar response compared with a 10% response rate (4 of 39 patients) in untreated controls. A response was considered positive when pretreatment and posttreatment biopsies and Pap smears detected an elimination of abnormal cells, and there was a decrease in or complete elimination of HPV or a decrease in the size of the cervical lesion. The authors of this study concluded that green tea extracts might be a potential therapy regimen for patients with HPV-infected cervical lesions.[21]

The best data on green tea's anticancer effects might be on prostate cancer. In vitro and in vivo studies showed that EGCG produces marked inhibition of both hormone-sensitive and hormone-insensitive prostate cancer cells. To demonstrate concentration within the prostate of EGCG after oral intake, men with clinically localized prostate cancer consumed six cups of green tea daily or water for 3 to 6 weeks before undergoing radical prostatectomy.[22] Using high-performance liquid chromatography, green tea polyphenols were not detected in prostate tissue or urine from men consuming water preoperatively. In contrast, both the methylated and nonmethylated forms of EGCG were detectable in prostate tissue and urine in men consuming green tea.

In another study in men undergoing radical prostatectomy for prostate cancer, men were given 1300 mg of green tea polyphenols daily until surgery. Serum was collected before initiation of the drug study and on the day of prostatectomy. Serum biomarkers including hepatocyte growth factor, vascular endothelial growth factor, insulin-like growth factor (IGF), insulin-like growth factor binding protein-3, and prostate-specific antigen (PSA) were analyzed by enzyme-linked immunosorbent assay. The results showed a significant reduction in serum levels of PSA, hepatocyte growth factor, and vascular endothelial growth factor in men with prostate cancer after brief treatment with green tea.[23] Even at this relatively high dosage of polyphenols, there was no elevation in liver enzymes.

A proof-of-principle clinical trial was designed to assess the safety and efficacy of green tea polyphenols for the chemoprevention of high-grade prostate intraepithelial neoplasia developing prostate cancer within 1 year after repeated biopsy.[24] Sixty volunteers with high-grade prostate intraepithelial neoplasia were given either a placebo or 600 mg of green tea polyphenol extract (GTPE) daily. After 1 year, only 1 tumor was diagnosed among the 30 GTPE-treated men (incidence, approximately 3%), whereas 9 cancers were found among the 30 placebo-treated men (incidence, 30%). Total PSAs did not change significantly between the two arms, but GTPE-treated men showed values constantly lower with respect to placebo-treated ones. International Prostate Symptom Score and quality of life scores of GTPE-treated men with coexistent benign prostate hyperplasia improved, reaching statistical significance in the case of International Prostate Symptom Scores. As a secondary observation, administration of GTPE also reduced lower urinary tract symptoms, suggesting that these compounds might also be of help for treating the symptoms of benign prostate hyperplasia. No significant side effects or adverse effects were documented.

These preliminary clinical results in men with prostate cancer provide significant validation of the anticancer effects and safety of higher dosage levels of green tea polyphenols.

Cancer Risk and Black Tea Consumption

In contrast to green tea, population studies analyzing black tea consumption are not as clear regarding cancer protection. Some early studies even indicated that black tea consumption might increase the risk for certain cancers (e.g., rectum, gallbladder, endometrium).[25,26]

For example, in one study, the relationship between black tea consumption and cancer risk was analyzed using data from an integrated series of case–control studies conducted in Northern

Italy between 1983 and 1990.[25] The data set included 119 biopsy-confirmed cancers of the oral cavity and throat, 294 of the esophagus, 564 of the stomach, 673 of the colon, 406 of the rectum, 258 of the liver, 41 of the gallbladder, 303 of the pancreas, 149 of the larynx, 2860 of the breast, 567 of the endometrium, 742 of the ovary, 107 of the prostate, 365 of the bladder, 147 of the kidney, 120 of the thyroid, and a total of 6147 controls admitted to the hospital for acute noncancerous conditions. The risk of developing cancer due to tea consumption was derived after allowance for age, sex, area of residence, education, smoking, and coffee consumption. Results indicated an increased risk with tea consumption for cancers of the rectum, gallbladder, and endometrium. There was no association with cancers of the oral cavity, esophagus, stomach, bladder, kidney, prostate, or any other site considered.

In another study, men of Japanese ancestry were clinically examined from 1965 to 1968.[26] For 7833 of these men, data on black tea consumption habits were recorded. Since 1965, newly diagnosed cancer cases have been identified: 152 colon, 151 lung, 149 prostate, 136 stomach, 76 rectum, 57 bladder, 30 pancreas, 25 liver, 12 kidney, and 163 at other (miscellaneous) sites. Compared with "almost never" drinkers, men who habitually drank black tea more than once a day had a four times greater chance of developing rectal cancer.[26]

Cardiovascular and Liver Disease

Epidemiologic, clinical, and experimental studies have established a positive correlation between green tea consumption and cardiovascular health. Green tea polyphenols exert vascular protective effects through multiple mechanisms, including antioxidative, antihypertensive, anti-inflammatory, antiproliferative, antithrombogenic, and lipid-lowering effects.[27] The underlying mechanisms for these effects are listed in Table 72-2.

Clinical studies are beginning to emerge to support the epidemiologic data. For example, in one double-blind, placebo-controlled study, 111 healthy adult volunteers were given a green tea preparation (GTP) containing 100 mg of L-theanine and 200 mg of a decaffeinated catechin green tea extract twice a day or a placebo. Before and after 3 weeks, blood pressure, serum lipids, serum amyloid-α (a marker of chronic inflammation), and serum malondialdehyde (a marker of oxidative stress) were measured. After 3 months, systolic blood pressure remained significantly lower. GTP lowered serum amyloid-α by 42% and lowered malondialdehyde by 11.9%. In men, there were 10- and 9-mg/dL reductions in total and low-density lipoprotein (LDL) cholesterol, respectively. In all subjects with a baseline LDL cholesterol level greater than 99 mg/dL, there was a 9 mg/dL lowering of total and LDL cholesterol.[28]

Just as in the studies with cancer, cigarette smoking may nullify some of these protective effects against cardiovascular disease. A study from the Netherlands evaluating inflammatory markers, such as interleukin-6, interleukin-1β, tumor necrosis factor-α, C-reactive protein, and fibrinogen, found no benefit for 59 healthy smoking volunteers who drank tea with regard to inflammation, hemostasis, and the endothelial cardiovascular risk factors measured.[29] Given other studies of green tea that showed little protection for smokers[18,19] (discussed in the section on "Cancer"), and the strong body of literature regarding its efficacy in nonsmoking populations, it is possible that the level of oxidative damage sustained by regular smoking may be too great for tea's demonstrated antioxidant capacities. However, it may also be that the dosage of green tea polyphenols must be much higher in smokers. In one double-blind study, 30 healthy male smokers were divided into 3 groups and given green tea beverages containing 0 mg (control group), 80 mg (medium-dose group), or 580 mg (high-dose group) of green tea polyphenols daily for 2 weeks.[30] Endothelial-dependent and endothelial-independent vasodilatation were investigated by measuring the forearm blood flow (FBF) responses to acetylcholine and sodium nitroprusside using venous occlusion strain-gauge plethysmography. The FBF response to acetylcholine significantly

TABLE 72-2 **Correlation Between Green Tea Consumption and Cardiovascular Health**

CARDIOPROTECTIVE EFFECTS	MECHANISMS	MOLECULAR TARGETS
Antioxidant effect	Scavenge free radicals	↓ $O2^{\bullet-}$, $NO^{\bullet}$, 1O2, $ONOO^-$
	Chelate metal ions	Chelate copper and iron
	↓ Redox active transcription factors	↓ NF-kB, AP-1
	↓ Prooxidant enzymes	↓ iNOS, XO
	Upregulate antioxidant enzymes	↑ Catalase, GPx, SOD
	Sparing of antioxidants	Sparing tocopherol
Improvement of lipid metabolism	↓ Cholesterol synthesis	↓ Squalene epoxidase
	↑ Cholesterol excretion	Bind to cholesterol
	↓ Cholesterol absorption	Bind to cholesterol
	↓ Triglycerides	↓ Phospholipase
	↓ Fatty acid synthesis	↓ Acetyl CoA carboxylase ↓ β-ketoacyl reductase of FAS
Improvement of endothelial function	↑ NO-dependent vasodilation	↑ eNOS
	↑ NO-independent vasodilation	↑ Prostacyclin ↑ Cytosolic cAMP, cGMP
Antiinflammatory effect	↓ Adhesion of leucocytes to ECs	↓ VCAM, MCP-1
	+ Apoptosis of monocytes	↑ Caspase 8 and 9
Antiproliferative effect	↓ VSMC growth	↓ PCNA ↓ PDGF
	↓ VSMC migration	↓ MMP-2
Antiplatelet and antithrombotic effects	↓ Platelet aggregation	↓ Cytoplasmic Ca^{2+} release PAF
	↓ Thrombosis	↓ Thromboxane A2 synthase Scavenge free radicals

ApoA1, apolipoprotein A1; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CoA, coenzyme A; EC, endothelial cells; eNOS, endothelial nitric oxide synthase; FAS, fatty acid synthase; GPx, glutathione peroxidase; iNOS, inducible nitric oxide synthase; MCP-1, monocyte chemotactic protein-1; MMP, matrix metalloproteinase; NF-κβ, nuclear factor-κβ; NO, nitric oxide; $O2^{\bullet-}$, superoxide anion; 1O2, singlet oxygen; $ONOO^-$, peroxynitrite radical; PAF, platelet activating factor; PCNA, proliferating cell nuclear antigen; PDGF, platelet-derived growth factor; SOD, superoxide dismutase; factor-α; VCAM-1, vascular cell adhesion molecule-1; VSMC, vascular smooth muscle cells; XO, xanthine oxidase.

Adapted from Babu PV, Liu D. Green tea catechins and cardiovascular health: an update. Curr Med Chem. 2008;15:1840-1850.

increased at 2 hours and at 1 and 2 weeks after green tea polyphenol intake in the high-dose group, but no increase was observed in the other groups. FBF responses to sodium nitroprusside did not alter in any group at any time point. A significant increase in plasma nitric oxide and a decrease in asymmetrical dimethylarginine, malondialdehyde, and 4-hydroxynonenal, C-reactive protein, monocyte chemotactic protein-1, and soluble CD40 ligand levels were detected after long-term consumption of high-dose green tea polyphenol. This study indicated that higher dosages might be required to overcome the oxidative stress of cigarette smoke.

Weight Loss

Green tea extracts have become a popular weight loss aid. The effects appear to require both the catechins and caffeine. Extracts containing both ingredients decreased body mass index (–0.55), body weight (–1.38 kg), and waist circumference (–1.93 cm) compared with caffeine alone. Studies that evaluated green tea catechins without concomitant caffeine administration did not show benefits on any of the assessed anthropometric end points. Green tea catechin and caffeine mixtures promote weight loss through thermogenesis and fat oxidation.[31,32]

Bone Health

Epidemiologic evidence showed an association between green tea consumption and the prevention of age-related bone loss in elderly women and men. There are five proposed mechanisms through which green tea protects bone health: (1) by mitigating bone loss through antioxidative stress action, (2) by mitigating bone loss through anti-inflammatory action, (3) by enhancing osteoblastogenesis, (4) by suppressing osteoclastogenesis, and (5) through its high content of fluoride and vitamin K1.[33]

PHOTOPROTECTIVE EFFECTS

Research showed that topical treatment or oral consumption of green tea polyphenols inhibits chemical carcinogen or ultraviolet (UV) radiation–induced skin tumorigenesis in different animal models. In one study, volunteers were treated with an extract of green tea or one of its constituents and subsequently exposed to graded doses of UV radiation 30 minutes later. UV-treated skin was examined clinically for UV-induced erythema, looking histologically for the presence of sunburn cells or Langerhans cell distributions for UV-induced DNA damage. On histologic examination, skin treated with green tea extracts had a reduced number of sunburn cells and protected epidermal Langerhans cells from UV damage. In a dose-dependent manner, epigallocatechin-3-gallate and epicatechin-3-gallate polyphenols proved to be the most efficient at inhibiting erythema. It was noted that the epigallocatechin and epicatechin fractions showed almost no effect. Green tea extracts also reduced the DNA damage that formed after UV radiation.[34]

ORAL CAVITY DISEASES

Inflammatory gingival reactions, tooth decay, and oral cancer may also benefit from the use of green tea. By studying the amount of dental plaque present, as well as a bleeding index, green tea chews and rinses have been shown to positively affect the level of gum inflammation.[35,36] One trial evaluated volunteers who held 2 grams of brewed black tea or unbrewed green tea leaves in the mouth for 2 to 5 minutes. Results showed that this simple use of tea leaves, acted upon by salivary esterases, released high levels of catechins and theaflavin gallates into the oral cavity.[37] Routine prophylaxis, as well as treatment of gum disease, may be well served by the addition of green tea support to standard brushing, flossing, and dental care regimens.

DOSAGE

The normal amount of green tea consumed by Japanese and other green tea drinking cultures is about 3 cups daily or about 3 grams of soluble components providing roughly 240 to 320 mg of polyphenols. For a green tea extract standardized for 80% total polyphenol and 55% EGCG content, this would mean a daily dose of 300 to 400 mg.

When selecting commercial green tea extracts, it is important to look for the level of EGCG, as well as total polyphenol content.

TOXICITY

Green tea is not associated with any significant side effects or toxicity. As with any caffeine-containing beverage, overconsumption may produce a stimulant effect (e.g., nervousness, anxiety, insomnia, irritability).

DRUG INTERACTIONS

Populations with marginal or deficient iron status have been shown to have lower serum ferritin or hemoglobin levels, or both, presumably due to iron binding.[38] Theoretical concerns have been raised for interactions with several drug classes, including amphetamines and anticoagulants due to the caffeine content of green tea, but no interactions have been reported in humans.

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CHAPTER 73

Capsicum frutescens (Cayenne Pepper)

Michael T. Murray, ND

Capsicum frutescens (family: Solanaceae)
Common names: cayenne pepper, capsicum, chili pepper, red pepper, American pepper

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GENERAL DESCRIPTION

Cayenne pepper (also known as chili or red hot pepper) is the fruit of *Capsicum annuum*, a shrubby, tropical plant that can grow up to 3 feet high. The fruit is technically a berry. Paprika is a milder and sweeter tasting fruit produced from a different variety of capsicum. Although cayenne pepper is native to tropical America, it is now cultivated in tropical locations throughout the world and has found its way into the cuisine of many parts of the world, particularly Southeast Asia, China, Southern Italy, and Mexico.

CHEMICAL COMPOSITION

The most important constituents of cayenne pepper are the pungent compounds, with capsaicin being the most prominent (Figure 73-1). Typically, cayenne pepper contains about 1.5% capsaicin and related principles. Other active constituents present include carotenoids, vitamins A and C, and volatile oils.

HISTORY AND FOLK USE

The folk use of cayenne pepper is quite extensive. It has been used for the following:

- Asthma
- Fever
- Sore throats and other respiratory tract infections
- Digestive disturbances
- Poultices
- Cancer

It has also been used as a counterirritant in the topical treatment of arthritis and neuralgia.

PHARMACOLOGY

The pharmacology of cayenne pepper centers around its capsaicin content. Interestingly, capsaicin, although hot to the taste, has actually been shown to lower body temperature by stimulating the cooling center of the hypothalamus.[1] The ingestion of cayenne peppers by cultures native to the tropics appears to offer a way for these people to deal with high temperatures.

When taken internally, cayenne pepper exerts a number of beneficial effects on the cardiovascular system. In addition to possessing several antioxidant compounds, studies have shown that cayenne pepper reduces the likelihood of developing atherosclerosis by reducing blood cholesterol and triglyceride levels and platelet aggregation, as well as increasing fibrinolytic activity.[2-4] (For the significance of these effects, see Chapter 148.) Cultures consuming large amounts of cayenne pepper have a much lower rate of cardiovascular disease.

When topically applied to the skin or mucous membranes, capsaicin is known to stimulate and then block small-diameter pain fibers by depleting them of the neurotransmitter substance P.[5] Substance P is thought to be the principal chemomediator of pain impulses from the periphery. In addition, substance P has been

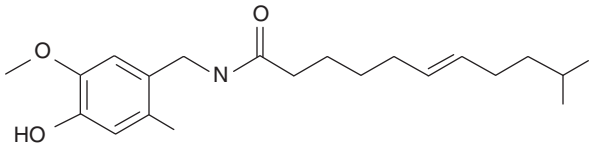


FIGURE 73-1 Capsaicin.

shown to activate inflammatory mediators into joint tissues in osteoarthritis and rheumatoid arthritis.[6]

CLINICAL APPLICATIONS FOR ORAL PREPARATIONS

Cayenne pepper exerts several beneficial effects on gastrointestinal function, including acting as a digestant and carminative.[7] Double-blind studies showed that red pepper consumption protects against aspirin-induced stomach damage and improves epigastric pain, fullness, and nausea scores in people with nonulcer dyspepsia.[8-10] In one study, the digestive-enhancing effects of capsicum were determined in 30 patients with functional dyspepsia and without gastroesophageal reflux (GER) disease and irritable bowel syndrome.[11] These patients received, before meals, randomly and in a double-blind manner, 2.5 g/day of red pepper powder or placebo for 5 weeks. The overall symptom score and the epigastric pain, fullness, and nausea scores of the red pepper group were significantly lower than those of the placebo group, starting from the third week of treatment. The decrease reached about 60% at the end of treatment in the red pepper group, whereas placebo scores decreased by less than 30%.

Capsicum does, however, lower the threshold for GER, presumably by direct effects on sensory neurons and may produce symptoms of GER.[12,13]

Thermogenic Aid

Capsicum ingestion may also prove to be helpful in promoting weight loss in obese individuals, because clinical studies showed capsicum increased the basal metabolic rate while reducing appetite and caloric intake.[14,15] In one study, after ingesting a standardized dinner on the previous evening, the subjects ate one of the following for breakfast: a high-fat meal, a high-fat meal with red pepper (10 g), a high-carbohydrate meal, or a high-carbohydrate meal with red pepper (10 g). Diet-induced thermogenesis was significantly enhanced by the addition of red pepper to either meal, but especially the high-fat meal.[16] In another study, 40 women and 40 men (mean age of 42 years and body mass index of 30.4) were randomly assigned to a capsinoid (6 mg/day) or placebo group.[17] Mean weight change was 0.9 and 0.5 kg in the capsinoid and placebo groups, respectively. There was no significant group difference in total change in adiposity, but abdominal adiposity decreased more in the capsinoid group (–1.11%) than in the placebo group (–0.18%), and this change correlated with the change in body weight. Changes in resting energy expenditure did not differ significantly between groups, but fat oxidation was higher at the end of the study in the capsinoid group.

Atherosclerosis and the Metabolic Syndrome

Capsicum exerts a number of effects beneficial in the prevention of atherosclerosis, including inhibiting low-density lipoprotein cholesterol oxidation, acting as an antioxidant, inhibiting platelet aggregation, promoting fibrinolysis, and improving arterial function.[18] Chili consumption also lowers postprandial hyperinsulinemia.[19]

CLINICAL APPLICATIONS FOR TOPICAL PREPARATIONS

Modern clinical use of cayenne pepper has focused on the use of topical capsaicin-containing preparations. Commercial ointments containing 0.025% or 0.075% capsaicin are available over the counter. These preparations may offer significant benefits in a number of conditions, including the pain associated with pain disorders, diabetic neuropathy, cluster headache, osteoarthritis, and rheumatoid arthritis. In addition, topically applied capsaicin may be useful in psoriasis.

Postherpetic Neuralgia

The first studies and approved use for topically applied capsaicin were in relieving postherpetic neuralgia. Numerous studies now document this Food and Drug Administration–approved application. For example, in one study, 39 patients with chronic postherpetic neuralgia (average duration 24 months) were treated with 0.025% capsaicin cream for 8 weeks. During therapy, the patients rated their pain. Nineteen patients (48.7%) substantially improved after the 8-week trial; 5 (12.8%) discontinued therapy due to side effects, such as intolerable capsaicin-induced burning sensations (4) or mastitis (1); and 15 (38.5%) reported no benefit. The decrease in pain ratings was significant after 2 weeks of continuous application. Of the responders, 72.2% still reported improvement 10 to 12 months after the study, with most continuing to apply the cream regularly.

In general, the results of this study were consistent with other studies (i.e., about 50% of people with postherpetic neuralgia responded to topically applied capsaicin [0.025%]).[16,20-24] Although this might not be a great response, it was better than the 10% response noted in the placebo group. Higher concentration (0.075% vs 0.025%) might produce better results (as high as 75% response).[25] Another study showed that capsaicin responders were characterized by higher average daily pain, higher allodynia ratings, and relatively preserved sensory function at baseline compared with nonresponders. In three of the "capsaicin responders," the area of allodynia expanded into previously nonallodynic and nonpainful skin that had normal sensory function and cutaneous innervation.[26]

Trigeminal Neuralgia

Topically applied capsaicin may be effective in reducing the pain of trigeminal neuralgia.[27] In one study, 12 patients were followed up for 1 year after the topical application over the painful area of capsaicin 3 times a day for several days. Six patients had complete and four patients had partial relief of pain; the remaining two patients had no relief of pain. Of the 10 patients who were responsive to therapy, 4 had relapses of pain within 95 to 149 days. No relapses followed the second therapy for the remainder of the year. These results are promising for a condition that usually does not respond to any therapy, short of surgery.

Postmastectomy Pain

Topically applied capsaicin may help in the relief of pain after breast reconstruction or mastectomy. In one double-blind study, 23 patients with postmastectomy pain syndrome applied either

capsaicin (0.075%) or vehicle (placebo) only cream 4 times daily for 4 to 6 weeks.[28] There was a significant difference in jabbing pain, in category pain severity scales, and in overall pain relief scales in favor of capsaicin. Five of 13 patients on capsaicin were categorized as having good-to-excellent responses, with 8 patients (62%) having 50% or greater improvement. Only 1 of 10 cases had a good response to vehicle, with 3 rated as 50% or better.

In another study, 14 patients with postmastectomy pain had significant pain relief after application of 0.025% capsaicin cream 4 times daily for 4 to 6 weeks.[29] Unpleasant or painful sensations to light touch or pressure in the painful area (hyperesthesia, allodynia) were also improved.

Mouth Pain Due to Chemotherapy or Radiation

In a study conducted at the Yale Pain Management Center, capsaicin was shown to dramatically reduce the pain from mouth sores as a result of chemotherapy or radiation treatment.[30] The interesting feature in this study was the vehicle used to deliver the capsaicin—taffy. The researchers chose taffy because it could be held in the mouth long enough to desensitize the neurons, its sugar decreased the initial burning sensation, and its soft edges would not aggravate sore mouths like a hard candy. All 11 patients in the Yale study said their pain decreased, in 2 cases stopping entirely, after eating the capsaicin-laced candy.

Diabetic Neuropathy

Topically applied capsaicin has been shown to be of considerable benefit in relieving the pain of diabetic neuropathy in numerous double-blind studies.[31-37] In one large double-blind, 8-week study, investigators at 12 sites enrolled 277 men and women with painful diabetic neuropathy of the hands and feet; 69.5% of the group applying the capsaicin cream (0.075%) showed improvement compared with 53.4% in those applying only the vehicle cream.

In another study, 40 patients applied either 0.075% capsaicin cream or placebo to their affected extremities daily. After 4 weeks, 76% of treated patients had some pain relief compared with 50% of placebo patients. In addition, those responding to capsaicin said their pain was cut in half, whereas those on placebo averaged between 15% and 20% relief.

Cluster Headaches

Several studies found that intranasal application of capsaicin ointment by a physician might relieve cluster headaches. In one double-blind study, patients with acute cluster headaches were randomized to receive either capsaicin or placebo in the nostril for 7 days.[38] Patients recorded the severity of each headache for 15 days. Headaches on days 8 to 15 of the study were significantly less severe in the capsaicin group versus the placebo group. There was also a significant decrease in headache severity in the capsaicin group on days 8 to 15 compared with days 1 to 7, but not in the placebo group. Episodic patients appeared to benefit more than chronic patients.

Arthritis

Topically applied capsaicin may be effective in relieving the pain of osteoarthritis and rheumatoid arthritis. Although one study showed it to be more effective in osteoarthritis, another study showed just the opposite.

In the double-blind study showing more effect in osteoarthritis, 7 patients with rheumatoid arthritis and 14 patients with osteoarthritis who had painful involvement of the hands applied either capsaicin 0.075% or vehicle only cream to the hands 4 times daily. Capsaicin reduced tenderness and pain associated with osteoarthritis, but not rheumatoid arthritis.[39]

In the study showing greater benefit for rheumatoid arthritis, 70 patients with osteoarthritis and 31 with rheumatoid arthritis received capsaicin or placebo for 4 weeks.[40] The patients were instructed to apply 0.025% capsaicin cream or its vehicle (placebo) to painful knees four times daily. Significantly more relief of pain was reported by the capsaicin-treated patients than the placebo patients throughout the study; after 4 weeks of capsaicin treatment, rheumatoid and osteoarthritis patients demonstrated mean reductions in pain of 57% and 33%, respectively. These reductions in pain were statistically significant compared with those reported with placebo. According to overall evaluations, 80% of the capsaicin-treated patients experienced a reduction in pain after 2 weeks of treatment.

Psoriasis

Excessive substance P levels in the skin have been linked to psoriasis. This finding prompted researchers to study the effects of topically applied capsaicin. In one double-blind study, 44 patients with symmetrically distributed psoriasis lesions applied topical capsaicin to one side of their body and a placebo to the other side.[41] After 3 to 6 weeks, significantly greater reductions in scaling and redness were observed on the capsaicin side. Burning, stinging, itching, and skin redness were noted by nearly half of the patients initially, but these diminished or vanished upon continued application.

In a later study, 197 patients applied capsaicin 0.025% cream or placebo cream 4 times a day for 6 weeks.[42] Efficacy was based on a physician's evaluation and a combined psoriasis severity score, including scaling, thickness, erythema, and pruritus. Capsaicin-treated patients demonstrated significantly greater improvement at the physician's evaluation and in pruritus relief, as well as a significantly greater reduction in combined psoriasis severity.

Pruritus Ani

Pruritus ani is a common condition that can be difficult to treat. Results from a double-blind study indicated that capsaicin was a safe and highly effective treatment for severe intractable idiopathic pruritus ani.[43] This study involved two 4-week treatment phases separated by a 1-week washout phase. Forty-four patients were randomized to receive locally either active capsaicin (0.006%) or placebo (menthol 1%) ointment over a 4-week period. After 4 weeks of treatment and a 1-week washout period, the placebo group began to receive capsaicin while the treated group received placebo (menthol 1%) for another 4 weeks. At the end of the controlled study, responders from both groups continued with capsaicin treatment in an open-label manner. Results indicated that 31 of 44 patients experienced relief during capsaicin treatment periods and did not respond to menthol; all patients who did not respond to capsaicin also did not respond to menthol. In 13 patients, treatment with capsaicin was unsuccessful: 8 patients did not respond to capsaicin treatment, 1 responded equally to capsaicin and placebo, and 4 others dropped out because of side effects.

DOSAGE

Cayenne pepper can be used liberally in the diet. Creams containing 0.025% or 0.075% capsaicin or poultices can be applied to affected areas up to four times daily.

TOXICITY

Capsicum is generally recognized as safe by the U.S. Food and Drug Administration. Contraindications to oral ingestion include aggravation or appearance of GER or other sensitivity. Studies showed that consumption of 3 grams of red chilies per day during the postoperative period after hemorrhoidectomy or surgery for anal fissures increased the intensity of typical postoperative symptoms, stool frequency, and the consumption of analgesics.[44,45]

Topically applied capsaicin may produce a local burning sensation; however, this effect goes away with time and rarely is severe enough to warrant discontinuation of use of the cream.

DRUG INTERACTIONS

Although several theoretical interactions have been postulated, no clinical cases have been documented. In particular, the use of capsicum has been cautioned in patients on anticoagulants or antiplatelet therapy.

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CHAPTER 74

Carnitine

Angela Sadlon, ND, and Michael T. Murray, ND

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INTRODUCTION

Carnitine is an essential nutrient for the transport of long-chain fatty acids into the mitochondrial matrix. Carnitine (β-hydroxy/γ-butyrobetaine) was originally isolated from meat extracts in 1905, and its exact chemical structure was determined in 1932 (Figure 74-1). However, despite extensive physiologic and pharmacologic studies in the 1930s, no physiologic role for carnitine was determined until 1955.[1-3]

The compound was virtually forgotten until Carter et al[4] created new interest in carnitine in 1952, when they established it as a growth factor for the meal worm *Tenebrio molitor* (hence carnitine's other name, "vitamin BT"—*B* for the family of vitamins and *T* for *Tenebrio molitor*). When other species of organisms were also shown to be dependent on carnitine, researchers began to reexamine its role in humans.

Researchers soon found that carnitine was essential in the oxidation of lipids.[1-3] When the first carnitine-deficient human subjects were described in 1973, it stimulated greater investigation.[5]

BIOSYNTHESIS

Carnitine is synthesized in humans from lysine and methionine. In nonmammalians, carnitine synthesis begins with stepwise methylation of free lysine by S-adenosylmethionine to produce trimethyllysine. In mammals, however, protein-bound trimethyllysine, rather than free lysine, appears to be the major precursor for carnitine synthesis.[1-3]

Trimethyllysine is then converted through a series of enzymatic reactions (occurring in the liver, kidney, brain, heart, and skeletal muscle) to butyrobetaine. However, the conversion of butyrobetaine to carnitine can only occur in the liver, kidney, and brain, since the enzyme required, butyrobetaine hydroxylase, is only present in these tissues.[1-3]

The synthesis of carnitine is largely controlled by the activity of butyrobetaine hydroxylase. This enzyme appears to be age dependent. In infancy, the activity of butyrobetaine hydroxylase has been shown to be only 12% of the normal adult mean. By 2.5 years, the activity is 30% of the adult mean, and by 15 years, the level is within a standard deviation of the adult mean.[1-3] These data would seem to indicate the importance of preformed carnitine in breast milk.

As apparent from Figure 74-2, two essential amino acids (lysine and methionine), three vitamins (ascorbate, niacin, and vitamin B_6), and a metal ion (reduced iron) are required for the synthesis of carnitine. Obviously, a deficiency of any one of these nutrients would result in significantly impaired carnitine synthesis.[1-3] However, research using knockout mice unable to synthesize vitamin C endogenously showed normal carnitine values (comparable to their vitamin C synthesizing counterparts), although they were vitamin C deficient. The researchers suggested that adequate levels of glutathione and glutathione peroxidase might compensate or replace the deficient vitamin C in the carnitine biosynthesis pathway.[6]

METABOLISM

Pharmacokinetics

The heart and skeletal muscles, as well as many other tissues, depend primarily on fatty acid oxidation as a source of energy. Because they cannot synthesize carnitine, its transport into these tissues is of critical importance.

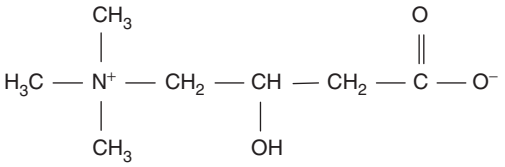
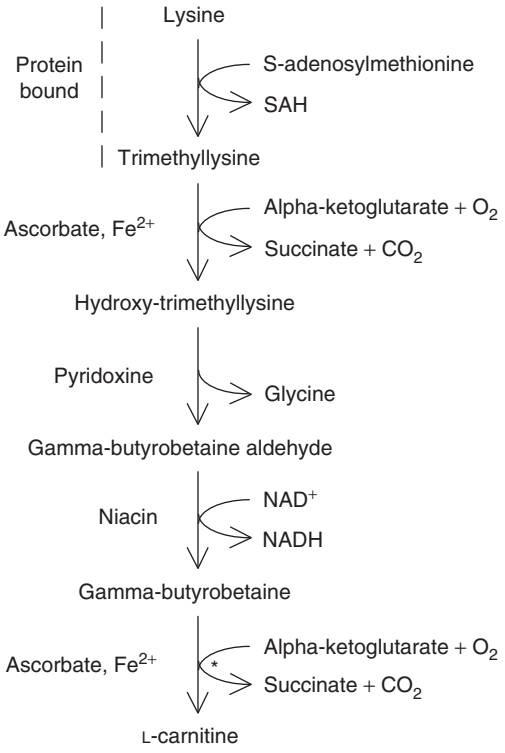


FIGURE 74-1 L-carnitine.



*In humans, the enzyme catalyzing this reaction occurs only in the liver, kidney, and brain

FIGURE 74-2 Biosynthesis of carnitine.

Specific carnitine-binding transport proteins were identified for several tissues (e.g., cardiac muscle, skeletal muscle, epididymis, liver, kidney) taking the serum carnitine into the cell.[1,3] Through this active transport mechanism, the tissues can concentrate carnitine up to 10 times greater than that found in plasma.

A small in vivo study measured the pharmacokinetics of carnitine in Chinese men and women participants. A 2000 mg single oral dose of L-carnitine (LC) had a half-life of approximately 60.3 hours compared with L-acetylcarnitine (LAC) at 35.9 hours and L-propionylcarnitine (LPC) at 25.7 hours. The maximum plasma concentration of LC, LAC, and LPC occurred at 3.4, 2.4, and 3.8 hours after ingestion, respectively, and at quantities of 84.7, 12.9, and 5.1 µmol/L, respectively. The researchers found comparable levels of carnitine absorption and metabolism between men and women, suggesting that gender should not affect dosage.[7]

Urinary excretion of unchanged carnitine is the major route of elimination of carnitine. Since the tubular reabsorption of carnitine by the kidneys is extremely efficient, the daily turnover of carnitine is estimated to be only 4% to 6% of the total body pool of the healthy individual.[1-3,7] Factors that increase carnitine excretion and degradation are discussed later in the section on "Deficiency."

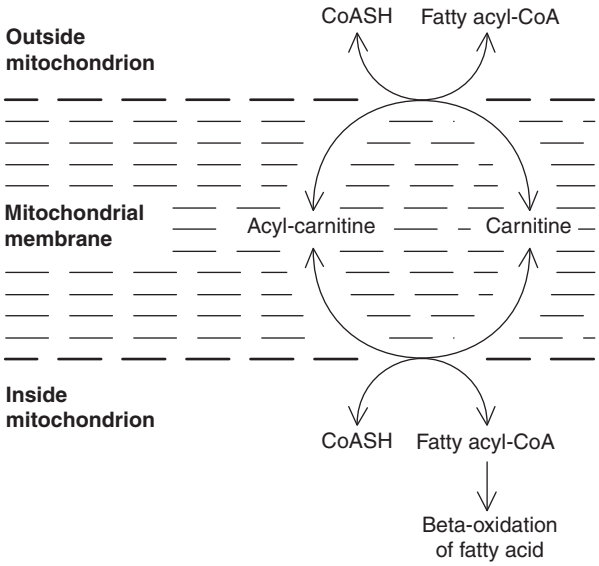


FIGURE 74-3 Role of carnitine in the transport of long-chain fatty acids through the inner mitochondrial membrane.

PHYSIOLOGIC FUNCTIONS

Carnitine's basic function is in the transport of long-chain fatty acids into the mitochondrial matrix and the facilitation of β-oxidation.[13] Because acyl coenzyme A formed in the endoplasmic reticulum or outer mitochondrial membrane cannot penetrate the inner mitochondrial membrane to the site of fatty acid β-oxidation, the acyl group must be transferred from coenzyme A to carnitine. The acyl-carnitine molecule then transports the fatty acid molecule to the mitochondrial surface of the inner mitochondrial membrane and releases the fatty acid into the matrix, where β-oxidation occurs. Figure 74-3 summarizes this process.

Carnitine has several other physiologic functions, including oxidation of the ketoacid analogs of the branched chain amino acids valine, leucine, and isoleucine.[1-3] This function is extremely important during fasting, starvation, and exercise.

DEFICIENCY

Carnitine deficiency may arise from several causes, as listed in Box 74-1.

Carnitine deficiency states have been classified into two major groups:

- Systemic carnitine deficiency
- Myopathic deficiency

Diagnosis of systemic carnitine deficiency can be made using serum or 24-hour urine samples. Total, free, and esterified carnitine levels should be determined. In myopathic carnitine deficiency, diagnosis requires skeletal muscle biopsy.[8]

To date, no patients with primary systemic carnitine deficiency have been identified. The systemic deficiency has always been secondary to some other factor rather than a defect in carnitine synthesis.[1-3,8,9]

The consequences of systemic carnitine deficiency are impaired lipid metabolism and lipid accumulation in the skeletal muscles, myocardium, and liver. Progressive muscle weakness with lipid storage myopathy is found in all patients.[1-3,8] In adults, auxiliary nonmitochondrial oxidation mechanisms are apparently stimulated, resulting in some degree of adaptation. This adaptation occurs in starvation, diabetes, high-fat diets, and other causes of secondary

BOX 74-1 Causes of Carnitine Deficiency

- Dietary deficiency of the precursor amino acids lysine and methionine
- Deficiency of any cofactor (e.g., iron, ascorbic acid, pyridoxine, niacin) required by the enzymes of the lysine to carnitine pathway
- Genetic defect of carnitine biosynthesis
- Defective intestinal absorption of carnitine
- Liver or kidney dysfunction that impairs carnitine synthesis
- Increased metabolic losses of carnitine due to catabolism, impaired tubular resorption, or genetic defect
- Defective transport of carnitine from tissues of synthesis to tissues where it is maximally used
- Increased carnitine requirement due to a high-fat diet, drugs (e.g., valproic acid), metabolic stress, or disease

carnitine deficiency. Systemic carnitine deficiencies usually respond dramatically to orally administered supplemental LC.[8,9]

Children are apparently unable to adapt to low carnitine levels as well as adults.[8] Several cases of carnitine deficiency in children, presenting a clinical picture resembling Reye's syndrome (acute encephalopathy associated with altered liver function due to lipid accumulation), have been reported.[9-11]

The clinical presentation of secondary carnitine deficiency in children includes hypotonia, failure to thrive, recurrent infections, encephalopathy, nonketotic hypoglycemia, and cardiomyopathy.[8] Several fatal cases of systemic carnitine deficiency have been reported.[9,12]

In primary myopathic carnitine deficiency, there is an inborn error of carnitine metabolism that is limited to skeletal muscle.[8,9] The defect appears to be in the transport of carnitine into the skeletal muscle as serum carnitine; the carnitine levels in other tissues are normal. Severe lipid storage myopathy is the result. Supplemental carnitine is generally of no value in myopathic carnitine deficiency. Rather, improvements have been noted using diets high in medium-chain triglycerides and low in long-chain triglycerides.[8]

CARNITINE AS A NUTRIENT

Analysis of several hundred foods for carnitine content indicates that meat and dairy products are the major dietary sources of carnitine.[3] In general, the redder the meat, the higher the carnitine content. Cereals, fruits, and vegetables contain little or no carnitine. Preliminary studies indicate that the daily diet contains 5 to 100 mg of carnitine.[3]

Carnitine in the Infant Diet

Oxidation of long-chain fatty acids, which requires carnitine, is well known to be critical to the survival and normal development of the newborn.[3] Carnitine concentrations in fetal and umbilical cord blood are higher than in maternal blood, suggesting the placenta may actively transport carnitine to the fetus, because carnitine synthesis is not fully developed.[3] The initial carnitine concentration in the newborn depends on maternal carnitine concentration.

Supplementation of carnitine during pregnancy may be necessary to ensure adequate tissue concentrations in the fetus, as well as the mother. Serum carnitine levels are typically lower in pregnant women than nonpregnant women, presumably due to increased excretion.[13,14]

BOX 74-2 Conditions That May Benefit from Carnitine Supplementation

- Cardiovascular diseases
- Angina pectoris
- Acute myocardial infarction
- Myocardial necrosis
- Arrhythmias and cardiotoxicity induced by drugs
- Familial endocardial fibroelastosis
- Cardiac myopathy
- Idiopathic mitral valve prolapse
- Elevated cholesterol levels
- Elevated triglyceride levels
- Enhancing physical performance
- Fatigue in person with celiac disease
- Alzheimer's disease, senile depression, and age-related memory defects
- Kidney disease and hemodialysis
- Diabetes
- Liver diseases
- Alcohol-induced fatty liver disease
- Liver cirrhosis
- Muscular dystrophies
- Low sperm counts and decreased sperm motility
- Chronic obstructive pulmonary disease
- Acquired immunodeficiency syndrome
- Inborn errors of amino acid metabolism
- Organic aciduria
- Glutaric aciduria
- Isovaleric acidemia
- Propionic acidemia
- Methylmalonic aciduria
- Toxicity from various drugs

The newborn infant is almost entirely dependent on external sources of carnitine.[3] Breast-fed infants have the best chance of achieving optimal carnitine concentrations. The bioavailability of carnitine from breast milk is significantly greater than that in cow's milk–based formulas,[15] and soy-based infant formulas contain no detectable carnitine.[3] Formula feeding may necessitate supplemental carnitine to achieve normal carnitine concentrations in these infants.

Carnitine administration to preterm infants has potentiated weight gain and growth.[16] In preterm infants, serum values of carnitine decrease dramatically due to limited storage capacity coupled with a decreased ability to synthesize carnitine. Administration of LC to preterm infants is considered important.

CLINICAL APPLICATIONS

Many disease states, in addition to classic as well as secondary carnitine deficiency, may benefit from carnitine administration. Evidence supports the assertion that supplemental carnitine may benefit the conditions listed in Box 74-2 and discussed later.

Carnitine is available in several different forms. The form being used must be LC alone or bound to either acetic (LAC) or propionic acid (LPC). The D form of carnitine (discussed later in the section on "Toxicology") should never be used. The reason for using carnitine will dictate the form used. For Alzheimer's disease and brain effects, it appears that LAC may provide the greatest benefit. For angina, LPC may be the best choice, because the myocardium appears to prefer it to LAC, followed by LC.[17,18] LC is,

however, the most widely available, least expensive, and best studied form of carnitine.

Cardiovascular Disease

Normal heart function is critically dependent on adequate concentrations of carnitine. A deficiency of carnitine in the heart would be similar to trying to run an automobile without a fuel pump. Despite plenty of fuel, there is no way to get it to the engine. Although the normal heart stores more carnitine than it needs, if the heart does not have a good supply of oxygen, carnitine levels quickly decrease. This lack of oxygen leads to decreased energy production in the heart and increased risk for angina and heart disease.

Oral LAC therapy (1 g twice daily) for 6 months showed a gradual but significant decrease in blood pressure in insulin resistant participants who had higher risk factors for cardiovascular disease (hypertension, hypertriglyceridemia, obesity, and/or family history of diabetes type 2). In the patients with greater insulin resistance, the insulin sensitivity was significantly increased. The overall adiponectin values increased. These benefits were slowly reversed during an 8-week follow-up after LAC discontinuation. There were no changes to participants' diet or lifestyle during this study. LAC was well tolerated in all participants.[19] It appears that LAC can improve aspects that are characteristic of metabolic syndrome, but without lifestyle and dietary modifications, the patient may potentially need long-term supplementation with carnitine.

Carnitine exerts a beneficial effect on blood lipids by lowering triglycerides (TGs) and total cholesterol levels while raising high-density lipoprotein (HDL) cholesterol. After 4 months of therapy with LC in patients with elevated blood lipids, typical changes observed were a 20% reduction for total cholesterol, a 28% decrease in TGs, and a 12% increase in HDL levels.[20,21] Due to the higher cost of carnitine compared with other natural agents (e.g., inositol hexaniacinate, garlic, and gugulipid), its use should be reserved for those cases unresponsive to these more cost-effective measures.

Angina and Recovery from Myocardial Infarction

Carnitine is useful in angina due to its ability to improve oxygen usage and energy metabolism by the myocardium. As a result of improving fatty acid usage and energy production, carnitine also prevents the production of toxic fatty acid metabolites.[22] These compounds are extremely damaging, because they disrupt cellular membranes. Changes in the properties of cell membranes throughout the heart are thought to contribute to impaired contraction of the heart muscle, increased susceptibility to irregular beats, and eventual death of heart tissue. Supplementing with carnitine increases heart carnitine levels and has been shown to prevent the production of toxic fatty acid metabolites, as well as boost antioxidant enzyme levels. In addition to angina, all of these effects make carnitine beneficial in recovery from a heart attack, cardiomyopathies, arrhythmias, and congestive heart failure.[23,24]

Numerous clinical trials demonstrated that carnitine improves angina and heart disease (note that all three commercial forms have been used).[23,25-32] Improvements were noted in exercise tolerance and heart function. The results indicated that carnitine is an effective alternative to drugs in cases of angina.

LPC may offer the greatest benefit in angina, as well as in other cardiovascular conditions. LPC is taken up by myocardial cells much more rapidly than other forms of carnitine.[17] In one study, LPC (15 mg/kg intravenously) significantly diminished myocardial ischemia as demonstrated by a significant 12% and 50% reduction in ST-segment depression and left ventricular end-diastolic pressure, respectively, during the atrial pacing test.[33] Left ventricular ejection fraction increased by 18%. Recovery of heart function after exercise occurred much quicker in the LPC group compared with the placebo group.

LC and LAC also showed good results. In one of the larger studies, 200 patients with exercise-induced stable angina received either standard therapy alone (e.g., nitroglycerin, calcium channel blockers, β-blockers, antihypertensives, diuretics, digitalis, antiarrhythmics, anticoagulants, hypolipidemics) or in combination with 2000 mg/day of LC over a 6-month period.[34] Compared with the control group, the patients on LC exhibited a significant reduction in premature ventricular contractions at rest, as well as an increased tolerance to exercise as demonstrated by an increased maximal cardiac frequency, increased maximal systolic blood pressure, cardiac output, and reduced ST-segment depression (70% reduction in the LC group versus no change in the control group). Reductions in low-density lipoprotein (LDL) cholesterol (8%) and TGs (12%) were also noted. These results are highly significant and provide a strong rationale for the inclusion of carnitine in patients using standard medical therapy.

In Italy, a large study involving 472 patients showed additional benefits.[35] The study was performed to evaluate the effects of LC administration on chronic left ventricular dilation in patients with acute anterior myocardial infarction. Placebo or LC was given at a dose of 9 g/day intravenously for the first 5 days and then 6 g/day orally for the next 12 months. Left ventricular volumes and ejection fraction were evaluated on admission, at discharge from hospital, and at 3, 6, and 12 months after acute myocardial infarction. A significant attenuation of left ventricular dilation in the first year after acute myocardial infarction was observed in patients treated with LC compared with those receiving placebo. The percent increase in both end-diastolic and end-systolic volumes from admission to 3-, 6-, and 12-month evaluation was significantly reduced in the LC group.

Congestive Heart Failure

Several double-blind clinical studies showed that carnitine (again, LPC appeared to be more effective than LC or LAC) improved cardiac function in patients with congestive heart failure.[23,36,37] In one double-blind study of LPC versus placebo in a group of 60 patients with mild to moderate (New York Heart Association [NYHA] classes II and III) congestive heart failure, LPC produced demonstrable benefit.[36] The group was made up of men and women between 48 and 73 years old receiving long-term treatment with digitalis and diuretics for at least 3 months and who still displayed symptoms. Thirty of these patients were chosen randomly and for 180 days received 500 mg of LPC three times a day in addition to their usual treatment. At basal conditions and after 30, 90, and 180 days, the maximum exercise time was evaluated using an exercise tolerance test performed on an ergometer bicycle, and the left ventricular ejection fraction was tested by echocardiography. After 1 month of treatment, the patients treated with LPC, compared with the control group, showed significant increases in the values of both tests, increases that became even more evident after 90 and 180 days. At the stated times, the increases in the maximum exercise time were 16.4%, 22.9%, and 25.9%, respectively. The ventricular ejection fraction increased by 8.4%, 11.6%, and 13.6%, respectively.

Even more obvious benefits were seen in a 3-year study of 80 patients with moderate to severe heart failure (NYHA class III to

IV) caused by dilated cardiomyopathy. After a period of stable cardiac function up to 3 months, patients were randomly assigned to receive either carnitine (2 g/day orally) or placebo. After a mean of 33.7 months of follow-up (range 10 to 54 months), 70 patients remained in the study: 33 in the placebo group and 37 in the carnitine group. At the time of analysis, 63 patients were alive. Six deaths occurred in the placebo group, and one death in the carnitine group. Survival analysis showed that patients' survival was statistically significant in favor of the carnitine group.[38]

Peripheral Vascular Disease

All three forms of carnitine (2 to 4 g/day) were shown to improve the walking distance without pain in patients with intermittent claudication. Presumably this improvement was the result of improved energy metabolism within the muscle, since carnitine was not shown to improve blood flow to the calf. LPC appeared to offer better effects than either LC or LAC.[39,40] However, in one double-blind study, LC at a dosage of 2 g twice daily demonstrated a 75% increase in walking distance after only 3 weeks of therapy.[41]

In the largest study with LPC, 485 patients with intermittent claudication were randomized to placebo or LPC (2 g/day) for 12 months. Maximal walking distance increased by 62% on LPC and by 46% on placebo in all patients. However, when only those patients with more severe disease status were analyzed, the maximal walking distance increased by 98% in the LPC group compared with only 54% in the placebo group.[42]

Enhancing Physical Performance and Relieving Fatigue

The ability to enhance exercise tolerance and physical performance with carnitine may not be limited to patients with cardiovascular disease, since carnitine supplementation was also shown to be of benefit in healthy subjects and athletes. Efficient use of fatty acids by skeletal muscle, like the myocardium, also depends on an adequate supply of carnitine.

Carnitine supplementation (usually 2 g two to three times daily) resulted in significant improvements in cardiovascular function in response to exercise in several double-blind studies in both athletes and normal subjects.[43-45] Compared with control groups, the subjects on carnitine showed not only improvements in exercise intensity over time, but also evidence of improved energy metabolism within the muscle (lowered blood lactic acid and free fatty acid levels). Obviously, the improved production of energy by the exercising muscle, as well as improved heart function, could be responsible for carnitine's ability to enhance physical performance.

Although at least three studies showed the benefits of carnitine on exercise performance to be of no more value than a placebo, carnitine supplementation should still be viewed as beneficial, especially in endurance-related events.[46-48] The reason behind this statement is the fact that studies demonstrated that carnitine improves energy-producing enzyme levels in long-distance runners.[49] These athletes received either a placebo or 2 g of LC twice daily for 4 weeks. Runners receiving LC showed a significant increase in enzymes involved in energy production (cytochrome C reductase and cytochrome oxidase). In contrast, there were no changes in the placebo group.

One study examined the influence of L-carnitine L-tartrate (LCLT) at a dosage of 2 g/day for 3 weeks on markers of purine catabolism, free radical formation, and muscle tissue disruption after squat exercise. Exercise-induced increases in plasma markers of purine catabolism (hypoxanthine, xanthine oxidase, and serum uric acid) and circulating cytosolic proteins (myoglobin, fatty acid-binding protein, and creatine kinase) were significantly reduced by LCLT supplementation. Exercise-induced increases in plasma malondialdehyde returned to resting values sooner during LCLT therapy compared with placebo. The amount of muscle disruption from magnetic resonance imaging scans during LCLT was 41% to 45% of the placebo area. These data indicated that LCLT supplementation was effective in assisting recovery from exercise.[50]

Interestingly, normal subjects taking carnitine have improved cardiovascular function and a more rapid return of heart rate to the resting rate after exercise.[51] The significance of these improvements is that carnitine apparently mimics the benefits in heart and vascular function produced by regular exercise training without working up a sweat.

Carnitine supplementation appeared to be beneficial in elderly subjects complaining of muscle fatigue.[52,53] In one double-blind study, 84 elderly subjects with onset of fatigue after even the slightest physical activity were randomized to receive carnitine 2 g twice daily or a placebo for 30 days. Fatigue scores decreased significantly by 40% (physical) and 45% (mental) in subjects taking carnitine, compared with 11% and 8%, respectively, in the placebo group. Other parameters improved significantly, including total fat mass, total muscle mass, total cholesterol, LDL cholesterol, HDL cholesterol, TGs, apolipoprotein-A1, and apolipoprotein-B.[52] In a similar study, researchers reported 2 g/day of LC given to centenarians had a comparable trend when looking at similar parameters.[53] The difference was 2 g twice daily showed greater improvement in most parameters measured.

Few clinical trials have been published regarding carnitine and fatigue relief in multiple sclerosis patients. Some studies reported significant benefit,[54,55] whereas another suggested better designed studies were needed to determine efficacy.[56] Because LC is well tolerated, it may be beneficial to try.

Celiac Disease

Celiac disease can be considered a secondary cause of carnitine deficiency due to the characteristic malabsorption component.[57] In a small double-blind placebo-controlled study (n = 47), tests were performed on participants with newly diagnosed celiac disease before and after 6 months of either a gluten-free diet (placebo) or a gluten-free diet plus LC (1 g twice daily; treatment group). Serum carnitine levels were significantly improved from baseline in both groups after implementing a gluten-free diet. In the treatment group, serum levels were comparable to the non-celiac control group. The LC group had significant improvement in fatigue compared with the placebo group as measured by the visual analogue scale. The measurement of OCTN2 (cell membrane transport protein with strong specificity for carnitine) by intestinal biopsies increased by 83% in all celiac patients on a gluten-free diet; however, the amount was still significantly less than that in the non-celiac controls.[58]

Even with asymptomatic celiac disease, the individual breakdown of the serum carnitine esters may be significantly decreased, with LAC sometimes decreased 50% to 80%.[59]

Alzheimer's Disease, Senile Depression, and Age-Related Memory Defect

Much research has been conducted over the past 20 years with LAC in the treatment of Alzheimer's disease, senile depression, and age-related memory defects. As described previously, LAC is a

molecule composed of acetic acid and LC bound together. This reaction occurs naturally in the human brain; therefore, it is not exactly known how much greater an effect is noted with LAC versus LC or LPC. However, LAC is thought to be substantially more active than these other forms of carnitine in conditions involving the brain.[60,61]

LAC is structurally related to acetylcholine, a major neurotransmitter responsible for memory and proper brain function. In Alzheimer's disease, and to a lesser extent the normal aging human brain, there is a defect in the utilization of acetylcholine. The close structural similarity between LAC and acetylcholine led researchers to begin testing LAC in Alzheimer's disease. The results have been encouraging.

Researchers showed that LAC does mimic acetylcholine and is of benefit not only in patients with early-stage Alzheimer's disease, but also in elderly patients who are depressed or who have impaired memory.[61] It has also been shown to act as a powerful antioxidant within the brain cell by stabilizing cell membranes, improving energy production within the brain cell, and enhancing or mimicking the function of acetylcholine.[62] In 2008, a study done on rats revealed a significant increase in the brain tissue's kinesin light-chain 1 gene expression with LAC administration. When the kinesin light-chain 1 gene was downregulated, amyloid deposition was accelerated.[63]

The results in delaying the progression of Alzheimer's disease have been promising. The studies have been well controlled and extremely thorough.[60,64-66]

Memory impairment need not be as severe as in Alzheimer's disease for LAC to demonstrate benefit.[67-69] In one double-blind study of 236 elderly subjects with mild mental deterioration, as evident by detailed clinical assessment, the group receiving 1500 mg of LAC daily demonstrated significant improvement in mental function, particularly in memory and constructional thinking.[69]

Many of the elderly have depression not only as a result of experiencing a great deal of loss in their lives but also because of the biochemical changes in the brain associated with aging. LAC was shown to improve depression in elderly subjects in double-blind studies using assessment scales standard to scientific research of antidepressant drugs (e.g., Hamilton Depression Scale, Clinical Global Impression, Sandoz Clinical Assessment). The usual dosage was 500 mg three times daily. Elderly subjects with the highest depression scores were usually the ones who benefited the most from LAC.[70,71]

LAC also appears helpful in enhancing the effects of acetylcholinesterase inhibitors. In one open study of oral LAC (2 g/day for 3 months), 23 patients with mild Alzheimer's disease (unresponsive to donepezil or rivastigmine alone) showed an increased response rate with LAC treatment as an addition to the acetylcholinesterase inhibitor (38% vs 50%, respectively). The response rate was a measurement of cognitive function, functional status, and behavioral symptoms.[72] This additive effect may be useful whenever a patient does not respond to either treatment alone.

Down Syndrome

Given that both Down syndrome and Alzheimer's disease are characterized by a deficit in cholinergic transmission, a study was conducted to assess the effect of a 90-day treatment with LAC in individuals with Down syndrome.[73] Treated Down syndrome patients showed statistically significant improvements of visual memory and attention, both in absolute terms and in comparison with the other groups. No improvement was found in mentally deficient non–Down syndrome subjects, so the favorable effect of LAC appears to be specific for Down patients. An effective dosage is 20 mg of LAC per 2 lb of body weight. The action of LAC in these pathologies may be related to its direct and indirect cholinomimetic effect.

Kidney Disease and Hemodialysis

Carnitine supplementation is much indicated in kidney diseases because the kidney is a major site of carnitine synthesis. Carnitine supplementation can be renoprotective. In one study, high amounts of dietary fructose had adverse effects (higher cholesterol and TGs, lower levels of antioxidants and hypertrophy) on rat kidneys, and concurrent carnitine supplementation (300 mg/kg per day intraperitoneal) was able to prevent the damage either partially or fully.[74]

Damage to the kidney or reduced kidney function has a profound effect on carnitine metabolism. It is well established that patients undergoing hemodialysis have carnitine deficiency due to the loss of considerable quantities of carnitine during dialysis, as well as decreased synthesis. Serum carnitine levels drop nearly 80% during hemodialysis.[1-3] Supplementation with LC (15 mg/kg of intravenous LC at the end of each hemodialysis) helps maintain carnitine status.[75]

Carnitine-treated dialyzed patients have also shown additional benefits, including the following[76–80]:

- Disappearance of angina pectoris and arrhythmias occurring during dialysis
- Reduction of muscle symptoms, including muscle cramps
- Increased muscle mass
- Significant improvement in chronic anemia as demonstrated by increased hematocrit, hemoglobin, and red blood cell count
- Improved insulin sensitivity and reduced stress on pancreatic β cells
- Decreased serum C-reactive protein (29%) and serum interleukin-6 (61%) values

Since the early 1990s, a major advancement in the treatment of anemia associated with hemodialysis is recombinant human erythropoietin therapy. However, this therapy is expensive and has side effects. In one study, LC 1 g intravenously after every dialysis session for 6 months led to a significant reduction in dosage, as well as improvements in membrane fragility and endogenous erythropoietin secretion.[81] Given the high cost of erythropoietin, if doctors are unwilling to follow this procedure, insurance companies should get involved and force dialysis units to employ LC.

Diabetes

Patients with diabetes typically have deficient carnitine status. Studies revealed relationships between low carnitine status and increased plasma fatty acids, which negatively affect insulin action, so it has been recommended that free carnitine determinations should be made even if the patient has good metabolic control.[82] Given the risk of atherosclerotic cardiovascular disease and reduced kidney and liver function found in diabetic patients, it may simply be more rational to supplement all diabetic patients with LC.

Carnitine supplementation was shown to greatly improve peripheral vascular function, as well as nerve function, in patients with diabetes.[83-86] Carnitine supplementation might also affect blood lipids in patients with type 2 diabetes, particularly lipoprotein(a). In a study in type 2 diabetes, 2000 mg of carnitine daily lowered lipoprotein(a) levels by roughly 20% after 6 months,

whereas in another study of patients with markedly elevated lipoprotein(a) levels, even greater reductions were noted.[87,88]

Insulin sensitivity can be improved with LC supplementation as shown in a 10-day investigation of newly diabetic men and women. The study consisted of 2 groups: the control group, which was given a hypocaloric diet to follow (55% carbohydrates, 25% lipids, 20% proteins), and the LC group, which consumed the same hypocaloric diet in addition to 2 g of oral LC twice daily. The LC group had no adverse reactions with 4 g/day for 10 days. Both groups had an improvement in fasting and postprandial serum glucose and decreased body weight. Insulin sensitivity improved significantly in the LC group (plasma insulin: 7.0 to 4.5 μU/mL; homeostasis model assessment of insulin resistance (HOMA-IR): 1.9 to 1.1) compared with the control group, which had no change in plasma insulin or HOMA-IR levels.[89]

Liver Disease

Carnitine plays an extremely important role in the usage and metabolization of fatty acids in the liver. Some evidence indicates that carnitine deficiency within the liver promotes fatty infiltration (also known as steatosis or liver congestion).[90]

Alcohol ingestion is a common cause of fatty infiltration of the liver. It has been suggested that chronic alcohol consumption results in a functional deficiency of carnitine. Carnitine was shown to significantly inhibit and reverse alcohol-induced fatty liver disease.[91]

Because carnitine normally assists fatty acid transport and oxidation in the mitochondria, a high liver carnitine level may be necessary to handle the increased fatty acid load produced by alcohol consumption or other liver injury.[92] Supplemental carnitine was shown to reduce free fatty acid levels in patients with liver cirrhosis and to reduce serum TGs and liver enzyme levels while elevating HDL cholesterol in alcohol-induced fatty liver disease.[90-92]

Carnitine has also proven helpful with hepatitis C in relieving the tremendous fatigue associated with interferon-α treatment. In one study, 50 patients with chronic hepatitis treated with interferon-α (3 million international units three times weekly) were given either carnitine (2 g/day) or placebo for 6 months. Patients treated with interferon plus carnitine showed a marked and significant reduction of both mental and physical fatigue levels.[93]

Muscular Dystrophies

Patients with various muscular dystrophies have reduced levels of carnitine in their skeletal muscles.[94-96] Although levels are not as low as those observed in patients with classic myopathic carnitine deficiency, the low carnitine levels are thought to contribute to the muscular weakness experienced by these patients. Unfortunately, it is undetermined if supplemental carnitine would be of any value in patients with muscular dystrophy.

Low Sperm Counts and Decreased Sperm Motility

Carnitine concentrations are extremely high in the epididymis and spermatozoa, suggesting a role for carnitine in male reproductive function.[1-3] The epididymis derives the majority of its energy requirements from lipids, as do the spermatozoa during transport through the epididymis. After ejaculation, spermatocytes depend on glycolysis of glucose and fructose and on oxidation of lactate and pyruvate. Carnitine (in the form of acetylcarnitine, which is derived from pyruvate) serves as a readily available substrate. The motility of ejaculated sperm correlates positively with acetylcarnitine content.[1,3] In human sperm, high carnitine concentrations are critical to sperm energy metabolism. Several studies showed that the level of free carnitine in seminal fluid was strongly correlated with sperm count and motility.[97,98] The lower the carnitine content, the more likely it is that a man is infertile.

Given the known physiologic role of carnitine in sperm function and its link to male infertility, a study was designed to assess the therapeutic effect of carnitine in men with low sperm counts and depressed sperm motility.[99] One hundred men selected from infertility clinics participated in the "Italian Study Group on carnitine and male infertility." Each subject was given 3000 mg of LC daily for 4 months.

The study results indicated that LC increased sperm counts and sperm motility, in both a qualitative and a quantitative manner:

- The number of ejaculated sperm increased from 142 to 163 billion.
- The percentage of motile sperm increased from 26.9% to 37.7%.
- The percentage of sperm with rapid linear progression increased from 10.8% to 18%.
- The mean sperm velocity increased from 28.4% to 32.5%.

The results were even more impressive when only patients with the poorest sperm motility were studied. This subgroup saw even more significant gains on all parameters. For example, the percentage of motile sperm increased from 19.3% to 40.9%, and the percentage of sperm with rapid linear progression increased from 3.1% to 20.3%.

Chronic Obstructive Pulmonary Disease

Patients with chronic respiratory insufficiency are often severely affected by even the simplest physical activity. Treatment with LC (2 g three times daily) resulted in significant improvements in exercise capability.[100]

Acquired Immunodeficiency Syndrome

Several reports indicated that systemic carnitine deficiency might be a problem in patients with acquired immunodeficiency syndrome (AIDS). Reduced levels of serum carnitine are most often found in AIDS patients. However, more important is the carnitine depletion in peripheral blood mononuclear cells (PBMCs). Even AIDS patients with normal serum carnitine levels demonstrated low levels of carnitine in white blood cells.[101] Increasing the carnitine content of peripheral white blood cells strongly improved lymphocyte function, highlighting the importance of carnitine to immune function.

LC was shown to prevent the toxicity of the drug azidothymidine (AZT) on the mitochondria of the muscle cells.[102] AZT poisons the mitochondria of the muscle, leading to abnormal energy production within the muscle, which manifests clinically as muscle fatigue and pain. If LC can prevent this negative effect of AZT in human patients with AIDS, it would be a major improvement in the clinical management of AIDS.

Preliminary studies indicated that LC supplementation could improve immune function and reduce the level of human immunodeficiency virus-induced immune suppression. When AIDS patients treated with AZT were given 6 g/day of LC, it led to significant increased PBMC proliferation and reduced blood levels of TGs and circulating tumor necrosis factor.[103] Given the suspected systemic carnitine deficiency, along with the tremendous

safety of use, carnitine supplementation appears to be warranted in treating AIDS.

Inborn Errors of Amino Acid Metabolism

Use of carnitine to treat inborn errors of metabolism involving the urea acid cycle appears to be well justified. Preliminary studies showed impressive therapeutic response to LC supplementation in cases of glutaric aciduria, isovaleric acidemia, propionic acidemia, and methylmalonic aciduria.[104-107]

Protection Against Drug Toxicity

Carnitine was shown to protect against the damaging effects on the heart produced by the chemotherapy drug adriamycin.[108] Carnitine was also shown to improve the symptoms attributed to anticonvulsant medications, such as valproic acid (trade names: Depa, Depakene, Depakote, and Deproic) and carbamazepine (trade names: Epitol and Tegretol).[109,110] However, a subsequent study challenged the need to administer carnitine prophylactically, because no significant differences were noted in well-being scores between the carnitine group and the placebo group.[111]

Attention Deficit Hyperactivity Disorder

Preliminary evidence indicated that carnitine might be beneficial in attention deficit hyperactivity disorder (ADHD). In one double-blind, placebo-controlled, double-crossover trial, 13 of 24 boys receiving carnitine demonstrated a significant positive response in school and home behavior.[112] However, researchers found no significant improvement in ADHD symptoms with LAC (500 to 1500 mg twice a day, weight dependent) in a U.S. multicenter, placebo-controlled trial of children 5 to 12 years old.[113]

In a double-blind, placebo-controlled trial on fragile X syndrome boys ages 6 to 13 years with symptoms of ADHD, LAC (20 to 50 mg/kg per day) produced a reduction in hyperactivity and improved social behavior compared with placebo counterparts. These improvements were measured by Conners' Parent Global Index Scale and the Vineland Adaptive Behavior Scale.[114]

DOSAGE

The daily dosage of LC in all of its forms has typically been between 1500 and 4000 mg in divided doses. According to the Council for Responsible Nutrition, the "observed safety level" of LC for long-term supplementation is 2000 mg/day. However, it also stated that "much higher levels have been tested without adverse effects and may be safe."[115]

TOXICOLOGY

LC is extremely safe, with potential side effects being gastrointestinally related, such as nausea and diarrhea. Again, only LC should be used. The D form, the mirror image of the L form, has side effects, indicating that it interferes with the natural L form of carnitine. Patients undergoing hemodialysis given a mixture containing D,L-carnitine for 45 days experienced muscle pain and loss of muscle function, presumably due to lack of energy.[116] The symptoms disappeared on cessation of D,L-carnitine supplementation. Subsequent studies showed that D-carnitine produced an LC deficiency in cardiac and skeletal muscle.[117] Although LC resulted in significant improvement in exercise tolerance in angina patients, D,L-carnitine actually dangerously reduced exercise tolerance in these patients.[118]

DRUG INTERACTIONS

No adverse interactions between carnitine and any drug or nutrient are known. Carnitine and coenzyme Q_{10} appear to work synergistically when combined.[119] The same is true for pantethine.[120]

Perhaps the most important interaction is with choline. In young adult women, daily choline supplementation (20 mg/kg body weight) resulted in a 75% lower urinary carnitine excretion than in controls, without significantly altering plasma carnitine concentrations. Studies in guinea pigs demonstrated that choline supplementation resulted in a significantly lower urinary excretion and higher skeletal muscle carnitine concentrations. These studies indicated that choline supplementation resulted in a conservation of carnitine and might increase intracellular carnitine levels.[121]

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CHAPTER 75

Centella asiatica (Gotu Kola)

Michael T. Murray, ND

Centella asiatica (family: Umbelliferae or Apiaceae)
Synonym: Hydrocotyle asiatica L.
Common names: gotu kola, Indian pennywort, South African pennywort, mandukaparni

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GENERAL DESCRIPTION

Centella asiatica is an herbaceous perennial plant native to India, China, Indonesia, Australia, the South Pacific, Madagascar, and southern and middle Africa. This slender, creeping plant flourishes in and around water. Although it grows best in damp, swampy areas, centella is often observed growing along stone walls or other rocky, sunny areas at elevations of approximately 2000 feet in India and Sri Lanka.[1]

Depending on the environment, the form and shape of centella can change dramatically. In shallow water, centella forms floating leaves, whereas in dry locations, the leaves are small and thin, and numerous roots are formed.[1]

Typically, the constantly growing roots give rise to reddish stolons. The round-to-reniform, smooth-surfaced leaves, found on furrowed petioles, can reach a width of 1 inch and a length of 6 inches. The leaf margin may be smooth, crenate, or slightly lobed. Usually three to six red flowers arise in a sessile manner or on short pedicels in axillary umbels at the end of 0.08- to 0.3-inch long peduncles. The fruit, formed throughout the growing season, is approximately 0.2 inches long with seven to nine ribs and a curved, strongly thickened pericarp.[1]

Historically, the entire plant was used medicinally, with harvesting occurring any time during the year.[1]

CHEMICAL COMPOSITION

Although the primary pharmacologically active constituents of *C. asiatica* are known to be triterpenoid compounds,[2] its exact chemical profile is difficult to determine due to duplicate names and contradictory findings. In addition, centella samples from India, Sri Lanka, and Madagascar apparently do not contain the same constituents.[3,4] In India, three (and possibly more) chemically different subspecies of *C. asiatica* have been found.[5]

The concentration of triterpenes in centella can vary between 1.1% and 8%, with most samples yielding a concentration between 2.2% and 3.4%.[5] Figure 75-1 illustrates the major triterpenoid components of *C. asiatica*.

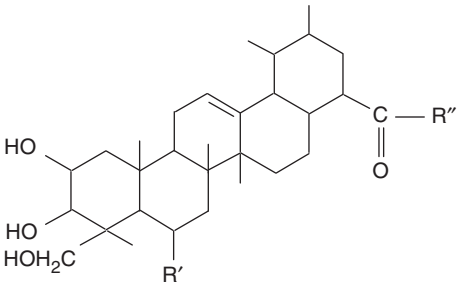
The Madagascar variety is most commonly used to produce standardized extracts. It yields triterpene concentrations of asiatic acid (29% to 30%), madecassic acid (29% to 30%), asiaticoside (40%), and madecassoside (1% to 2%).[2]

Centella also contains a green, volatile oil composed of an unidentified terpene acetate (which accounts for 36% of the total oil), camphor, cineole, and other essential oils. Centella oil also contains glycerides of fatty acids; various plant sterols such as campesterol, stigmasterol, and sitosterol; and various polyacetylene compounds.[1,2]

Other notable compounds isolated from centella include the flavonoids kaempferol, quercetin, and their glycosides; myoinositol; sugars; a bitter substance (vellarin); amino acids; and resins.[1,2]

HISTORY AND FOLK USE

Centella has been used as a medicine in India since prehistoric times and is thought to be identical to the plant mandukaparni, listed in the *Susruta Samhita* (one of the



Compound	R′	R″
Asiatic acid	H	OH
Madecassic acid	OH	OH
Asiaticoside	H	O-glucose-glucose-rhamnose
Madecassoside	OH	O-glucose-glucose-rhamnose

FIGURE 75-1 The triterpene compounds of *Centella asiatica*.

valuable treatises in Ayurveda). Centella was also used extensively as a medicine, both internally and externally, by the people of Java and other islands of Indonesia. The medicinal use of centella in India and Indonesia centered around its ability to heal wounds and relieve leprosy, although it was also considered to be one of the "Rasayana"(rejuvenator) herbal medicines and was used to enhance memory and prolong life.[1,2]

In the nineteenth century, centella and its extracts were incorporated into the Indian pharmacopeia, in which, in addition to being recommended for wound healing, it was recommended for the treatment of skin conditions such as leprosy, lupus, varicose ulcers, eczema, and psoriasis. It was also used to treat diarrhea, fever, amenorrhea, and diseases of the female genitourinary tract.[1]

In China, the leaves are prescribed for turbid leukorrhea and toxic fevers, whereas the shoots are used for boils and fevers. The plant is also used in the treatment of fractures, contusions, strains, and snakebites.[1] Centella was also used in China to delay senescence. One of the reported "miracle elixirs of life," centella's reputation as a promoter of longevity stems from the report of Chinese herbalist LiChing Yun, who reportedly lived 256 years. LiChing Yun's longevity was supposedly a result of his regular use of an herbal mixture chiefly composed of centella.[6,7]

C. asiatica was first accepted as a drug in France in the 1880s. Since then, centella extracts have been used to treat many of the previously listed conditions, along with those described later in the section on "Clinical Applications".

Centella, or gotu kola, has aroused much curiosity in American consumers. Many confuse gotu kola with kola nuts and assume gotu kola's rejuvenating activity is nothing more than the stimulant effect of caffeine. However, gotu kola is not related to the kola nut (*Cola nitida* or *Cola acuminata*), nor does it contain any caffeine.

PHARMACOLOGY

The majority of pharmacologic investigations on *C. asiatica* focused on the triterpene's wound healing and venotonic activity.[1,2] Although the exact mechanism of action has not yet been fully determined, a number of interesting observations have been made:

- In one of the early pharmacologic investigations of centella, Boiteau and Ratsimamanga[8] demonstrated that asiaticoside substantially hastened the healing of experimentally induced wounds. These authors concluded that asiaticoside worked selectively in stimulating the rapid and healthy activity of the reticuloendothelial system.

BOX 75-1 Physiologic Effects of *Centella asiatica* on Connective Tissue

- Stimulates hair and nail growth[1,8-10]
- Increases vascularization of connective tissue[1,8-10]
- Increases the formation of mucin and structural glycosaminoglycans, like hyaluronic acid and chondroitin sulfate[1,8-10,12]
- Increases the tensile integrity of the dermis[1,8-10]
- Increases keratinization of epidermis through stimulation of the stratum germinativum[1,10,12-14]
- Possesses a eutrophic or balancing effect on connective tissue[1,10]

- Additional studies on the mechanisms of action of centella's enhancing wound healing showed that asiaticoside, given orally, by intramuscular injection, or by implantation to rats, mice, guinea pigs, and rabbits, produced a wide range of effects, as shown in Box 75-1.
- The efficacy of centella in stimulating collagen synthesis was demonstrated in human tissue cultures.[13] Interestingly, this research also demonstrated an added benefit when vitamin C was added to the experimental cultures.
- The outcome of centella's complex actions is a balanced multiphasic effect on cells and tissues participating in the process of healing, particularly in connective tissues. Enhanced development of the normal connective tissue matrix is perhaps the prime therapeutic action of *C. asiatica.*
- Centella was shown to enhance the connective tissue structure of the perivascular sheath, reduce sclerosis, and improve blood flow through the affected veins.[1,10]

More recent investigations focused on some of centella's effects on the central nervous system, cognitive function, stress, and anxiety.[2] The major effects are an enhancement of cholinergic mechanisms, as well as a significant antioxidant action via increasing glutathione levels.[77,78] Presumably, these mechanisms are responsible for the improvements in mental function noted in both animal and clinical trials. Excellent results in improving cognitive function and memory were seen in animal models of Alzheimer's disease.[79]

Centella was also shown to possess other diverse pharmacologic effects in experimental models, including antiulcer, antimicrobial, immunomodulatory, and spasmolytic activity.[2]

CLINICAL APPLICATIONS

Obviously, from the brief description of centella's pharmacologic activity given earlier, it is a valuable agent for the healing of wounds and treatment of venous insufficiency, and may also prove useful in improving mental function. Table 75-1 provides an abridged list of documented clinical applications of *C. asiatica*. The more popular uses of this valuable plant are discussed as follows in alphabetical order.

Burns

The standardized extract from *C. asiatica* has been used effectively in the treatment of patients with second- and third-degree burns caused by boiling water, electrical current, or gas explosion. Daily local application or intramuscular injections of the extract, or both, resulted in excellent results when treatment began immediately after the accident. The extract prevented or limited the shrinking and swelling of the skin caused by skin infection, and it inhibited scar formation, increased healing, and decreased fibrosis.[18,19]

TABLE 75-1 **Clinical Applications of *Centella asiatica***

CONDITIONS	REFERENCES
Anal fissure	15
Bladder ulcer	16, 17
Burn	18, 19
Cellulite	20-25
Cirrhosis	26-28
Dermatitis	20, 29
Fibrocystic breast	30
Hemorrhoid	31
Keloid	32-34
Leprosy	11, 19, 35, 36
Lupus erythematosus	37
Mental retardation	38
Mycosis fungoides	37
Peptic ulcer	39, 40
Perineal lesion	41
Periodontal disease	42
Retinal detachment	43
Scleroderma	44-47
Skin ulcer	48-55
Surgical wound	8, 43, 49, 56-61
Tuberculosis	8, 62
Venous disorder	63-75, 82-86
Wound healing	8, 43, 49, 56-61

Cellulite and Striae Gravidarum

Standardized extracts of *C. asiatica* demonstrated good results in the treatment of cellulite and prevention of stretch marks during pregnancy in a number of clinical studies.[2,10,20-25] In the treatment of cellulite, Bourguignon[20] observed the action of the extract on several types of cellulite in 65 patients who underwent other therapies without success. Over a period of 3 months, good results were produced in 58% of the patients and satisfactory results in 20%. Other investigations showed a similar success rate (more than 80%).[21-24]

The effect of centella in the treatment of cellulite appears to be related to its ability to enhance connective tissue structure and reduce sclerosis by acting directly on fibroblasts.

Cirrhosis of the Liver

Darnis et al[26] reported on the therapeutic use of an extract of *C. asiatica* in alcohol-induced cirrhosis (six patients), cirrhosis of unknown etiology (two patients), and chronic hepatitis. In the cirrhosis patients, improvement in the histologic findings and regression of inflammatory infiltration were observed. No effect was observed in the patients with chronic hepatitis. Other reports supported the use of centella in fibrotic conditions of the liver.[27]

Keloids

The standardized extract of *C. asiatica* demonstrated impressive clinical results in the treatment of keloids and hypertrophic scars.[31-33] Its mechanism of action appears to be multifaceted, but is basically due to reducing the inflammatory phase of scar formation while simultaneously enhancing the maturation phase of scar formation.

Keloids and hypertrophic scars are characterized by a prolonged inflammatory phase that may go on for months or even years without progressing to the maturation phase. The inflammatory phase is characterized histologically by large numbers of immature, swollen collagen bundles intermingled with inflammatory debris, whereas the maturation phase is characterized by mature fibrocytes, normal collagen fibers, and few inflammatory cell elements.

In one study, 227 patients with keloids or hypertrophic scars were treated by oral administration with a standardized centella extract (effective dosage 60 to 90 mg). The centella extract was used alone in 139 patients (the curative group), and 88 used the extract along with surgical scar revision (preventive group).[31]

In the curative group, 116 patients (82%) were found to have benefited from the extract after 2 to 18 months, either by relief of their symptoms or by disappearance of the inflammatory phase. In a double-blind substudy of 46 of the 139 patients, 22 of 27 receiving the extract improved, whereas only 9 of 19 given a placebo improved.

In the preventive group, the centella extract also demonstrated a significant positive effect. The therapeutic course in these patients began a few weeks before surgery. If a positive response was observed, the patient was brought to surgery and kept on the centella extract for 3 months. (This method of preselection allowed the researchers to offer other forms of therapy to unresponsive patients.) Clinical improvement was observed in 72 of the 88 patients (79%).

Leprosy

Several investigators reported impressive clinical results using *C. asiatica* and its extracts (oral, intramuscular, or topical) in the treatment of leprosy in both uncontrolled and controlled studies.[11,19,34,35] The therapeutic response was comparable to that of dapsone, the standard allopathic drug used in the treatment of leprosy.

In addition to its wound-healing activity, it appears that oxyasiaticoside, an oxidized form of asiaticoside, inhibited the growth of the tubercle bacillus in vitro and in vivo by dissolving the waxy coating of *Mycobacterium leprae*.[8]

Improving Mental Function and Quality of Life

Although long used to promote improved mental function, the first clinical investigation involving centella significantly increased the mental abilities of 30 developmentally disabled children.[37] After a 12-week period, the children were more attentive and better able to concentrate on assigned tasks.

Centella may also help improve mental function and quality of life in the elderly based upon its historical use and the results from a double-blind study of 80 elderly subjects.[89] The subjects were randomly assigned to receive placebo or standardized extract of *C. asiatica* at doses of 250, 500, and 750 mg once daily for 90 days. The subjects were evaluated to establish baseline data of physical performance using the 30-second chair stand test, hand grip test, and 6-minute walk test. The health-related quality of life was assessed using a standard questionnaire. These assessments were repeated every month throughout the 3-month experimental period using the aforementioned parameters. Moreover, 1 month after the cessation of *C. asiatica* treatment, all subjects were also evaluated using these parameters again. The results showed that after 2 months of treatment, *C. asiatica* at doses of 500 and 750 mg/day increased lower extremity strength assessed via the 30-second chair stand test. In addition, the higher doses of *C. asiatica* improved the life satisfaction subscale within the physical function subscale. Therefore, the results from this study appear to support the traditional reputation of

C. asiatica on strength improvement, especially in the lower extremities of the elderly. *C. asiatica* also possesses the potential to be a natural resource for vigor and strength increase in healthy elderly persons.

Centella is also being investigated for its potential in Alzheimer's disease as an inhibitor of β-amyloid formation.[91,92]

Relieving Anxiety

Centella is viewed as an anxiolytic on the basis of in vitro models and emerging clinical evidence. An early study was conducted in humans to measure the effect of centella on reducing the acoustic startle response. After a single administration of centella, subjects experienced a significantly reduced acoustic startle response compared with the placebo—a clear indication of significant anti-anxiety action.[80] In an open clinical study in patients with generalized anxiety disorder, a 70% hydroethanolic extract of *C. asiatica* (500 mg/capsule, twice daily, after meal) was shown to significantly (P <0.01) attenuate anxiety-related disorders and reduce the stress phenomenon and depression.[90] The next needed step is a double-blind, placebo-controlled trial evaluation.

Scleroderma

The standardized extract of *C. asiatica* was tested in several trials in the treatment of scleroderma (including systemic sclerosis).[43-46] In addition to decreasing skin induration, patients noticed a lessening of arthralgia and improved finger motility. Presumably, the positive therapeutic response was a result of centella's eutrophic effect on connective tissue, thereby preventing the excessive collagen synthesis observed in scleroderma.

Venous and Microcirculatory Disorders

The most well-documented clinical utility for standardized extract of *C. asiatica* is in the treatment of chronic venous insufficiency, venous hypertension, and microcirculatory disorders.[62-74,81-87]

In the treatment of chronic venous insufficiency, significant improvement in symptomatology (e.g., feelings of heaviness in the lower legs, paresthesias, nocturnal cramps), physical findings (e.g., edema, telangiectasias, trophic ulcers, vein distensibility), and functional capacity (improved venous flow) was observed in approximately 80% of patients in the clinical trials.[1,10,62-74]

In studies of patients with venous hypertension (ambulatory venous pressure >42 mm Hg), detailed evaluations using laser Doppler flowmetry, transcutaneous oxygen, and carbon dioxide tension measurements, as well as determination of capillary filtration rate, ankle circumference, and ankle edema, along with detailed symptom evaluation, clearly demonstrated that centella extracts were clinically effective in dealing with this disorder.[81-83]

The standardized extract of *C. asiatica* also showed an ability to improve diabetic microangiopathy, it prevented the edema and microcirculation alterations seen during medium- to long-distance flights, and it normalized the echographic character of carotid arteries with significant plaque.[85-87]

Wound Healing

Standardized extracts of *C. asiatica* were shown in many clinical studies to greatly aid wound repair.* The types of wounds healed include the following:

- Surgical wounds, such as episiotomies and ear, nose, and throat surgeries
- Skin ulcers due to arterial or venous insufficiency
- Traumatic injuries to the skin
- Gangrene
- Skin grafts
- Schistosomiasis lesions
- Perineal lesions produced during childbirth

DOSAGE

The majority of clinical studies on *C. asiatica* used proprietary formulas available in Europe (e.g., Madecassol, TECA, Centelase). These standardized extracts contain asiaticoside (40%), asiatic acid (29% to 30%), madecassic acid (29% to 30%), and madecassoside (1% to 2%).

Because the concentration of triterpenes in centella varies between 1.1% and 8%, it is difficult to calculate an appropriate dosage when simply using the crude plant material. However, because most samples yield a concentration between 2.2% and 3.4%, approximately 2 to 4 g/day of crude plant material would contain an appropriate quantity of triterpenes, although it is unknown if this correlates with the clinical efficacy of the standardized extracts.

Daily dosages of the various forms of centella are as follows:

- Standardized extract (40% asiaticoside, 29% to 30% asiatic acid, 29% to 30% madecassic acid, and 1% to 2% madecassoside): 60 to 180 mg/day
- Crude dried plant leaves: 2 to 4 g/day
- Tincture (1:5): 10 to 20 mL/day
- Fluid extract (1:1): 2 to 4 mL/day

TOXICOLOGY

C. asiatica and its extracts are well tolerated, especially orally.[1,2] There is one report of three case histories of women (61, 52, and 49 years old) who developed jaundice after taking *C. asiatica* for 30, 20, and 60 days, respectively.[88] However, there was little description or validation of the product in question. Nonetheless, the hepatic lesions were quite significant on biopsy (granulomatous hepatitis with marked necrosis and apoptosis, chronic hepatitis with cirrhotic transformation and intense necroinflammatory activity, and granulomatous hepatitis). All patients improved with *C. asiatica* discontinuation and ursodeoxycholic acid 10 mg/kg per day.

The topical application of a salve containing centella was reported to cause contact dermatitis, although quite infrequently.[1]

Although the oral administration of asiaticoside at a dose of 1 g/kg body weight was not proved toxic in toxicology studies, the toxic dose of asiaticoside by intramuscular application to mice and rabbits was reported as 40 to 50 mg/kg body weight.[1]

Asiaticoside was implicated as a possible skin carcinogen when repeated applications were used in an experimental animal model.[76] Teratologic studies using the extract in rabbits proved negative.[31]

DRUG INTERACTIONS

There are no known drug interactions at this time.

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CHAPTER 76

Chinese Prepared Medicines

Mark Harrison Nolting, ND, LAc DiplAc, DNBAO

CHAPTER CONTENTS

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INTRODUCTION

This chapter focuses on one very popular and widely used segment of Chinese herbal medicine (CHM): the Chinese prepared medicines (CPMs). These preparations were referred to as patent medicines for hundreds of years, then more properly as prepared medicines, and as the regulatory oversight of such products evolved (at least in the United States and Europe), as herbal supplements. The landscape of these "over-the-counter" (OTC) medicines (or supplements) is changing due to regulation, economics (large global profits), adulterants, endangered and extinct species, as well as basic supply and demand. Chinese "patent" medicines were exported from China to the tune of $160 million U.S. dollars in 2009, a growing number partly due to the increased effort by the Chinese government to promote traditional Chinese medicine (TCM) globally.[1] There is a sense in China (among some in the government) that the Chinese have lost ground over the years in the trading of herbal medicines, as well as in the marketing of their traditional medicine. As the global herb market rapidly develops, China still finds itself accounting for only "three to five percent of the market."[2]

East Asian medicine (EAM) is defined as a "medical system that arose in East Asia deriving from the traditional concepts of Qi and Yin-Yang Theory. EAM has developed various interventions such as acupuncture and moxibustion, massage and physical manipulation, diet therapy, herbal medicine, meditation and exercise."[3,4] Although acupuncture is the global face of Chinese or EAM, CHM is the therapeutic core. The "new face" of EAM is the hope, among Asian governments, "that high-volume screening and rigorous clinical trials will unlock the secrets of ancient herbal remedies and that the results will pass muster with Western scientists."[5]

The CHM (Zhong-Yao in Chinese pin-yin) pharmacy has evolved over many hundreds of years, and is massive in scope and application, as the following "snapshot" of usage in China indicates:

Listed medicinal plants: 11,146
Animal drugs: 1581
Mineral drugs: 80
Processed remedies: 50
Clinically "proven" folk medicines: 5000
Traditional formulas: 84,464[6]

CHM is widely practiced across the world. In the United States, CHM is widely taught in most acupuncture school curriculums. However, for the most part, many students among the 60 accredited schools in the country concentrate on acupuncture with CHM as a secondary study,[7] but not all by any means. In California specifically, CHM is a major part of the study, licensure, and practice of acupuncturists.[8]

CPM is the OTC medicine of the traditional Chinese pharmacy, which includes thousands of various preparations of classic and conventional Chinese herbal formulas. Much of this medicine has been in constant use for hundreds, even thousands, of years, often maintaining original formulations.

One example is a frequently sold CPM called Jie Geng Wan (Platycodon Root Pills).[9] The source of this respiratory system medicine is the *Jing Kui Yao Lue Fang Lun* ("synopsis of the Golden Chamber"), written by Zhang Zhong Jing in 219 A.D.[10] Zhu, writing in his highly useful and informative *Clinical Handbook of Chinese Prepared Medicines*, explained the following:

The overtaxed Sung-dynasty merchant, as well as the frazzled Ming mother, appreciated the simple convenience and economy of a well-prepared herbal pill, powder, or syrup as much as does his or her modern counterpart.

Yan Bian Lian, the phrase commonly used when referring to these Zhong Cheng Yao ("Chinese Ready-to-be-Taken Medicines"), may best express fundamental reason-for-being of ready-to-take medicaments in any tradition: "Effectiveness, Convenience, Economy."[10]

Secret family (or company) recipes called patent medicines were first produced in the Song Dynasty (960 to 1234 AD) and were dispensed by government agencies, such as the Imperial Benevolent Prescriptions of the Taiping Period.[11] Few true patent medicines exist anymore in the Chinese pharmacy. Many of these medicines have become part of the public domain, making it more appropriate to refer to them collectively as CPMs.

"Keeping Chinese medicine formulae as trade secrets has led to some losses of knowledge and experience accumulated over generations. Drugs as well as dietary supplements are subject to regulations and disclosure requirements; it has become increasingly difficult for Chinese medicine (CM) practitioners to keep their prescriptions and treatment methods as trade secrets. In 1993, the Chinese government issued the Regulations on the Protection of Traditional Chinese Medicines which, to this date, provides administrative protection to certain prescriptions and manufacturing processes."[12]

Unfortunately, there are too many dubious CPMs in the worldwide market that have been adulterated in various ways, some containing Western prescriptive medicines, toxic elements, and endangered species often hidden from the unsuspecting consumer.[13] Consumers may find in their quest for safe, natural, and effective medicine serious, unexpected medical consequences. This is an issue that deserves scrutiny by consumers, practitioners, and regulators alike.

Typical images of the U.S. "Wild West" include cowboys, American Indians, farms, and the frontier life. However, there was another, lesser known presence in the West: the lives of Chinese immigrants. Many came to America seeking life on the "Gold Mountain," the view of America that had been created in China during the 1800s. According to Paul Buell, writing in his *Chinese Medicine on the Golden Mountain* book:

When in the mid-nineteenth century Chinese immigrants began to arrive in America, all kinds of traditional medical practitioners came with them… well-practiced Chinese medicine was often superior to contemporary western practice.[14]

The immigrants, mostly men, left their families to mine for gold. Many ended up working as miners or other laborers. They brought with them their traditional form of Chinese medicine and their traditional herbal medicine, which included various forms of CPM. CHM medicine is a highly evolved system of traditional medicine that draws from a materia medica composed of thousands of individual herbs (herbs in TCM include plant, mineral, and animal).[10,15] CPMs would generally be considered an adjunct to CHM in most practices, because they are convenient and good alternatives to the strong, bitter-tasting decoctions often used in practice. Many practitioners, particularly in the West, prefer to use granulated Chinese herbs or powdered herbs.

GLOBAL MARKET

The market for CPMs is huge. More than 5000 "licensed patent medicines" are estimated to exist in China.[16] According to China Today, exports of CHMs worldwide reached 20 billion dollars in 2002. About 5% of this amount was China's share, and prepared medicines comprised less than one third of this. In China, the famous Tong Ren Tang factory, which exports the most CPMs in China, earned 14.5 million dollars.[17]

Outside of the enormous "inside China market," the growing interest and use of natural medicine worldwide are driving the consumption of prepared medicines rapidly upward. As mentioned previously, this growth has sparked abuse and problems with product labeling and safety that the entire profession is working to counteract.

Although Chinese medicine and pharmacy began to spread outside of China's borders nearly 2000 years ago, it is only in the past 30 years that interest has grown in North America. Much of this is due to former President Richard Nixon's trip to the People's Republic of China in the early 1970s and subsequent reporters' visits and articles, especially those of James Reston of the *New York Times*. The growth of acupuncture and oriental medical practices, such as herbal medicine, in the United States has been steady since that time.

The traditional loose herb recipes used in CHM are cooked and made into medicinal soups, which are often bitter and difficult for the American palate. The Chinese solution to this dilemma was to increase the use of raw licorice in the formula and to offer sugar wafers to the patient to help offset the bitter taste, although most Chinese welcome a bitter taste as a normal part of Asian cuisine. The prepared medicines offer an alternative to traditional preparations. A number of companies, particularly in Taiwan and California, have begun to popularize the manufacture and sale of powder and tincture formulas in the single herb form to help "bridge" the traditional form and the prepared, more palatable, forms of medicine. This allows the practitioner to still use the traditional approach, that of mixing and adjusting the formulas tailored to the patient's individual diagnosis. Prepared formulas are fixed, of course, and do not allow any adjustments in the ingredients.

Before the mid-1970s, the U.S. Food and Drug Administration (FDA) restricted the import and sale of traditional medicines by ethnic groups. New legislation and court rulings since then have lifted these restrictions, which, coupled with the explosion of acupuncture on the American health scene, has opened the door to the spread of prepared medicines.[16]

Now, due to this rapid growth in the sale and use of prepared medicines, problems with adulterants and false labeling are increasing, especially in California, where a multiagency herbal medicine task force involving numerous California and federal government agencies was formed in response. The California Department of Health Services documents state that "most imported Asian patent medicines do not fully comply with California laws."[18] Although some of these violations are potentially dangerous and may involve toxic ingredients and the inclusion of endangered species, many involve labeling issues, which can often be sorted out by revising the labeling at the company of origin.

FORMULATIONS AND PREPARATIONS

CPMs are prepared in numerous different forms. As far back as 200 BC, Chinese pharmaceuticals had a surprising level of sophistication. Pills were bound together using a wide variety of animal and human substances.[18] Box 76-1 lists 15 of the most common dose forms of CPM. In China, prepared medicines are produced at factories located throughout the country. Reputation and awards are

BOX 76-1 Common Dose Forms of Chinese Prepared Medicines

- Pills (honey, water, glue, extract)
- Paste
- Concentrated
- Powders
- Granules
- Pellet
- Tablets
- Syrup
- Mixtures
- Dripping pills
- Capsule
- Hard
- Soft extract
- Enteric
- Wine
- Tinctures
- Liquid extracts
- Plasters (adhesive)
- Ointments
- Medicinal distillates
- Tea
- Injections
- Suppositories
- Lozenges

Modified from the Pharmacopeia Commission of PRC. Pharmacopeia of the People's Republic of China (English edition 1997), vol 1. Beijing: Chemical Industry Press, 1997:A3-A14; Chen JK, Chen TT. Chinese Herbal Formulas and Applications. Pharmacological Effects & Clinical Research. 2009 City of Industry, CA: Art of Medicine Press, Inc., 2009:16-18.

important to these mainland Chinese operations. Factories such as the Chongqing Tong Jun Ge Medicine Works in the Sichuan province, built in 1908, are proud of their products. This factory produces more than 200 medicines in 14 therapeutic categories.[19]

Roadside and rooftop billboards across China extol the benefits of "famous" CPMs, as well as displaying the awards various formulas have received over the years. Longevity is an important virtue attributed to specific herbs and formulas in Asian medicine. Ginseng, in all its many species and preparations, is the most revered and used herb in China. The pursuit of longevity is central to its popularity, aside from the fact that it is a highly useful and effective herb. An interesting side note is that the American species of ginseng, *Panax quinquefolius*, is exported in great quantities to China, only to be repackaged and exported back to Western markets. American ginseng is considered a milder, more "supportive" ginseng in action, making it more suitable for the elderly and weak.

Ginsengs are part of the tonic herb family, a major classification that does not exist in the conventional Western pharmacy. The most famous factory for herbal medicine products in China is the Tong Ren Tang Pharmacy in Beijing. The Tong Ren Tang Pharmacy, first established in 1669, has been operated by the same family for more than 317 years. Prepared medicines produced in this factory have generally been held in the highest reputation in China, where the factory has supplied medicines to Chinese royalty over several centuries. The drug control acts implemented by the Chinese government in the 1970s and 1980s have helped to further guarantee quality control of prepared medicines in China, and companies such as the Tong Ren Tang pride themselves on following these standards.[10]



ADULTERANTS, ENDANGERED SPECIES, AND STANDARDS

The issue of adulterants and endangered species has increasingly threatened the reputation of CPM as safe and effective. The massive historical and growing contemporary usage of these products in Asia and the world often obscures these quality and ethical realities. The use of tiger bone, rhino horn, bear gallbladder, and seahorse are realities in a system of medicine that spans the centuries. Raising the consciousness of practitioners who grew up in that culture is the task of education to reshape that culture. Trafficking of illegal products is tied to big money, and separation between this practice and the legitimate market can be challenging. Western pharmaceuticals find their way into "herbal" products as "secret" ingredients that boost the effectiveness of the actions. Government control in the countries of origin is one thing, but controlling this globally, given widespread corruption and conflicting priorities, is a difficult task. The fundamental question remains: "Is the product purchased today in the Asian supermarket or local health food store free of adulterants and endangered species?"

Many prepared medicines made outside mainland China lack the same quality controls as the factories within China. Factories and sellers within China can be visited and found to have good-quality products determined to be safe and free of adulterants. In 1975, an herbal-based preparation called Toukuwan was manufactured in Hong Kong by the Nan-Lien Pharmaceutical Company and widely promoted in the United States as a treatment for rheumatism and arthritis. The FDA banned the importation of Toukuwan after it discovered four drugs, including valium, in the Chuifong preparation. Various prescription drugs have also been discovered in other prepared medicines. The *Journal of the American Medical Association* also reported four cases of agranulocytosis caused by prepared medicines in 1975, before the FDA ban. The Chuifong product has continued to appear under various names such as "miracle herb" since 1975.[20,21] Caution must be used when purchasing and prescribing prepared herbal medicines, and we recommend using only well-known and reputable manufacturers.

If consumers are in doubt, we recommend using products produced at American or Australian companies, which typically are subject to far more quality-control standards than those in Asia, and always consulting practitioners who research the origins of the various products they use and recommend.

In May 1994, Traffic USA and the World Wildlife Fund published "Prescription for Extinction: Endangered Species and Patented Oriental Medicines in Trade."[22] This report gave insight into the vast number of endangered species being used in natural medicine. The report indicated which products and traditional formulas contained endangered or threatened species, according to Appendices I, II, and III of the Convention on International Trade in Endangered Species (CITES) of Wild Fauna and Flora.[23]

Lu,[24] writing in the *China Daily*, described new European regulations in 2004 regarding the importation of CHMs into the European market. He stated the following:

> *The directive regulates that manufacturers who export herbal medicines to the EU market must get the union's GMP (Good Manufacturing Product) certificate, products quality must comply with EU pharmacopoeia, and importers should have import licenses.… But generally speaking, the directive, which for the first time grants TCM legal status as medicines, will benefit Chinese medicine makers to explore the European market in the future. Currently, most of the TCM products exported to the EU market are under the category of food, native produce, health products, or pharmaceutical ingredients, instead of medicine. Industry experts said that when one TCM product is registered as traditional herbal medicine in the EU, it indicates great market potentials. First, the market value of TCM will be greatly lifted compared to being sold as food or pharmaceutical ingredients. Second, the legal status as medicine would allow TCM to join EU countries' hospitalization insurance system. And EU's recognition of TCM will help reduce possible unfair treatment of*

Chinese medicines from other countries. Meanwhile, domestic makers should strengthen research and development, dismiss some ingredients which are unacceptable to western people, and develop products to cater for the huge European market.

Hong Kong, long a stronghold of TCM despite a restrictive anti-TCM atmosphere under British rule, has upgraded its standards for Chinese herbs. The Chinese Medicine Council of Hong Kong was formed in 1999 to protect public health and consumers' rights and to ensure the professional standard of Chinese medicine practitioners and the trade of Chinese medicines. On the council's website, Shaw[16,25] discussed the trailblazing approach Australia took to create standards for the practice and sale of CHMs:

In that country (Australia), products were either "listed" or "registered." Listed products were of certified quality and were required to have supporting evidence of safety from the literature. No claims regarding efficacy could be made. Registered products equated to those with a license in the UK.

Shaw also referred to the 1996 report "Towards a Safer Choice," which resulted from a review of the practice of TCM in Australia. The report concluded that regulation of CHMs and acupuncture practitioners was necessary and led to the Chinese Medicine Regulation Act of 1999, which set out statutory regulation for such practitioners in the state of Victoria. The intention was that regulation would eventually be brought in on a national scale. Shaw emphasized that this was being done for the benefit of the public, not practitioners.

Summing up, Shaw listed five elements for improving the safety of CHMs:

- Research into efficacy and safety
- Training of practitioners
- Quality herbs
- Adverse effect monitoring
- Appropriate regulation

Also on the council's website is a valuable list of safety concerns raised by Anderson[20] of the Hong Kong Medicines Control Agency, listed as follows:

- Lack of adequate authentication
- Intentional or accidental substitution
- Use of toxic substances and heavy metals (e.g., arsenic disulphide)
- Use of toxic animal materials (e.g., Bufo secretions)
- Use of synthetic drugs (e.g., corticosteroids, nonsteroidal anti-inflammatory drugs)
- Inadequate or inaccurate labeling

DISPENSARY GUIDE

CPM serves a number of different therapeutic purposes in and out of the practitioner's office. First and foremost, it is best prescribed within the principles of prescribing of traditional CHMs. For example, clearing heat or dispelling dampness formulas require some understanding of the philosophy underlying these principles. If CHMs are just prescribed cookbook style, then individual patient reactions cannot be understood and tracked properly, and the full effect of the formulas will not be appreciated.

Secondly, CPM can augment and support traditional decoction style prescribing. Thirdly, CPM is most valuable in acute prescribing and generally lends itself to OTC use. OTC use is best with input from trained Chinese medicine practitioners. In the case of Yin Chiao, described in the following, this widely used effective formula is most often prescribed at the onset of colds. Then there is the formula called Chuan Xin Lian (Andrographis anti-inflammatory tablets), which has tremendous effectiveness in inhibiting common bacterial infections, almost an "herbal antibiotic."[10] A final example of useful CPM in acute prescribing is the famous formula called Yunnan Baiyao. This is the most important CPM one should have at hand (according to general usage), at home and on the road. It is an emergency medicine stated as useful in all cases of injury. The signature of Yunnan Baiyao as traditionally dispensed involves little bottles of yellow powder with a tiny red "emergency" pill that is said to help revive critically injured individuals. Yang and Liang[26] described it as follows:

Yunnan Baiyao, literally meaning Yunnan White medicine, smells like a walk through an exotic forest. That's a clue to its composition: a dozen or so herbs from the southwestern flora-abundant province of Yunnan—but exactly which herbs remains a state secret. Successfully used for more than 80 years, Yunnan Baiyao, now available in several forms, is a veritable cure all and an essential, trusty family medicine in China.

Due to the questionable standards of prepared medicines manufactured in Asia and generally outside China, it is suggested that practitioners scrutinize the labels of products from unknown sources or avoid them all together. With correct labeling, ingredients of prepared medicines should be obvious to anyone who can read Latin or Chinese herbal names.

In recent years, prepared medicine companies have become well established in the United States. Several high-quality manufacturers are now producing more suitable formulas. These tinctures, powders, and capsules are usually based on well documented classic formulas.

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CHAPTER 77

Cimicifuga racemosa (Black Cohosh)

Michael T. Murray, ND

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Cimicifuga racemosa (family: Ranunculaceae)
Common names: black cohosh, macrotys, rattleweed, black snake root

GENERAL DESCRIPTION

Cimicifuga racemosa is a perennial herb native to North America that grows on hillsides and in woods at higher elevations from Maine and Ontario to Wisconsin, Georgia, and Missouri. The large, creeping rhizome produces stems up to 9 feet high. The ovate or oblong leaflets are 1 to 6 inches long and 4 inches wide, whereas the smaller leaflets are ternate, then pinnate, and sometimes even further divided. Small, white, fetid flowers grow in long racemes from May to August. The rhizome is the portion of the plant used for medicinal purposes.

CHEMICAL COMPOSITION

C. racemosa contains at least three important natural product groups that contribute to its pharmacology: cycloartane triterpene glycosides, such as actein and 26-deoxyactein; phenylpropanoid esters; and phenolic compounds, such as caffeic acid derivatives, including ferulic acid and isoferulic acid (Figures 77-1 and 77-2).[1-3] Early reports showed that it also contained the phytoestrogen flavonoid formononetin, but more recent analysis demonstrated that this compound was not contained in either the crude herb or standardized extracts. At this point, despite extensive chemical, biological, and clinical studies, neither the active constituents nor the exact mode of action of black cohosh have been determined.[4] Currently, the standardization of cimicifuga preparations is based on the content of triterpene glycosides, calculated as 26-deoxyactein. Other important triterpene glycosides include actein and cimicifugoside (aglycone cimegenol).

HISTORY AND FOLK USE

The generic name cimicifuga comes from the Latin *cimex*, a bug, and *fugo*, to drive away, alluding to its use as a vermifuge. Native Americans used cimicifuga rhizomes for the relief of pain during menses and childbirth, as well as snakebite. The rhizome of *C. racemosa* was listed in the National Formulary from 1936 to 1950 and in the U.S. Pharmacopeia from 1820 to 1936. Eclectic physicians in the early part of the twentieth century used cimicifuga in gynecologic disorders, as well as rheumatoid and myalgic pain.

Although use in the United States declined dramatically from 1950 to 1995, cimicifuga preparations were used extensively in Europe during this same period, primarily as a natural alternative to hormone replacement therapy (HRT) during menopause. This popularity was based on substantial empiric and clinical evidence.

PHARMACOLOGY

The primary pharmacologic effects of cimicifuga appear to revolve around its ability to impact endocrine regulatory mechanisms.[5-8] In the past, this activity was thought to be related to various phytoestrogenic components of cimicifuga, with formononetin perhaps being the most significant.[9] However, this line of reasoning has been questioned by the lack of formononetin in clinically studied cimicifuga

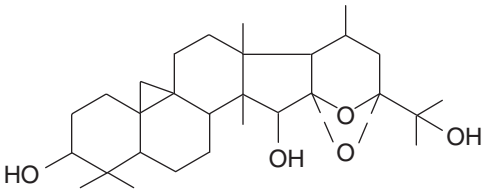


FIGURE 77-1 Cimigenol.

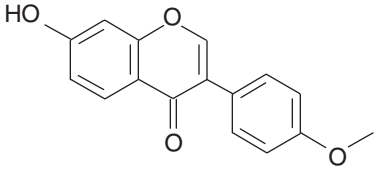


FIGURE 77-2 Formononetin.

extracts, as well as equivocal reports on phytoestrogen activity. Current thinking is that certain cimicifuga components exert selective estrogen receptor modulator (SERM) activity with no action in the uterus, but that beneficial effects do occur in the hypothalamo/pituitary unit and in the bone.[5,10,11]

Cimicifuga's primary effect on endocrine regulatory mechanisms appears to be the result of complex synergistic actions of its key ingredients. Evidence suggests that these compounds act on both the hypothalamus and vasomotor centers to produce significant clinical benefits in menopause. For example, one study to determine the endocrinologic actions of cimicifuga extract involved treating 110 women with either cimicifuga extract (supplying a total daily dose of 8 mg of 27-deoxyactein) or placebo.[8] After 2 months of treatment, luteinizing hormone (LH) decreased by 20% in the cimicifuga group compared with the placebo group. Unlike estrogens, cimicifuga does not affect the release of prolactin and follicle-stimulating hormone. Researchers then divided the extract into three distinct types of active compounds on the basis of their ability to reduce LH secretion in ovariectomized rats and to compete in vitro with 17-β-estradiol for estrogen receptor binding sites, as follows:

- Constituents that did not bind to estrogen receptors but did suppress LH secretion
- Constituents able to bind to estrogen receptor sites and to inhibit LH secretion
- Compounds that did bind to estrogen receptors but did not inhibit LH secretion

The authors concluded that "the LH suppressive effect of *C. racemosa* extracts observed in menopausal women and ovariectomized rats is caused by at least three different synergistically acting compounds."

Apparently, one of cimicifuga's key pharmacologic effects is inhibition of the secretion of LH by the pituitary gland. This effect is accomplished equally by components that do and do not bind to estrogen receptors. If cimicifuga was simply mimicking the effects of estrogen, it would certainly alter the secretion of other pituitary hormones just like estrogen, but it does not. It appears that enhancement of dopaminergic activity is the responsible mechanism for some of these central effects on menopausal symptoms.[5,12]

Cimicifuga extracts also appear to exert some beneficial effects on preventing bone loss. In an experiment carried out on ovariectomized rats, cimicifuga extract increased the expression of collagen I and osteocalcin. Similarly, other animal studies demonstrated that cimicifuga extract significantly reduced the urinary parameters of increased bone metabolism and bone loss. The effects in these animal models were similar to raloxifene, a well-confirmed SERM.

TABLE 77-1 **Cimicifuga in the Treatment of Menopause**

SYMPTOM	PERCENTAGE NO LONGER PRESENT	PERCENTAGE IMPROVED	TOTAL PERCENTAGE IMPROVED
Hot flashes	43.3	43.3	86.6
Profuse perspiration	49.9	38.6	88.5
Headache	45.7	36.2	81.9
Vertigo	51.6	35.2	86.8
Heart palpitation	54.6	35.2	90.4
Ringing in the ears	54.8	38.1	92.9
Nervousness/ irritability	42.4	43.2	85.6
Sleep disturbances	46.1	30.7	76.8
Depressive moods	46.0	36.5	82.5

Importantly, although early studies reported a direct estrogenic effect with cimicifuga, the current perspective is that ethanol and isopropanol extracts of black cohosh do not contain formononetin or other estrogenic flavonoids and, therefore, do not bind to the estrogen receptor, upregulate estrogen-dependent genes, or stimulate the growth of estrogen-dependent tumors in in vitro and animal models.[5,13,14]

CLINICAL APPLICATIONS

C. racemosa extracts are by far the most widely used and thoroughly studied natural alternatives to HRT in menopause. Clinical studies showed that cimicifuga extracts relieved not only hot flashes but also depression and vaginal atrophy.[5,15-23]

Although evidence indicates that cimicifuga may provide benefit in other gynecologic complaints such as premenstrual syndrome, amenorrhea (both primary and secondary), dysmenorrhea, polymenorrhea, uterine fibroids, and fibrocystic breast disease, its primary clinical application is menopause.[22-26]

Menopause

In one of the first clinical studies, a large open study involving 131 doctors and 629 female patients, cimicifuga extract (two tablets twice a day, providing a daily dose of 4 mg 27-deoxyactein) produced clear improvement of menopausal symptoms in more than 80% of patients within 6 to 8 weeks.[18] As shown in Table 77-1, both physical and psychological symptoms improved.

Most patients reported noticeable benefits within 4 weeks after the onset of cimicifuga therapy. After 6 to 8 weeks, complete resolution of symptoms was achieved in a large percentage of patients. Cimicifuga was well tolerated, since there was no discontinuation of therapy, and only 7% of patients reported mild transitory stomach complaints.

In one of the first double-blind studies, 60 patients were given cimicifuga extract (two tablets twice a day providing a daily dose of 4 mg 27-deoxyactein), conjugated estrogens (0.625 mg/day), or diazepam (2 mg/day) for 12 weeks.[19] Results from standard indexes of menopausal symptoms indicated a clear advantage of cimicifuga extract over both drugs. Cimicifuga's effect on relieving depressive mood and anxiety associated with menopause was far superior to either diazepam or conjugated estrogens, as shown in Table 77-2.

One of the most used assessments in clinical studies in menopause is the Kupperman Menopausal Index. This quantitative assessment

TABLE 77-2 **Effect on Kupperman Menopausal Index of Cimicifuga Compared with Conjugated Estrogens and Diazepam**

TREATMENT GROUP	BEGINNING	AT 12 WK
Cimicifuga	35	14
Conjugated estrogens	35	16
Diazepam	35	20

of menopausal symptoms is achieved by grading severity: severe = 3, moderate = 2, mild = 1, not present = 0. The symptoms assessed are the following:

- Hot flashes
- Depressive moods
- Profuse perspiration
- Feelings of vertigo
- Sleep disturbances
- Loss of concentration
- Headache
- Joint pain
- Nervousness/irritability
- Heart palpitation

The results of the Kupperman Menopausal Index from this trial clearly demonstrated cimicifuga extract's superiority over conjugated estrogens and diazepam, especially when safety and side effects were taken into consideration.

In another early double-blind study, 80 patients were given cimicifuga extract (two tablets twice a day, providing a daily dose of 4 mg 27-deoxyactein), conjugated estrogens (0.625 mg/day), or placebo for 12 weeks.[20] Cimicifuga produced better results in the Kupperman Menopausal Index, the Hamilton anxiety test, and the vaginal lining than estrogens or placebo. The number of hot flashes experienced each day dropped from an average of five to less than one in the cimicifuga group. In comparison, the estrogen group only dropped from 5 to 3.5. Even more impressive was the effect of cimicifuga on the vaginal lining. Although both conjugated estrogens and the placebo produced little effect, a dramatic increase in the number of superficial cells was noted in the cimicifuga group.

In a double-blind study of 110 women, cimicifuga extract (two tablets twice a day, providing a daily dose of 4 mg 27-deoxyactein) was shown to exert significant improvements in menopausal symptoms.[8] In addition to providing relief of hot flashes, cimicifuga once again demonstrated impressive results on the vaginal lining, as confirmed by vaginal smear.

In one study, 60 women less than 40 years old, who had hysterectomies leaving at least one intact ovary, received one of the following: cimicifuga extract (two tablets twice a day, providing a daily dose of 4 mg 27-deoxyactein), estriol (1 mg/day), conjugated estrogens (1.25 mg/day), or estrogen–progestin combination (Trisequens, one tablet a day).[21] Although the hormone therapies produced better results as determined by a modified Kupperman's Menopausal Index, cimicifuga still displayed significant effects in relieving the symptoms of "surgical menopause." These results indicated that cimicifuga could be a suitable alternative to estrogens in women having partial, and possibly even complete, hysterectomies.

In perhaps the most detailed double-blind study to date, cimicifuga extract was evaluated for its effect on menopausal symptoms, bone metabolism, and on the endometrium compared with those of conjugated estrogen and placebo.[22] The 62 postmenopausal women were treated either with black cohosh extract (40 mg/day), 0.6 mg conjugated estrogen, or matching placebo for 3 months. Results indicated that the black cohosh extract was equipotent to conjugated estrogen and superior to placebo in reducing menopausal complaints. Both black cohosh extract and conjugated estrogen produced beneficial effects on bone metabolism, but the black cohosh extract had no effect on endometrial thickness, which was significantly increased by conjugated estrogen. Vaginal superficial cells were increased with cimicifuga and conjugated estrogen treatment. These results seemed to confirm that cimicifuga extracts contain substances with SERM activity (i.e., with desired effects in the brain/hypothalamus, bone, and vagina, but without exerting uterotropic effects).

Women being treated with tamoxifen most often experience symptoms similar to menopause. To examine the effect of cimicifuga extract on hot flashes caused by tamoxifen adjuvant therapy in young premenopausal breast cancer survivors, 136 breast cancer survivors (ages 35 to 52 years) who had been treated with segmental or total mastectomy, radiation therapy, and adjuvant chemotherapy were randomly assigned to receive tamoxifen 20 mg/day orally or tamoxifen plus black cohosh extract (20 mg/day).[23] The duration of treatment was 5 years for tamoxifen, according to international standards for adjuvant therapies, and 12 months for the black cohosh extract. Follow-up included clinical assessment every 2 months; the primary goal was to record the number and intensity of hot flashes. Results indicated that almost half of the patients getting the black cohosh extract were free of hot flashes. Only 24.4% of patients taking black cohosh extract experienced severe hot flashes compared with 73.9% of the women taking tamoxifen alone.

In one of the largest studies, 629 women with menopausal complaints were seen by 131 general practitioners.[27] In this study, as early as 4 weeks after beginning the therapy, a clear improvement in the menopausal ailments was seen in approximately 80% of the women. After 6 to 8 weeks, complete disappearance of symptoms occurred in approximately 50%.

A 2007 randomized, double-blind, controlled 3-month study was done in China, enrolling 244 menopausal women.[28] Women were assigned to either an isopropanolic extract of black cohosh containing 40 mg/day or 2.5 mg/day tibolone. There was a significant trend (57.08%) that women given Remifemin responded better than they did to tibolone in terms of efficacy–risk balance, and black cohosh was clearly superior to tibolone if the safety profile for abnormal bleeding, endometrial thickening, breast pain, vaginal discharge, and edema was followed. Recent studies indicated that black cohosh might produce beneficial effects on bone metabolism by stimulating osteoblasts in addition to a weak effect on maturation of vaginal cells.[29,30]

Five recent studies showed no effect on menopausal symptoms with black cohosh use, including no effect on cognitive function.[31-35] Possible reasons included in some of the studies were the use of an alcoholic extract versus an isopropanolic extract, or the confounding health issues of the women studied.

Recent studies also used the combination trial of black cohosh and St. John's wort. In one study, the mean Menopause Rating Scale score decreased 50% in the treatment group and 19.6% in the placebo group.[36] The Hamilton Depression Rating Scale score decreased 41.8% in the treatment group and 12.7% in the placebo group. In both measures, the results in the group using the St. John's wort and black cohosh were significantly superior to that of the placebo group.

Another black cohosh/St. John's wort trial was carried out in perimenopausal or postmenopausal Korean women.[37] Healthy perimenopausal women with typical climacteric symptoms and

not on HRT for at least the previous 3 months were given a 264 mg tablet containing 0.364 mL of extract from black cohosh equivalent to 1 mg terpene glycosides and 84 mg of St. John's wort extract with 0.25 mg hypericin. Forty-two women in the treatment group and 35 women in the placebo group completed the study. Mean Kupperman index scores at 4 and 12 weeks were significantly lower in the treatment group ($P \leq 0.002$). At the end of the study, the average decrease in the Kupperman Index was 20 points in the treatment group and only 8.2 points in the placebo group ($P < 0.001$). Vaginal dryness and low libido were two symptoms that did not improve, but the average hot flash scores was significantly lower in the black cohosh/St. John's wort group.

Despite some studies demonstrating no benefit of black cohosh, the collective findings in black cohosh studies and long-term clinical anecdotal evidence on black cohosh indicate that it is most effective for menopause symptoms of day time or night time hot flashes, mood swings, sleep disorders, and body aches.

DOSAGE

The dosage of cimicifuga is based on its content of 27-deoxyactein, which serves as an important biochemical marker to indicate therapeutic effect. The dose of the cimicifuga extract used in the majority of clinical studies was 40 mg of black cohosh isopropanolic extract supplying 2 mg of 27-deoxyacteine twice daily. Approximate dosage recommendations using other (nonstandardized) forms of *C. racemosa* are:

- Powdered rhizome: 1 to 2 g
- Tincture (1:5): 4 to 6 mL
- Fluid extract (1:1): 3 to 4 mL (1 tsp)
- Solid (dry powdered) extract (4:1): 250 to 500 mg

The German Commission E recommended that treatment with cimicifuga be limited to 6 months (which is also the standard recommendation for HRT); however, this recommendation was made before detailed toxicology studies, discussed in the following section, "Toxicology." Based on currently available data, cimicifuga is appropriate for long-term continued use.

TOXICOLOGY

The standardized extract of *C. racemosa* providing 1 mg of 27-deoxyactein in 40 mg of extract per tablet has been used in Germany since 1956 and has a remarkable safety record. A comprehensive review including preclinical and clinical research in estrogen-sensitive populations, including women at risk for breast cancer and breast cancer survivors, as well as human cell lines most relevant to breast cancer, confirmed this safety record. No serious side effects have ever been reported.[38] Cimicifuga offers a suitable natural alternative to HRT for menopause, especially when HRT is contraindicated (e.g., in women with a history of cancer, unexplained uterine bleeding, liver and gall bladder disease, pancreatitis, endometriosis, uterine fibroids, and fibrocystic breast disease).

Because cimicifuga extract shows some, albeit weak, estrogenic activity, researchers sought to determine Remifemin's effect on an established breast tumor cell line whose growth in vitro depends on the presence of estrogens. The results from these experiments showed no stimulatory effects, but rather inhibitory effects as well as an ability to promote apoptosis in these cells.[39,40] Furthermore, combining black cohosh with tamoxifen was shown to potentiate the inhibitory effects of tamoxifen.

Detailed toxicology studies were also performed on black cohosh extracts. No teratogenic, mutagenic, or carcinogenic side effects were noted. The no-effect dosage in a 6-month long-term toxicity study in rats was at 1800 mg/kg body weight—roughly 90 times the therapeutic dose.[41] A 6-month toxicologic study in rats is comparable to an unlimited treatment time in humans.

Lastly, in 2008, the Expert Committee of the U.S. Pharmacopeia's Council of Experts did an updated review of safety information for black cohosh.[42] Regulatory agencies in Australia, Canada, and Europe released statements and guidelines regarding the potential association between black cohosh products and hepatotoxicity. The committee analyzed human clinical case reports, adverse event reports, animal and toxicologic data, historical uses, and regulatory status. Thirty reports on the use of black cohosh and possible liver damage were analyzed. All the reports of liver damage were considered to be possibly caused by black cohosh, and none were probable or certain. None of the animal toxicologic or pharmacokinetic information revealed adverse information about black cohosh. The committee determined that the link between black cohosh and reports of liver damage was weak and "not of certain causality." They cited incomplete case information, unknown products, confounding variables (e.g., alcohol use or concurrent medications), preexisting risk factors for liver damage, and no animal data or pharmacologic data pointing to a mechanism of action that would cause a concern. Despite these limitations, the increase in reports between 2002 and the present resulted in the committee's recommendation that black cohosh products should have a label with a cautionary statement, which is a change from the Expert Committee's previous decision.[42]

DRUG INTERACTIONS

There is concern that black cohosh might harm the liver. Taking black cohosh along with medication that might also harm the liver requires proper monitoring.

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CHAPTER 78

Citicoline (CDP-Choline)

Irfan Qureshi, ND, John R. Endres, ND, and Alexander G. Schauss, PhD, FACN

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INTRODUCTION

Citicoline (cytidine diphosphocholine) is a mononucleotide composed of ribose, cytosine, pyrophosphate, and choline. As an endogenous compound, citicoline is an essential intermediate in the synthesis of cell membrane structural phospholipids, and its formation is the rate-limiting step in phosphatidylcholine synthesis.

Citicoline is also an exogenous source for acetylcholine synthesis, a key neurotransmitter, and a member of the group of molecules that play important roles in cellular metabolism known as nucleotides.[1]

First identified in 1955 by Kennedy et al,[2] and synthesized in 1956, citicoline has been studied in Europe, Japan, and the United States for several decades. It is widely available as an approved drug for the treatment of neurologic disorders in many countries and is sold as a dietary supplement in the United States.

Citicoline Versus Choline

Choline is a component of the diet and is produced in the brain, albeit in small amounts. Due to its low endogenous production, it is considered an essential nutrient and classified with the B vitamin complex. It plays several essential roles in human physiology, including enhancement of structural integrity and signaling for cell membranes, supporting acetylcholine synthesis, and synthesis of betaine, a methyl donor.[3]

When taken orally, citicoline is hydrolyzed in the intestinal tract and in circulation to form choline and cytidine, which is the nucleoside of cytosine. Citicoline provides the brain with a source of choline and cytidine, which are efficiently used in the Kennedy cycle to generate phospholipids. Although choline on its own is preferentially used for the synthesis of acetylcholine, cytidine is highly efficiently used in the brain for the synthesis of various nucleotides (Figure 78-1). Studies in neuronal cell lines showed that cytidine administration increased the incorporation of choline into membrane phosphatidylcholine.[4]

In terms of safety, choline is a substance with a low level of toxicologic concern. Administering choline with cytidine, in the form of citicoline, lowers the toxicity index by twenty-fold.[5] Furthermore, citicoline administration is significantly different than administration of choline in cases of cerebral ischemia caused by stroke and other conditions. Citicoline's therapeutic effects in such conditions stem from its ability to: (1) increase phosphatidylcholine synthesis, the primary component of neuronal membranes; (2) enhance acetylcholine synthesis, ameliorating the symptoms resulting from ischemic loss of cholinergic neurons; (3) promote the synthesis of several other membrane phospholipids, including phosphatidylethanolamine and phosphatidylserine, leading to repair and regeneration of axons and synapses; and (4) prevent the accumulation of free fatty acids and the generation of free radicals at the site of ischemia, thereby preventing the initiation of a proinflammatory cascade of events.[5]

BIOAVAILABILITY/PHARMACOKINETICS

The pharmacokinetics of an oral dose of ^{14}C-labeled citicoline has been studied in humans. Administration of a single 300 mg dose to healthy adults was shown to have nearly complete absorption, with less than 1% of the labeled compound found in feces after a 5-day collection period. Absorption of citicoline gave rise to

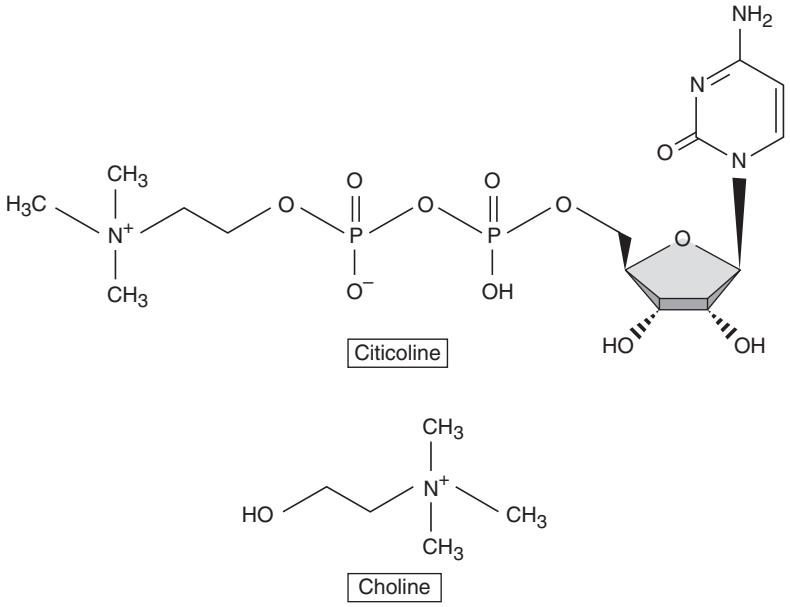


FIGURE 78-1 Chemical structures of citicoline and choline.

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Please refer to the printed publication.

FIGURE 78-2 Major metabolic pathways for citicoline. Modified from Weiss GB. Metabolism and actions of CDP-choline as an endogenous compound and administered exogenously as citicoline. Life Sci. 1995;56(9):637-60.

two chromatographic peaks in concentrations of radioactivity in plasma, the first at 1 hour, and the second, larger peak at 24 hours after dosing. The main route of excretion was found to be via respiratory carbon dioxide, with significant excretion also occurring through urine (Figure 78-2). After 5 days, 16% of the administered dose was recovered, suggesting that the remainder was incorporated into tissues or was available for biosynthetic and biodegradative pathways.[6]

A pharmacokinetic study in rats using ^{14}C-methyl-labeled citicoline confirmed almost complete absorption with oral administration, with calculated oral bioavailability being approximately 92% of that obtained from intravenous (IV) dosing. The absorption was categorized as slow and complete with sustained blood levels, the highest being at around 5.5 hours after administration. Radioactive labeling found citicoline and its metabolites widely distributed throughout tissues, including distribution of metabolites to the brain, confirming their ability to participate in the synthesis of phospholipids.[7]

A confirmatory study, again using radio labeled citicoline in rats, found 62.8% of total radioactivity was distributed in brain

tissue as phospholipids, including phosphatidylcholine and sphingomyelin. These results suggested that metabolites of orally administered citicoline were available in the brain for resynthesis of endogenous citicoline.[8] Although only a small percentage of the total citicoline dose crosses the blood–brain barrier as choline and cytidine, the utilization of these precursors in brain tissue for phospholipid biosynthesis is extremely efficient.[4]

MECHANISM OF ACTION

Citicoline has several important mechanisms of action, leading to a broad range of beneficial effects on neurologic function. In cerebral ischemia, citicoline primarily acts by increasing the synthesis of phosphatidylcholine, the primary neuronal membrane phospholipid, and enhancing the production of acetylcholine. Oral citicoline administration increases plasma levels of choline and cytidine, which are building blocks used to restore neuronal membrane integrity.[5]

Interestingly, citicoline seems to have differential effects on phosphatidylcholine synthesis in younger versus older adults. Phosphatidylcholine is an essential compound for cell membrane integrity and repair. It is normally reduced in brain cell membranes as a result of aging. A study using protein magnetic resonance spectroscopy to measure brain concentrations of cytosolic choline-containing compounds before and after a single oral dose of citicoline found that the choline resonance in the brain of younger individuals increased, whereas it decreased in older subjects. It was presumed that the cytidine component of citicoline enhanced the incorporation of brain choline into neural cell membrane phosphatidylcholine in older subjects, resulting in the decrease.[9]

The ability of citicoline to stimulate brain phospholipid synthesis in humans was further supported by studies showing that healthy subjects consuming 500 mg/day orally for 6 weeks (administered as Cognizin citicoline) had increased levels of phosphodiesters in brain tissue, such as glycerophosphocholine and glycerophosphoethanolamine, as assessed by phosphorus magnetic resonance spectroscopy. These findings supported citicoline's ability to increase phosphatidylcholine synthesis.[10] Findings from a study of healthy middle-aged adults confirmed these results, but suggested that the increase in phosphorus metabolites attributed to citicoline intake was regionally specific, with the frontal lobe being the preferred site of deposition, ultimately enhancing frontal lobe energetics and improving phospholipid membrane turnover. This area of the brain contributes to memory function by supporting vigilance, attention, and working memory capacity, and by reducing mental fatigue. Because citicoline's effect was most prominent in this brain region, this is a likely explanation for its clinical benefit of improved cognitive function.[11]

Citicoline may further benefit patients experiencing ischemia by decreasing the accumulation of free fatty acids at the site of the lesion, which occurs as a result of neuronal cell damage and death. Soon after initiation of ischemia, there is a significant increase in proinflammatory arachidonic acid, glycerols, and free fatty acids, caused by the breakdown of neuronal membranes. Toxic metabolites as well as prostaglandins, thromboxanes, and free radicals can accumulate, leading to further damage. Animal studies showed that intracerebral administration of citicoline before induction of ischemia reduced the increase in free fatty acids, arachidonic acid, and other toxic metabolites, attenuating free radical damage and restoring membrane function.[5]

Some evidence points to the ability of citicoline to normalize neurotransmitter release patterns. In conditions of cerebral hypoxia, which exist in ischemia, norepinephrine release may decrease, whereas the release of dopamine may increase. In several animal models, citicoline was shown to inhibit the impairment of neurotransmitter release in hypoxic conditions. Furthermore, citicoline administration to rats kept in a chronic hypoxic state reduced behavioral deteriorations and increased survival time. Additional studies found that citicoline was able to increase the dilation of blood vessels in animals with cerebral microcirculation injury, significantly increasing cerebral blood flow.[4]

Citicoline shows neural restorative effects, presumably via action on the dopaminergic system of the central nervous system. Rats with substantia nigra lesions were shown to regenerate nerve cells after treatment with citicoline, indicating its protective effect in this region. Further studies found that citicoline administration to rats increased striatal dopamine synthesis. Several other investigations in animal models yielded evidence of citicoline's ability to enhance dopaminergic synthetic pathways.[4] This was a result of the activation of tyrosine hydroxylase and inhibition of dopamine reuptake, which is related to citicoline's activity on phospholipid synthetic pathways. Citicoline is also known to have effects on serotonin and norepinephrine.[12] Studies in rats showed that citicoline improved learning and memory capacity and enhanced motor performance and coordination in aged rats. These findings provided further evidence for citicoline's cholinergic activity.[13]

Additional mechanisms of citicoline's neuroprotective effects were highlighted in recent research. Studies suggested that citicoline enhanced the preservation of an inner mitochondrial membrane component known as cardiolipin, which is important for preservation of mitochondrial function. Citicoline facilitated the preservation of sphingomyelin, which promotes signal transduction in nerve cells. Citicoline exhibited direct antioxidant effects, because research showed that it has an ability to stimulate glutathione synthesis and activity of the enzyme glutathione reductase. Furthermore, citicoline attenuates lipid peroxidation. These downstream effects may be attributable to citicoline's larger function of attenuating the activation of phospholipase A_2, thus reducing inflammation in neural tissues and in general.[14] Citicoline was shown to have direct free radical suppressive effects, as seen in animal models of transient cerebral ischemia, in which citicoline had a suppressive effect on hydroxyl radical generation.[15]

Citicoline may significantly impact brain remodeling activity. In an animal model, citicoline treatment significantly increased the length and branch points of dendrites, which led to an increased efficiency of sensory information processing.[16] This mechanism of activity could potentially account for a significant portion of citicoline's neurorestorative functions.

CLINICAL APPLICATIONS

Learning and Memory

Experiments in animals and humans provided evidence of citicoline's ability to promote important cognitive processes, including learning ability and memory functions. Clinical studies evaluating citicoline administration for cognitive enhancement have been conducted for several decades. A review of trials utilizing citicoline as a treatment for senile alterations of memory in 1991 found significant benefits in patients with cerebral insufficiency and chronic cerebrovascular disease.[17]

A randomized, double-blinded, placebo-controlled study was undertaken to assess the effects of citicoline supplementation on verbal memory function in 95 healthy subjects aged 50 to 85 years (47 women and 48 men) who were administered citicoline

(500 mg orally twice daily) or placebo for 3 months. The study subjects were well educated (mean, 14.3 years of education). Baseline testing included a logical memory assessment test, which was used to classify those with relatively inefficient memories. At the end of the initial study, 32 individuals (16 from the citicoline group and 16 from the placebo group) from this pool were recruited to participate in a follow-up crossover study. The initial study found citicoline improved delayed recall for only those with relatively inefficient memory at the beginning of the trial. In the follow-up crossover study, the dose of citicoline was increased to 2000 mg/day. In this subgroup, the higher dose of citicoline improved immediate and delayed logical memory.[18]

An open-label crossover trial consisting of 24 elderly individuals without dementia, but with demonstrable memory impairment (assessed by comparison with 24 healthy young control subjects), showed that oral citicoline (500, 1000, or 300 mg/day combined with nimodipine [90 mg/day]) significantly improved memory performance compared with the no treatment periods, as evidenced by reduced error scores on word recall tasks, immediate object recall, and delayed object recall.[19]

Alzheimer's Disease and Dementia

Citicoline supplementation has been well studied in Alzheimer's disease and vascular dementia. A study of 19 patients (mean age 66.21 ± 1.48 years) given oral citicoline at a dosage of 1000 mg/day for 30 days found significant improvements in cognitive function in the subgroup of patients with early-onset Alzheimer's disease and a trend toward increased cognitive function in the overall group, as assessed by brain electrical mapping. Brain spectral data readings provided an indication that the brains of early-onset Alzheimer's patients showed greater damage than those of late-onset Alzheimer's patients, whereas both groups had the same degree of cognitive impairment. It was postulated that the therapeutic effects of citicoline might be mediated by an enhancement of cholinergic neural transmission, activation of repair mechanisms to rejuvenate neuronal membranes, a regulatory effect on parameters associated with blood flow and circulation, as well as regulation of several immunologic responses, which, if left unchecked, would lead to potential neuronal dysfunction and cell death.[20]

In further studies, oral administration of citicoline (1000 mg/day) to 20 patients (age range 57 to 78 years) with early- or late-onset Alzheimer's disease resulted in improvements in mental function, particularly in the early-onset group. This 1-month treatment with citicoline resulted in an increased blood flow velocity from baseline measures (assessed by transcranial Doppler ultrasound) in the middle cerebral artery, which has been found to decrease with age, possibly resulting in neuropathologic changes. Citicoline's cholinergic effects and influence on cytokine production might also partially account for its benefits.[21]

Researchers investigated the regulatory effects of citicoline on blood histamine levels. Alterations in the histamine system are present in Alzheimer's disease, as high levels have been found in several central nervous system regions, cerebrospinal fluid, and serum. Histamine may also participate in the aging process, with histamine-related changes reported in several different tissues, including the central nervous system. In one study, 14 individuals with Alzheimer's disease (7 early-onset, 7 late-onset) were administered citicoline (1000 mg/day for 30 days). Blood histamine measurements were taken at baseline, at 2 hours after administration of the first dose, and after 30 days of treatment with citicoline. All participants experienced an acute reduction in blood histamine levels; after 30 days, early-onset Alzheimer's patients saw a decrease in blood levels of histamine of about 55% compared with baseline, whereas late-onset individuals saw a 45% decrease. Early-onset patients clearly had higher baseline levels of histamine than late-onset patients. Reducing endogenous histamine excesses may support cognitive function, as excessive histamine levels have been implicated in etiopathogenic events in Alzheimer's disease.[22]

The effects of citicoline administration (1000 mg/day orally for 3 months) were assessed in a trial in patients with senile dementia (Alzheimer's disease and multi-infarct dementia) to elucidate whether the nutrient was able to restore immune function and improve mental parameters. The study consisted of four groups: control subjects (n = 8), early-onset Alzheimer's subjects (n = 11), late-onset Alzheimer's subjects (n = 7), and multi-infarct dementia subjects (n = 10). After 3 months of treatment, citicoline supplementation improved mental performance in all groups (including controls), as assessed by several standard assessment tools (including the Mini-Mental State Examination and the Hamilton Rating Scale for Depression). Early-onset Alzheimer's patients showed increased levels of interleukin-1β at baseline. Citicoline administration normalized these levels in the early-onset Alzheimer's group. The researchers concluded that citicoline showed benefit in senile dementia patients as a restorative and palliative treatment, improving vascular risk factors, stabilizing immune function, and improving mental performance.[23] Further studies corroborated these effects of citicoline.[24]

Citicoline was further studied in a double-blinded, placebo-controlled randomized trial in 30 patients with apolipoprotein-E (Apo-E) genotyped Alzheimer's disease. All 30 participants were categorized as having mild to moderate dementia. Citicoline (1000 mg/day orally) or placebo was administered daily for 12 weeks, and its efficacy was further evaluated on the basis of each of the individuals' Apo-E genotype. The development of certain symptoms of Alzheimer's disease is correlated with differing Apo-E genotypes. The results of the study showed that clinical interview-based impression of change scores worsened significantly in the placebo group, whereas a clear trend toward improvement in the citicoline group was observed. In those individuals bearing the ε4 allele of the Apo-E (Apo-E4), citicoline was found to induce significant improvements on the cognitive function subscale of the Alzheimer's disease assessment scale. Furthermore, statistically significant improvements in Alzheimer's disease assessment scale scores were found with citicoline administration in the subset of Apo-E4 patients with mild cognitive deterioration (as assessed by Global Deterioration Scale scores less than 5). An overall increase in cerebral blood flow velocity was also seen with citicoline compared with placebo, whereas beneficial changes were further noted in brain bioelectrical activity.[25]

Parkinson's Disease

Citicoline may also benefit individuals with Parkinson's disease. Citicoline was administered by intramuscular (IM) injection to 20 patients (aged 52 to 76 years) at a dosage of 1000 mg/day for 15 days, followed by 500 mg/day for an additional 15-day period. (All of these patients received levodopa alone or in combination with other drugs before and during the trial.) The patients had improved scores on the Columbia rating scale (one of several validated and reliable rating tools for disability in Parkinson's[26]) by 7.3%, and also had measurable improvements in rigidity, time to walk 10 meters, time to turn over, and handwriting test scores. Results from a self-assessment revealed that symptomatology was improved in 15 of the 20 patients, including improvements in

speech, gait, posture, tremor, agility, and slowness of movements. Five patients showed minor improvements in dyskinesia; however, this was otherwise unaffected by citicoline treatment.[27]

Additionally, citicoline has a levodopa-sparing effect and an ability to increase dopamine synthesis. A trial of 85 Parkinson's disease patients were randomly assigned to two groups: patients received either their usual dose of levodopa (mean 381 mg/day) or half their usual dose (mean 196 mg/day). Both groups were simultaneously administered 1200 mg citicoline (400 mg orally three times daily); it was found that the group consuming half of their usual levodopa dose plus citicoline had significant improvements at week 6 (which was the end of the fourth week of citicoline administration) on the Webster Rating Scale, a measure of neurologic and clinical symptoms. This trial indicated that citicoline has the ability to compensate for the reduction of levodopa dosage, potentially contributing to a reduction in side effects associated with long-term levodopa usage.[28]

A similar trial was performed in 30 individuals with Parkinson's disease in which the participants were treated with levodopa and concomitantly received 500 mg of citicoline by IM injection daily for 30 days. Significant improvements in neurologic signs were noted (including moderate improvements in facial expression and digital skill, and marked improvements in ability to rise from a seated position, posture, and gait) as well as improvement in certain electrophysiologic parameters. An increase in dyskinesia was noted as a side effect in this group. In the second phase of the trial, the levodopa dosage was reduced by one-third. This decrease restored the incidence of dyskinesia to pretreatment levels, whereas the therapeutic response remained stable.[29]

An additional double-blinded, placebo-controlled, crossover design trial, in which citicoline (500 mg/day IM) or placebo was administered to 30 Parkinson's disease patients already on levodopa and a dopa decarboxylase inhibitor, found that citicoline induced improvements in bradykinesia. There was a 26.97% improvement from baseline on the Webster Rating Scale. This improvement was highly statistically significant compared with baseline and compared with placebo. Significant improvements were also noted in rigidity with citicoline treatment, whereas no such improvement occurred with placebo.[30]

Stroke and Cerebral Ischemia

Multiple trials have shown positive benefits with citicoline administration in stroke and cerebral ischemia. Researchers conducted a multicenter, double-blinded, placebo-controlled trial to evaluate the efficacy of citicoline administration in patients with acute cerebral infarction. The study consisted of 272 Japanese patients with a confirmed diagnosis of cerebral infarction and a mild to moderate impaired level of consciousness. Patients were randomly assigned to receive citicoline (1000 mg/day IV) or placebo for 14 days. When assessed at days 7 and 14, citicoline treatment resulted in significant improvements in level of consciousness and neurologic status in acute stroke patients.[31]

A second multicenter, randomized trial conducted in the United States (the U.S. Citicoline Stroke Treatment Study) also yielded positive results in acute stroke patients. Initial treatment was begun within 24 hours of stroke onset and continued orally for 6 weeks. Three dose groups of citicoline were established (500, 1000, or 2000 mg/day) in addition to the placebo group. The Barthel Index was used as the primary outcome measure to assess functional improvement. In the 500 mg/day citicoline group, the odds ratio for improvement was 2.0, and in the 2000 mg/day group, the ratio was 2.1, signifying that individuals in these groups were twice as likely to achieve higher Barthel scores than those in the placebo group. Overall, the results showed that citicoline (500 or 2000 mg/day groups) significantly improved functional recovery after 6 weeks of treatment compared with placebo, as assessed at the 12-week follow-up visit. Interestingly, the group taking 1000 mg/day of citicoline did not show a comparable benefit in this study. This was a puzzling result because all baseline characteristics of each group were essentially identical, except for weight, which was higher in this group than in the other treatment groups. The authors postulated this might have played a role in the outcome.[32]

A multicenter randomized placebo-controlled trial (RCT) in acute stroke patients (National Institute of Health [NIH] Stroke Scale scores higher than 5) given an oral dose of citicoline (500 mg/day) for 6 weeks found no benefits for stroke recovery, unlike earlier studies. However, a significant confounding factor might have impacted the analysis. More participants with milder strokes, as assessed by the NIH criteria, ended up populating the placebo arm of the study, which likely adversely affected the ability to see a treatment effect of citicoline.[33]

A larger Phase III multicenter RCT assessed the effectiveness of high-dose citicoline (2000 mg/day for 6 weeks) for stroke recovery. This study featured recruitment from 118 stroke centers from which 899 patients were randomized to receive citicoline or placebo. Unlike earlier trials that assessed the efficacy of citicoline in moderate stroke patients, this study recruited participants with NIH Stroke Scale scores of 8 or higher, designating more severe strokes. The major end point of this trial was a comparison of the proportion of individuals with an improvement of 7 or more points on the NIH Stroke Scale as assessed at week 12. Although no significant differences were noted between groups using the NIH Stroke Scale, a benefit was seen for citicoline on the Barthel Index at 6 weeks, as a significantly higher proportion of those in the citicoline group returned to their baseline function.[34]

Hazama et al[35] conducted a double-blinded, placebo-controlled trial in 1980 to assess the impact of citicoline administration as an adjunct to regular rehabilitation in poststroke recovery from hemiplegia. Citicoline was administered once daily for 8 weeks to patients continuing rehabilitation who were assigned to one of three groups: citicoline high-dose group (1000 mg/day IV), citicoline low-dose group (250 mg/day IV), or placebo (isotonic saline). Upper and lower limb joint range of motion was assessed at intervals throughout the study, as were subjective symptoms, neurologic signs, and mental symptoms. Significant improvements were noted in functional recovery in the upper limb in all groups, with dose-dependent improvements noted in both citicoline groups, which were significantly superior to placebo by week 8. No significant differences were noted between groups in the lower limb, although both citicoline groups showed a slightly higher rate of improvement compared with placebo.[35]

Citicoline was evaluated in a randomized, placebo-controlled study consisting of 92 patients with chronic cerebrovascular conditions. Individuals received citicoline (1000 mg/day IM) or placebo for two treatment cycles of 4 weeks each with a 1-week interval between cycles. The results of the study showed that citicoline significantly improved attention ability by decreasing the number of wrong responses on the Toulouse-Piéron Test for nonverbal stimuli. Furthermore, a constant and progressive improvement was noted with citicoline treatment on memory tests and on emotional and behavioral assessments.[36]

Citicoline treatment of patients with hemorrhagic, nontraumatic cerebral infarction was found to enhance the recovery of muscular strength associated with recuperation. A double-blinded

randomized trial conducted with 32 study subjects divided between those receiving 250 mg of citicoline IV twice daily or a placebo for 14 days showed that, compared with baseline, muscular strength in the citicoline group increased significantly more than in the group receiving placebo.[37]

An editorial published in the *Journal of Neurological Sciences* described the conclusions from a meta-analysis (published in the journal *Stroke* in 2002), which declared citicoline to be the first clinically effective neuroprotective agent in ischemic stroke. This significant editorial recommended that citicoline be the agent of choice in trials of combination therapy for stroke with thrombolytic agents because of its high level of safety and efficacy in promoting recovery from ischemic conditions.[38] Furthermore, a review by The Cochrane Collaboration analyzed the outcomes from several trials utilizing citicoline in the treatment of cognitive and behavioral symptoms resulting from chronic cerebral conditions in the elderly. Researchers ultimately included 14 studies in their review. Their analysis of the trials that met the specified inclusion criteria revealed that citicoline showed benefits for improved memory function and behavior in elderly individuals with chronic cerebral disorders.[39]

Traumatic Head Injuries

Research into the beneficial effects of citicoline for traumatic head injuries and concussions has been ongoing for several years. Injuries to the brain decrease the production of cell membrane phospholipids, resulting in an accumulation of intracellular water, leading to cytotoxic edema and possible deterioration of the hematoencephalic barrier. Citicoline can have therapeutic benefits in these conditions, because it is a precursor for the synthesis of neuronal membrane phospholipids. A single-blinded randomized study assessing the use of IV citicoline (1 g every 6 hours for 2 days, followed by 1 g every 8 hours on the third and fourth days) in addition to conventional therapy in 216 patients with severe or moderate head injuries found citicoline to be superior to conventional therapy alone—as assessed by the Glasgow Outcome Scale 3 months after injury. Citicoline also showed a trend towards shortening the hospital stay for severe head injury patients while improving motor, cognitive, and mental symptoms.[40] The authors cited earlier research on citicoline in treating moderate to severe head injuries, which showed that citicoline increased chances of recovery to a nondependent condition (including the ability to walk and perform activities of daily living), improving quality of life. Citicoline also improved levels of consciousness assessed at 60 days after injury in traumatic coma patients and reduced the percentage of patients showing focal neurologic signs at 60 and 90 days postinjury.[40]

Citicoline therapy may also help alleviate postconcussional symptoms. In one randomized trial with 14 young adults (median age 25 years in the citicoline group and 20 years in the placebo group) with mild to moderate head injuries, participants were administered 1 g of citicoline orally or a placebo. Assessments included tests of memory function, fluency, and attention. Although results at 1 month did not reach statistical significance, the group given citicoline trended towards higher improvement in several categories at the follow-up visit, including improvements in recognition memory, and decreased incidence of headaches, dizziness, and tinnitus.[41]

A review article examining trials of citicoline for the treatment of traumatic head injuries, including in children as young as age 5, espoused the benefits of citicoline therapy for improving neurologic signs and symptoms, the level of consciousness, and enhancing recuperation and facilitating electroencephalographic improvements. The review highlighted several trials related to traumatic coma patients treated with citicoline, which led to better recovery of motor function and walking ability compared with placebo. The overall results of these trials indicated that citicoline treatment reduced the duration of coma and the incidence and severity of mental and motor deficits associated with traumatic head injuries. Citicoline was also shown to be safe and well tolerated in patient populations of several age ranges and with various types of traumatic head injuries.[42]

EYE HEALTH AND VISUAL FUNCTION

Several trials with citicoline showed beneficial effects on eye health, specifically in cases of amblyopia and glaucoma. Amblyopia, or lazy eye, is the leading cause of decreased visual acuity in children, resulting in poor depth perception. Glaucoma is a leading cause of blindness in U.S. adults and is a group of conditions resulting in damage to the optic nerve, usually as a result of elevated intraocular pressure.

Amblyopia

An open trial and a pilot double-blinded follow-up study were conducted to assess possible benefits of citicoline therapy in patients with amblyopia. The open trial consisted of 50 patients (mean age, 16.6 years) who were administered citicoline (1000 mg/day IM) for 15 days. Visual acuity of both eyes was tested 1 week after the initiation of treatment and continuing at weekly intervals for the first month, and then on a monthly basis for an additional 6 to 18 months. For the double-blinded portion of the study, 10 patients were divided into 2 groups: 1 group received citicoline (1000 mg/day IM), and the other group received placebo. Citicoline improved visual acuity in 92% of the patients in the open study. Improvements were noted in both the sound and amblyopic eyes and were highly statistically significant. In the double-blinded study, significant improvements were noted between groups, with the citicoline group showing enhanced visual acuity.[43]

Another trial of citicoline took place in 45 children with amblyopia aged 5 to 9 years old. Participants were divided into three treatment groups: group A received 500 mg of citicoline daily via IM injection for 10 days every 6 months; group B received the same dosage of citicoline as group A in combination with 1 hour of occlusion (of the sound eye) per day; and group C received daily occlusion therapy alone. Although visual acuity improved in all groups at the end of the treatment period, treatment with citicoline was found to enhance the effect of occlusion therapy. Visual acuity improved in 73% of participants in group A, 86.6% of group B, and 66.6% of group C.[44]

An open-label trial with oral citicoline (800 to 1200 mg/day of citicoline according to body weight for 30 days) plus partial occlusion therapy in 61 children (aged 5 to 10 years) found that citicoline contributed to stabilizing the gains obtained during the treatment period when assessed at the 60-day posttreatment follow-up visit. Those receiving occlusion therapy alone showed a decrease in visual acuity gains at the 60-day follow-up, whereas those in the citicoline group maintained the gains achieved with occlusion therapy.[45]

Citicoline likely influences improvements in visual acuity in amblyopic individuals by stimulating the availability of several neurotransmitters and neuromodulators. It also enhances the activity of endogenous dopamine, while improving vascular aspects of neurologic function.[46]

Glaucoma

A randomized clinical study evaluating the effects of citicoline in 40 patients with open-angle glaucoma, who received either daily IM injections containing 1000 mg of citicoline or placebo for 60 days, found that citicoline significantly improved visual evoked potential (a measure of bioelectrical activity of the visual cortex in response to visual stimuli) and the pattern-electroretinographic (used to evaluate the functional integrity of the innermost retinal layers) parameters compared with placebo. Patients in the citicoline group were then divided into two age-matched groups after a 120-day washout period. In one of these groups, the washout period was extended for an additional 120 days, whereas the second group received a further 60-day treatment of citicoline. This second group showed further improvements in visual evoked potential and pattern-electroretinographic parameters, indicating citicoline's ability to enhance retinal function and visual cortical response in glaucoma patients.[47]

A double-blinded RCT assessing the benefits of citicoline in glaucoma patients confirmed that administration of citicoline for 60 days (1000 mg/day IM) was superior to placebo and significantly improved retinal function and cortical bioelectrical responses. This particular trial included an analysis of 8 years of follow-up data.[48]

A review examining the potential mechanisms through which citicoline exerts its beneficial influence in glaucoma patients theorized that citicoline's ability to enhance the synthesis of phosphatidylcholine and other cell-membrane phospholipids was a major factor of improvement. Glaucoma is considered a neurodegenerative disease in which the pathology extends to retinal ganglion cells. Death of these cells is likely a result of apoptotic mechanisms. The enhancement of phosphatidylcholine synthesis as a result of citicoline intake countered the neuronal apoptotic mechanisms associated with glaucoma and conferred neuroprotection.[49]

Ischemic Optic Neuropathy

Nonarteritic ischemic neuropathy is an irreversible ischemic event associated with the intraocular optic nerve. The condition occurs acutely and painlessly, yet induces a loss of visual acuity and visual field. In a pilot study designed to assess citicoline's effect on this condition, 26 patients with at least a 6-month history of nonarteritic ischemic optic neuropathy were divided into two groups: one received treatment consisting of oral citicoline (1600 mg/day) for 60 days, whereas the second group received no treatment. After the 60-day treatment cycle, there was a washout period of 120 days. After this, a second period of treatment with citicoline for 60 days was instituted in the original citicoline group. A third group of 14 age-matched healthy subjects provided control data. At the end of treatment, statistically significant improvements were noted in visual evoked potential, visual acuity, and pattern-electroretinographic parameters in the citicoline group compared with pretreatment values, whereas no such changes were observed in the untreated group of nonarteritic ischemic neuropathy subjects.[50]

EMERGING CLINICAL APPLICATIONS

Substance Abuse

Citicoline has been considered as an adjunct treatment for cocaine dependence by researchers in the field in recent years. The justification for its use stems from citicoline's ability to repair neuronal membranes, which are damaged by cocaine use, and its ability to increase central nervous system dopamine levels, attenuating cravings for cocaine and other abused substances.[51]

A small double-blinded, placebo-controlled trial in 14 subjects with a history of cocaine dependence found that oral citicoline (500 mg twice a day for 14 days) caused no adverse events and also attenuated some measures of cocaine craving and drug use.[52]

An additional experiment in eight healthy occasional cocaine users investigated the influence of citicoline pretreatment on cocaine-induced cardiovascular and behavioral effects and plasma levels of cocaine. The primary outcome measure was to determine the safety of coadministration of citicoline with cocaine. Because citicoline did not adversely impact cardiovascular end points associated with acute cocaine intake, the use of citicoline in this patient population was presumed to be safe. Although citicoline did not block the acute subjective effects of cocaine use, cocaine users experienced a high incidence of major cerebrovascular events. Thus, the authors speculated that citicoline could play a role in attenuating these undesirable consequences of cocaine use, although further studies are needed to investigate these potential benefits.[53]

Individuals with bipolar disorder are at an increased risk for substance abuse, with cocaine use being particularly common in this condition. Both the disorder and cocaine use are associated with mood symptoms and cognitive deficits. Given these commonalities, a 12-week double-blinded RCT was conducted to assess the impact of citicoline supplementation on 44 individuals with bipolar disorder and cocaine dependence. Citicoline resulted in an improvement in some aspects of declarative memory. However, no evidence for antidepressant properties was seen with the use of citicoline. There was also a significantly lower probability of a positive urine test for cocaine at the end of the study in the citicoline group.[54]

Infectious Disease

A recently published article highlighted the role citicoline might play as an adjunctive therapeutic agent for the treatment of disease arising from an infectious etiology. The pathology of infectious disease involves dysregulation of the host immune response. Although currently available treatments target the infectious agent, they do little to address the concurrent neurologic abnormalities. These consequences, if unaddressed, lead to eventual mortality in a high percentage of cases. In the case of cerebral malaria, studies highlighted cytokine-induced endothelial inflammation and the compromised blood–brain barrier as major pathologic factors leading to the associated neurologic signs and symptoms. Ischemia is a large underlying mechanism for damage in sepsis as well as cerebral malaria. Because these underlying issues are similar to conditions such as stroke and myocardial infarction, it is likely that citicoline would benefit these patients as an adjunct treatment for sequelae of sepsis and cerebral malaria.[2]

Appetite Control and Satiety

Given citicoline's ability to enhance cognitive function, confer neuroprotection, and support neuroregenerative effects, and its action to support dopaminergic activity in the brain, researchers investigated the potential of citicoline administration for controlling appetite and promoting satiety. In this particular study, the effect of oral citicoline supplementation (as Cognizin citicoline, 2000 mg/day) for 6 weeks was assessed by functional magnetic resonance imaging to elucidate cortico-limbic responses to images of various foods, along with subjective ratings of appetite and measures of weight. Sixteen healthy adults (age range of 40 to 57 years, and a body mass index range of 20.1 to 38.6 kg/m^2) were included

in the study. Eight participants were assigned to a low-dose citicoline group (500 mg/day), and the other eight were assigned to the high-dose group (2000 mg/day). The results of the study indicated that self-assessment ratings for appetite declined significantly between visits in both groups, with the magnitude of decline in the high-dose group reaching statistical significance. No significant between-group differences were noted for the magnitude of weight change. The high-dose citicoline group also showed higher activation within the right lateral orbitofrontal cortex and left amygdala during visual perception of high-calorie foods than the low-dose group when assessed by functional magnetic resonance imaging. This might indicate that high-dose citicoline leads to appetite suppression and feelings of satiety by increasing the responsiveness of these regions to images of calorie-rich foods.[55]

Mental Health

Citicoline's influence on cognitive capacity and neurologic health, including modulatory activity on neurotransmitter production and function, make it a logical choice for supporting mental health. A small trial evaluated the effect of citicoline administration in eight depressed patients (500 mg/day IM, as 300 mg at 8 AM and 200 mg at 5 PM) for 21 days or longer. On the day preceding the beginning of treatment, plasma growth hormone was measured, levels of which indicated reduced growth hormone secretion in these patients. Significant improvements were noted in seven of eight participants (treatment was discontinued in one participant because of a noted suicidal tendency) when assessed using the Hamilton Rating Scale for depression. Although the study was small, the results indicated the potential for significant benefit from citicoline therapy in depressed individuals.[56]

A preliminary study considered combination treatment of citicoline with galantamine for schizophrenic patients. Evidence suggested that α7 nicotinic choline receptors have decreased functionality in schizophrenia. Citicoline provides choline, which is a known α7 nicotinic choline receptor agonist. Galantamine is a modulator of α7 nicotinic choline receptor function and was used to enhance the efficiency of choline binding to these receptors. Six schizophrenic patients consuming 2 g of citicoline in combination with 24 mg of galantamine daily participated in this 12-week open-label pilot study. The combination was well-tolerated by all of the participants, with transient side effects occurring (all of which resolved within a few days), including gastrointestinal symptoms, restlessness, and syncope. No cardiovascular events or symptoms occurred, with five of the six participants having lower than baseline diastolic blood pressure readings at the end of the study. Improvements were noted in five of six patients on the Clinical Global Impressions inventory and the Positive and Negative Syndrome Scale. Total Positive and Negative Syndrome Scale scores and Clinical Global Impressions severity scale scores decreased over the study period, providing encouraging results, suggesting that the combination therapy was potentially effective.[57]

SAFETY AND DOSING

Clinical investigations using citicoline revealed a favorable safety profile with few reports of any major adverse events. The most common adverse reports were related to digestive disturbances. Citicoline has also been found to have a lack of significant adverse events in children, as evidenced by its use in clinical trials with pediatric subjects with amblyopia[44] and children with traumatic head injuries.[42]

Citicoline has undergone several toxicologic evaluations in multiple animal species and has proven to have a high level of safety. Single-dose acute oral toxicity studies were performed in mice and rats, with a median lethal dose of 27.14 g/kg in mice and 18.5 g/kg in rats. Chronic oral toxicity tests in dogs (1.5 g/kg per day for 6 months) and subchronic intraperitoneal dosing studies in rats (1 g/kg per day for 12 weeks) showed no abnormal signs.[12]

An acute 14-day study and a 90-day subchronic toxicity evaluation of Cognizin citicoline in rats revealed that the supplement was well tolerated. In the 14-day study, a single dose of 2000 mg/kg showed no abnormalities, and in the 90-day repeated oral dosing study, doses of 100, 350, and 1000 mg/kg per day resulted in no mortality in the animals. In male rats, slight increases in serum creatinine were noted in the two highest dose groups, whereas in female rats, a dose-related increase in renal tubular mineralization was noted and attributed to an increase in phosphorus intake as a result of high citicoline consumption. Mineralization in female laboratory rats of all universally used strains is a common incidental finding as a result of a decreased calcium/phosphorus ratio in the diet. Because citicoline yields a significant amount of phosphorus—thus influencing the calcium/phosphorus ratio—this finding was not unexpected.[58]

A drug surveillance study was recently published examining the efficacy and safety of oral citicoline intake in acute ischemic stroke. The study of 4191 Korean patients confirmed a high level of safety for citicoline (500 to 4000 mg/day for 6 weeks or longer) with an incidence of 37 adverse events in 31 patients (only 0.73% of patients experienced adverse events). Adverse events in all but 1 of the 31 patients showed no relationship to citicoline administration. Thirty-two of the 37 (nearly 84%) patients reported events resolved over a mean of 9 days after onset. Furthermore, no dose-related effects of citicoline on the occurrence of adverse events were noted. The most frequent side effects included minor nervous system-related complaints (n = 8) (numbness, headache, tingling sensations) followed by gastrointestinal symptoms (n = 5) (abdominal discomfort, diarrhea).[59]

Effective dosing of citicoline based on data from clinical trials ranges from 500 to 2000 mg/day. Based on evidence from trials in children as young as 5 years of age,[42,44] citicoline is safe for use in pediatric and adult populations. Oral doses of up to 1200 mg/day have been used in children.[45] Studies using oral, IM, and IV dosing of citicoline in children and adults, with minimal occurrence of adverse events, affirmed its high level of safety.

DRUG INTERACTIONS

Citicoline has a levodopa-sparing effect, potentiating its benefits and reducing certain side effects associated with long-term levodopa use.[28-30]

CONCLUSIONS

Citicoline is a novel compound with a very broad spectrum of benefits in conditions associated with symptoms of neurologic dysfunction. Citicoline acts at multiple levels to support and maintain neural health and optimal cognitive function. Citicoline promotes cholinergic and dopaminergic functions, and supports phospholipid synthesis and incorporation into cell membranes. Citicoline enhances antioxidant mechanisms in the body, while suppressing the damaging effects of free radicals on neural tissue. It also promotes antiinflammatory activities and optimizes patterns associated with the release of neurotransmitters. Given its widespread activity on neural tissue, citicoline should be considered a comprehensive therapeutic agent for supporting brain health.

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CHAPTER 79

Coenzyme Q_{10}

Laurie K. Mischley, ND, Jason Allen, ND, MPH, and Michael T. Murray, ND

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INTRODUCTION

Coenzyme Q_{10} (CoQ_{10}) is an endogenous proenzyme synthesized naturally in the human body.[1] Because of its ubiquitous presence in nature and its quinone structure, CoQ_{10} is also known as ubiquinone (Figure 79-1). The two major physiologic actions of CoQ_{10} are (1) as a cofactor in the production of adenosine triphosphate (ATP), and (2) as an antioxidant. Because most cellular functions depend on an adequate supply of ATP, CoQ_{10} is essential for the health of virtually all human tissues and organs. Cellularly, the highest concentration of CoQ_{10} is found in the inner mitochondrial membrane, where it facilitates energy production, but CoQ_{10} is found in the cell membranes of many organelles where it plays a role in membrane stability.[2] CoQ_{10} is the only endogenously synthesized lipid soluble antioxidant.[3] In its role in electron transport, the CoQ_{10} molecule continuously goes through an oxidation-reduction cycle. As it accepts electrons, it becomes reduced to ubiquinol. As it gives up electrons, it becomes oxidized to ubiquinone. In contrast to other antioxidants, this compound inhibits both the initiation and the propagation of lipid and protein oxidation. In its reduced form, ubiquinol, the CoQ_{10} molecule holds electrons rather loosely, so the CoQ_{10} molecule will quite easily give up one or both electrons and, thus, act as an antioxidant. It is especially protective against the oxidation of bases of mitochondrial DNA. In addition, ubiquinol is responsible for regenerating vitamin E from the α-tocopheroxyl radical and, thereby interfering with the propagation step of lipid peroxidation.

Biosynthesis of CoQ_{10} starts from acetyl coenzyme A (CoA) and flows through a multistep process of the mevalonate pathway to produce farnesyl-PP, the direct precursor for not only CoQ_{10}, but also cholesterol, dolichol, and isoprenylated proteins. The long isoprenoid side-chain of CoQ_{10} is synthesized by trans-prenyltransferase, which condenses farnesyl-PP with several molecules of isopentenyl-PP, all in the trans configuration. The next step involves condensation of this polyisoprenoid side-chain with 4-hydroxybenzoate, catalyzed by polyprenyl-4-hydroxybenzoate transferase. Hydroxybenzoate is synthesized from tyrosine or phenylalanine. In addition to their presence in mitochondria, these initial two reactions also occur in the endoplasmic reticulum and peroxisomes, indicating multiple sites of synthesis in human cells. Nonetheless, numerous conditions are now known to arise in which the body's synthetic capacity is insufficient to meet CoQ_{10} requirements. Susceptibility to CoQ_{10} deficiency appears to be greatest in cells that are the most metabolically active, such as the brain and heart. Tissue deficiencies or subnormal serum levels of CoQ_{10} have been reported to occur in a wide range of medical conditions and decline with advancing age.[3]

A need for supplemental CoQ_{10} could theoretically result from the following:

- Impaired CoQ_{10} synthesis due to nutritional deficiencies
- A genetic or acquired defect in CoQ_{10} biosynthesis or utilization
- Increased tissue needs resulting from a particular illness
- The requirement to prevent the side effects of medical intervention

Because oral administration of CoQ_{10} can increase tissue levels, it is possible to correct CoQ_{10} deficiency and its associated metabolic consequences by supplementation.[4]

Coenzyme Q_{10} Deficiency

Inherited CoQ_{10} deficiency has been associated with five major clinical phenotypes: (1) encephalomyopathy, (2) severe infantile multisystemic disease, (3) cerebellar

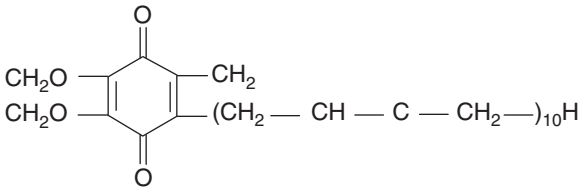


FIGURE 79-1 Ubiquinone

ataxia, (4) isolated myopathy, and (5) nephrotic syndrome. In a few patients, pathogenic mutations have been identified in genes involved in the biosynthesis of CoQ_{10} (primary deficiencies) or in genes not directly related to CoQ_{10} biosynthesis (secondary deficiencies). Respiratory chain defects, reactive oxygen species production, and apoptosis contribute to the pathogenesis of primary CoQ_{10} deficiencies.[5,6]

Acquired CoQ_{10} deficiency is less well established. There are two major factors that lead to deficiency of CoQ_{10} in humans: reduced biosynthesis, and increased utilization or need by the body. The typical dietary intake of CoQ_{10} is 3 to 5 mg,[7] so dietary lack is probably not a significant contributor to CoQ_{10} deficiency. As mentioned previously, endogenous synthesis is a multistep process that can be affected by aging, disease status, and various medications. Some chronic disease conditions (cancer, heart disease, etc.) are not only associated with reduced biosynthesis, but also increased demand for CoQ_{10}. Measurements of plasma CoQ_{10} levels have been used to detect deficiencies and are by far the most common clinical assessment of CoQ_{10} status.[8] Normal plasma levels are believed to range from 0.45 to 1.5 mcg/mL (or 0.46 to 1.78 µmol/L), with 93% to 100% being the reduced form, ubiquinol.[8,9] Some studies used a functional assessment using an assay that measures the citric acid cycle (Krebs cycle) enzyme succinate dehydrogenase-CoQ_{10} reductase.[10] CoQ_{10} acts as a critical coenzyme to this enzyme, so if the enzyme is fully saturated with CoQ_{10} in vivo, addition of exogenous CoQ_{10} does not increase enzyme activity. Additional methods for assessing CoQ_{10} status are also becoming available.[5,11,12]

Coenzyme Q_{10} Absorption and Pharmacokinetics

After gastric emptying, CoQ_{10} is absorbed along with other lipids as chylomicron particles in the small intestine. The primary site of uptake of exogenous CoQ_{10} is the duodenum, followed by the colon, then the ileum, and then the jejunum. Absorption in the ileum and colon regions supports the possibility of an enterohepatic recirculation of CoQ_{10}. This possibility is further strengthened by the presence of a second peak in plasma levels about 24 hours after administration of either ubiquinone or ubiquinol. Absorption appears to be a complex process involving both active and passive mechanisms.

In the liver, CoQ_{10} is incorporated with lipoproteins and released into the blood. In plasma, CoQ_{10} is almost totally associated with lipoproteins, where it has greatest affinity for very low-density lipoprotein (VLDL) and LDL cholesterol. The CoQ_{10} is then distributed to peripheral tissues for uptake by cells and their mitochondria.

Commercial Forms and Dosage Considerations

Commercially CoQ_{10} is primarily produced via a yeast fermentation process using *Schizosaccharomyces pombe*. An alternate source of manufacturing is chemical synthesis using solanesol isolated from the tobacco plant.

A very important consideration in the clinical application of CoQ_{10} is its pharmacokinetics. CoQ_{10} as ubiquinone is a crystalline powder that is insoluble in water and has poor absorption characteristics as a result. Ubiquinol has greater solubility and has been promoted as having greater bioavailability that ubiquinone,[4,13] but there are limited data currently available and many questions remain to be answered, since ubiquinol is easily oxidized to ubiquinone and absorption studies to date have been suspect. Ubiquinone has an extensive history of use, particularly in oil-based soft-gelatin capsules. Several technologies are now used to enhance the bioavailability of ubiquinone, such as particle size reduction (nanonization) and solubility enhancement via use of emulsifying agents, carriers, and self-emulsifying systems.[14] For example, complexing ubiquinone to a soy peptide ($BioQ_{10}$ SA) has shown exceptional bioavailability because the soy peptide emulsifies the CoQ_{10} and helps usher it into the bloodstream.[15] Given the excellent absorption of this form of ubiquinone, the advantage of ubiquinol over regular ubiquinone appears to have more to do with its improved solubility than because it is in the ubiquinol form.

In light of the pharmacokinetic issues, proper clinical dosing is yet to be determined for CoQ_{10}. Therefore, some have suggested that therapeutic targeting will likely be based upon achieving specific plasma CoQ_{10} levels (e.g., more than 3.5 mg/mL) or tissue saturation.[8,16,17] Prescribing a set dosage, even a milligram per kilogram body weight dosage, at this time is a best guess scenario without confirmation by monitoring CoQ_{10} blood levels, given the differences noted in absorption rates among the different forms as well as the inter-individual variability.

Numerous studies have now been conducted claiming enhanced absorption of one form or another.[4] However, there are shortcomings in most of these studies, and some of the studies appear to have been set up to show an advantage for commercial reasons. For example, ubiquinol is being promoted as the best absorbed form of CoQ_{10}, yet the published studies were set up in a curious fashion. In the one study examining ubiquinol absorption, the administration of the ubiquinol was always with a total of CoQ_{10} capsules that included the emulsification agents diglycerol monooleate, canola oil, soy lecithin, and beeswax, and although the study utilized a placebo, it did not compare ubiquinol with ubiquinone.[13] It is possible that ubiquinone might have fared just as well if emulsified as well as the ubiquinol in this study. Absorption studies showed that when CoQ_{10} was given with food, it was absorbed twice as fast and at least two-fold greater than on an empty stomach.[18] It is believed that food-induced secretion of bile acids is responsible for the improved absorption.

What is known based on current absorption studies is that eventually a steady state is produced (usually after 3 to 4 weeks of constant dosing), and the absorption of CoQ_{10} may be limited in some individuals. Dosages that exceed an individual's absorptive capacity for CoQ_{10} may have minimal effect on efficacy and unnecessarily increase the cost of treatment. When single dosages of CoQ_{10} begin to exceed 300 mg, the percentage of CoQ_{10} absorbed declines. Plasma CoQ_{10} levels at a dosage of 900 mg/day (as ubiquinone in a oil suspension in a soft gel capsule) are not significantly greater than a 600 mg/day dosage. Divided dosages (e.g., two or three times a day) result in higher plasma levels compared with single dosages, especially at higher dosage levels.

TABLE 79-1 **Coenzyme Q_{10} Plasma Levels**

DOSE AND FORM	ESTIMATED PLASMA LEVELS IN MICROGRAMS PER MILLILITER
100 mg	
Ubiquinone powder in hard gelatin capsule	1.25
Ubiquinone suspended in oil in soft gelatin capsule with rice bran oil	1.8
Ubiquinone solubilized in soft gelatin capsule	2.25
Ubiquinone powder nanonized	2.25
Ubiquinone emulsified with soy peptide in soft or hard gelatin capsule	2.50
Ubiquinol in soft gel capsule	2.50
300 mg	
Ubiquinone powder in hard gelatin capsule	2.5
Ubiquinone suspended in oil in soft gelatin capsule with rice bran oil	3.5
Ubiquinone solubilized in soft gelatin capsule	5.0
Ubiquinone powder nanonized	5.0
Ubiquinone emulsified with soy peptide in soft or hard gelatin capsule	7.0
Ubiquinol in soft gel capsule	7.0

Despite the challenges, based upon existing data from published studies, an attempt can be made to calculate the approximate plasma levels of CoQ_{10} for different commercial forms at 100 and 300 mg doses for at least 30 days with several caveats. First, these are estimates only, based upon a typical 75 kg body weight. Keep in mind that absorption of CoQ_{10} in any form is likely enhanced considerably if taken with a large meal that includes some fat. Lastly, considerable pharmacokinetic studies in humans have indicated significant interindividual variability in CoQ_{10} absorption, underscoring the need for monitoring CoQ_{10} plasma levels during clinical studies and perhaps clinical use of CoQ_{10} as well (Table 79-1).

The optimal dose of CoQ_{10} for many clinical indications is not known, and plasma or target tissue levels of CoQ_{10} are likely the primary determinant of efficacy, rather than the dose.[16,19] Current opinion based upon the scientific literature is that an acceptable therapeutic plasma target level of CoQ_{10} should be at least 2.5 mg/mL,[20] but levels higher than 3.5 mcg/mL may be necessary for optimum improvement in neurodegenerative diseases and myocardial function.[8,16,19] The usual starting dosage for CoQ_{10} is generally 100 to 200 mg/day. Where possible, the dosage of CoQ_{10} should be adjusted according to the response of the patient and, preferably, by monitoring plasma CoQ_{10} levels for 3 to 4 weeks of constant dosing, when steady-state plasma concentrations occur. Less is known about the ability of CoQ_{10} and the dose required to reach the central nervous system. Again, divided dosages result in higher plasma levels compared with single dosages, e.g., taking 100 mg twice a day produces higher plasma levels compared with taking 200 mg once a day.[21]

CLINICAL APPLICATIONS

Given the central role of CoQ_{10} in mitochondrial function and cellular antioxidant protection, its clinical applications are extensive. There are so many conditions where CoQ_{10} may offer benefit that there is no question that it should be considered a conditionally essential nutrient. The specific uses of CoQ_{10} are described in the following:

- General antioxidant
- Cardiovascular disease
 - Cardiomyopathy
 - Congestive heart failure
 - Protection during cardiac surgery
 - Hypertension
- Cancer
- Diabetes mellitus
- Male infertility
- Parkinson's disease
- Friedreich's ataxia
- Muscular dystrophy
- Immune function
- Acquired immunodeficiency syndrome (AIDS)
- Toxicant exposure
- Topical antiaging effects

General Antioxidant

Numerous studies have shown CoQ_{10} can reduce oxidative damage, DNA strand damage, LDL oxidation, and formation of lipid peroxides, thereby supporting its use as a general antioxidant.[2,22] In particular, CoQ_{10} is often used to counteract the reduced synthesis of CoQ_{10} associated with aging. After the age of 35 to 40 years, humans slowly begin to lose their ability to synthesize CoQ_{10}.[23] It has been proposed that the increase in age-associated diseases is due in part to decreased protection afforded by CoQ_{10} as both an antioxidant and a facilitator of energy production at a cellular level. Therefore, COQ_{10} is often recommended to counteract this effect.

For example, recent studies identified oxidative stress as a promoting factor for dry mouth (xerostomia) and the development of Sjögren's syndrome, a condition associated with significant dry mouth. Basically, oxidative damage leads to the inability of salivary cells to produce enough ATP to secrete sufficient amounts of water. CoQ_{10} exerts antioxidant effects, but its main action in relieving dry mouth may be by increasing energy (ATP) production, allowing the saliva producing cells enough energy to secrete more saliva into the mouth. In one double-blind study, 66 patients, including 31 with dry mouth, were given either ubiquinol or ubiquinone orally at a dosage of 100 mg/day, or a placebo for 1 month.[24] Salivary secretion and salivary CoQ_{10} content were analyzed before and after treatment. Among the dry mouth patients treated with ubiquinone, salivary secretion increased significantly from 0.7 g/2 min before treatment to 1.2 g/2 min after 1 month of treatment. Among the patients treated with ubiquinol, salivary secretion also increased significantly from 0.8 g/2 min before treatment to 1.4 g/2 min after treatment. In normal subjects without dry mouth, salivary secretion increased with ubiquinone (from 4.9 to 5.7 g/2 min) at a statistically significant level, but did not differ significantly after treatment with ubiquinol (from 3.5 to 3.8 g/2 min). Either form of CoQ_{10} exhibited a marked increase in salivary CoQ_{10} concentration (ubiquinol more than ubiquionine in dry mouth, ubiquinone more than ubiquinol in normal subjects), suggesting that the observed increase in salivary secretion was attributable to the effect on salivary levels of CoQ_{10}.

Cardiovascular Disease—General Considerations

Enhancing myocardial function is an important, although frequently overlooked, component of the overall prevention and treatment of cardiovascular disease. CoQ_{10} plays a key role in energy production and is therefore essential for all energy-dependent processes, including heart muscle contraction. CoQ_{10} deficiency has been documented in patients with various types of cardiovascular disease. Whether a decline in CoQ_{10} levels is a cause or a consequence of heart disease is unclear. Cardiac cells are highly metabolically active, and thus have higher mitochondrial coenzyme requirements to maintain ATP production. In addition to its role in cellular energetics, exogenously administered CoQ_{10} acts as an antioxidant to inhibit LDL oxidation,[25] decreases proinflammatory cytokines interleukin-6 and tumor necrosis factor-α, and attenuates markers of oxidative and nitrative stress in a dose-dependent manner.[2]

CoQ_{10} deficiency is common in patients with various types of cardiovascular disease.[2,26] Approximately 75% of patients who had cardiac surgery were shown to be deficient in myocardial CoQ_{10}. Concentrations of CoQ_{10} declined progressively in both blood and myocardial tissue with increasing severity of heart disease.[27] Myocardial deficiencies of CoQ_{10} were also found in the majority of patients with aortic stenosis or insufficiency, mitral stenosis or insufficiency, diabetic cardiomyopathy, tetralogy of Fallot, atrial septal defects, and ventricular septal defects.[28]

Cardiomyopathy

Cardiomyopathy can take several forms, but all are manifested by weakening of the heart muscle associated with inadequate heart pumping or other functional problems. The well-established role of CoQ_{10} as a facilitator of mitochondrial energy production lends strong rationale for a role of CoQ_{10} supplementation in all forms of cardiomyopathy.

A prospective, randomized, double-blind, placebo-controlled trial was conducted in 38 children with idiopathic dilated cardiomyopathy. After 6 months of supplementation, there was a statistically significant ($P = 0.011$) improvement in diastolic function, leading the authors to conclude that "administration of coenzyme Q_{10} is useful in ameliorating cardiac failure in patients with idiopathic dilated cardiomyopathy."[29]

In one study, 126 patients with dilated cardiomyopathy received 100 mg/day of CoQ_{10} for up to 66 months. After 6 months of treatment, the mean left ventricular ejection fraction (LVEF) increased from 41% to 59% ($P < 0.001$) and remained stable thereafter with continued treatment. After 2 years, 84% of the patients were still alive, and at 5.5 years, 52% were alive.[30] These survival rates were considerably better than the published survival statistics of patients given conventional therapy (i.e., 2-year survival rate of 50% for symptomatic cardiomyopathy, and 1-year survival rate of 50% for decompensated cardiomyopathy).

In another study, 88 patients with cardiomyopathy received 100 mg/day of CoQ_{10} for 1 to 24 months. Significant improvements in at least two of three cardiac parameters (LVEF, cardiac output, and New York Heart Association [NYHA] class) were seen in 75% to 85% of the patients. Approximately 80% of the patients improved to a lower (i.e., more favorable) NYHA functional class.[20]

In a double-blind, crossover trial, 19 patients with cardiomyopathy received 100 mg/day of CoQ_{10} or a placebo, each for 12 weeks. Compared with placebo, CoQ_{10} treatment significantly increased cardiac stroke volume and LVEF. Eighteen patients reported improvement in activity while taking CoQ_{10}.[31]

Congestive Heart Failure

The potential of CoQ_{10} as a treatment for congestive heart failure (CHF) was suggested as early as 1967 by Japanese researchers.[32] In 1976, these same investigators administered 30 mg/day of CoQ_{10} to 17 patients with CHF. All of the patients improved, and nine (53%) became asymptomatic after 4 weeks of treatment.[33] Numerous studies since have demonstrated that CoQ_{10} supplementation resulted in an improvement of stroke volume, LVEF, cardiac output, cardiac index and end-diastolic volume index.[2,34,35]

In the largest multicenter trial completed to date, 2664 patients in NYHA classes II and III CHF received 50 to 150 mg/day of CoQ_{10} (78% of patients received 100 mg/day of CoQ_{10}). After 3 months of supplementation, the results showed a low incidence of side effects, and the following proportion of patients had improvements in clinical signs and symptoms[36]:

- Cyanosis, 71.8%
- Edema, 78.6%
- Pulmonary rales, 77.8%
- Enlargement of the liver area, 49.3%
- Jugular reflux, 71.81%
- Dyspnea, 54.7%
- Palpitations, 75.4%
- Sweating, 79.8%
- Subjective arrhythmia, 63.4%
- Insomnia, 60.8%
- Vertigo, 73.1%
- Nocturia, 53.6%

The results of these uncontrolled studies were confirmed in several double-blind trials. Some 641 patients with CHF (NYHA classes III or IV) were randomly assigned to receive placebo or CoQ_{10} (2 mg/kg per day) for 1 year while continuing conventional therapy. The number of patients requiring hospitalization during the study for worsening heart failure was 38% less in the CoQ_{10} group than in the placebo group ($P < 0.001$), and episodes of pulmonary edema were reduced by about 60% in the CoQ_{10} group compared with the placebo group ($P < 0.001$).[37]

These positive results with CoQ_{10}, however, have not been seen in all studies. In one double-blind study, 55 patients with CHF in NYHA classes III and IV, with ejection fractions less than 40%, and peak oxygen consumption less than 50% during standard therapy, were randomly assigned to receive CoQ_{10} (200 mg) or placebo. Analysis indicated that there were no changes in ejection fraction, peak oxygen consumption, and exercise duration in either group. Possible explanations for failure to achieve a therapeutic benefit in this study (and others) may be the result of CoQ_{10} not being strong enough to produce significant effects in more severe stages of CHF or the fact that blood levels of CoQ_{10} did not reach sufficient levels. Although the mean serum concentration of CoQ_{10} increased from 0.95 to 2.2 mcg/mL, in 19 of 22 patients on CoQ_{10}, blood levels were below the suggested threshold of 2.5 mcg/mL.[38]

A more recent study administered CoQ_{10} 100 mg three times a day for 4 weeks to 21 patients with CHF in a double-blind, placebo-controlled, crossover design. CoQ_{10} administration resulted in a threefold increase in plasma CoQ_{10} levels, improved left ventricular contractility, and subsequently enhanced functional capacity, without any side effects.[39]

A meta-analysis of randomized controlled trials recently confirmed that CoQ_{10} supplementation improved LVEF and cardiac output. An ongoing trial, Q-SYMBIO (Symptoms, Biomarker status [BNP], and Long-term Outcome), will address whether CoQ_{10} supplementation extends survival in patients with CHF.[40]

An important consideration in patients with CHF in NYHA class IV, is that they often fail to achieve adequate plasma CoQ_{10} levels (>2.5 mcg/mL) on supplemental ubiquinone at dosages up to 900 mg/day. In one study, seven patients with subtherapeutic plasma CoQ_{10} levels (mean level, 1.6 mcg/mL, on an average dose of 450 mg of ubiquinone a day [150 to 600 mg/day]) were changed to an average of 580 mg/day of ubiquinol (450 to 900 mg/day) with follow-up plasma CoQ_{10} levels, clinical status, and ejection fraction measurements by echocardiography.[41] Mean plasma CoQ_{10} levels increased from 1.6 to 6.5 mcg/mL. Mean ejection fraction improved from 22% (10% to 35%) to 39% (10% to 60%) and NYHA class improved from a mean of class IV to a mean of class II (classes I to III). In this study, ubiquinol dramatically improved absorption in patients with severe heart failure, and the improvement in plasma CoQ_{10} levels was correlated with both clinical improvement and improvement in measurement of left ventricular function.

Protection During Cardiac Surgery

Cardiopulmonary bypass (CPB) is used in coronary artery bypass surgery, cardiac valve repair, and numerous other surgical procedures. CPB, although permitting life-saving surgical procedures, is known to induce oxidative stress. A prospective study of 30 individuals who underwent CPB randomized these patients to oral CoQ_{10} (150 to 180 mg/day) or placebo for 7 to 10 days preoperatively. The group that received CoQ_{10} had significantly fewer reperfusion arrythmias, lower requirements for inotropic agents, mediastinal drainage and blood products, and shorter hospital stays compared with the control group.[42]

Postoperative low cardiac output is a major cause of early death after cardiac surgery. Fifty patients who underwent cardiac surgery for acquired valvular lesions were randomly assigned to receive 30 to 60 mg/day of CoQ_{10} for 6 days before surgery or to a control group that did not receive CoQ_{10}. Postoperatively, a state of severe low cardiac output developed in 48% of the patients in the control group, compared with only 12% of those in the CoQ_{10} group. These results suggested that preoperative administration of CoQ_{10} increased the tolerance of the heart to ischemia during aortic cross-clamping.[43]

Hypertension

The majority of studies exploring CoQ_{10} in the treatment of high blood pressure have been uncontrolled, or have used CoQ_{10} in combination with conventional antihypertensive medical treatments, making these studies difficult to interpret. In one study, 109 patients with essential hypertension received CoQ_{10} (average dose, 225 mg/day) in addition to their usual antihypertensive regimen. The dosage of CoQ_{10} was adjusted according to clinical response and blood CoQ_{10} levels (the aim was to attain blood levels >2 mg/mL). The need for antihypertensive medication declined gradually, and after a mean treatment period of 4.4 months, about half of the patients were able to discontinue between one and three drugs.[44] A review of studies on CoQ_{10} in the treatment of hypertension (12 clinical trials, 362 patients) concluded that in hypertensive patients, CoQ_{10} has the potential to lower systolic and diastolic blood pressure, without significant side effects. Among all included studies, decreases in systolic blood pressure ranged from 11 to 17 mm Hg and in diastolic blood pressure from 8 to 10 mm Hg.[45] In 3 of the 12 studies, CoQ_{10} was given in addition to existing antihypertensive medication, and in 1 of these, more than 50% of the patients were able to cease taking at least 1 antihypertensive medication during the trial.

The mechanism for the antihypertensive action of CoQ_{10} is thought to be due to its counteracting vasoconstriction, resulting from impaired ability of the endothelium to induce nitric oxide mediated relaxation of underlying smooth muscle.[45]

Cancer

Because of its role in enhancing immune function, CoQ_{10} has been considered as a possible anticancer agent. In one study, 32 women with breast cancer, who were classified as "high risk" because of tumor spread to the axillary lymph nodes, received 90 mg/day of CoQ_{10}, along with vitamins C and E, β-carotene, and essential fatty acids. In six of these women, the tumor became smaller. During the 18-month treatment period, none of the patients died (the expected number of deaths was four), and none showed signs of further distant metastases. Six patients had an apparent partial remission. In addition, patients receiving CoQ_{10} required fewer pain killers.[46] In follow-up, a pilot study using this nutrient cocktail evaluated the survival of 40 patients with end-stage cancer over 9 years. Median survival of individuals receiving the CoQ_{10}-containing nutrient cocktail was 40% longer than median predicted survival using the calculated Kaplan-Meier curve.[47]

Anthracyclines are a class of drugs used in cancer chemotherapy for a wide range of tumors. The clinical value of these agents is limited by their cardiotoxicity, which is believed to be due to irreversible damage to heart cell mitochondria. These agents cause severe oxidative stress in cardiac inner mitochondrial membranes, resulting in damage to mitochondrial DNA and subsequent myocyte death.[48]

Research from the 1980s showed that cancer patients receiving doxorubicin (Adriamycin), a commonly used anthracycline, had lower myocardial levels of CoQ_{10} than did controls, and that the magnitude of CoQ_{10} depletion was directly related to the severity of cardiac impairment.[49] To determine the effect of CoQ_{10} supplementation on doxorubicin cardiotoxicity, seven patients receiving doxorubicin were also given 100 mg/day of CoQ_{10}, beginning 3 to 5 days before doxorubicin was started. Another seven patients (control group) received doxorubicin without CoQ_{10}. Cardiac function deteriorated significantly in the control group, whereas patients given CoQ_{10} had little or no cardiotoxicity, although the cumulative dose of doxorubicin in the CoQ_{10} group was 50% greater than that in the control group.[50] These preliminary data, coupled with strong scientific rationale, suggest that CoQ_{10} supplementation should be considered for the prevention and treatment of anthracycline-induced cardiotoxicity.

Physical Performance

Because CoQ_{10} is involved in energy production and its concentration in muscle is correlated with performance, it is possible that supplementation may enhance aerobic capacity, muscle performance, and recovery.[51-53] In one study, six healthy sedentary men (mean age, 21.5 years) performed a bicycle ergometer test before and after taking CoQ_{10} (60 mg/day) for 4 to 8 weeks.[54] CoQ_{10} treatment improved certain performance parameters, including work capacity at submaximal heart rate, maximal workload, maximal oxygen consumption, and oxygen transport. These improvements ranged from 3% to 12% and were evident after about 4 weeks of supplementation. In a double-blind study in sedentary men, 100 mg/day of CoQ_{10} showed performance-enhancing effects during repeated bouts of supramaximal exercises.[55]

Although these studies suggest that administration of CoQ_{10} improves physical performance in sedentary individuals, other publications are conflicting. Larger studies are needed to confirm the performance enhancement capacity of CoQ_{10}.[56]

Diabetes Mellitus

Low tissue levels of CoQ_{10} have been consistently reported in diabetic patients. There are several mechanisms by which CoQ_{10} may be of therapeutic value in diabetes.[57,58] Improved blood pressure and long-term glycemic control have been reported with CoQ_{10} supplementation (100 mg twice daily).[59] Enhancement of endothelial function may offer some protection against arteriopathies.[60] A study of 80 dyslipidemic type 2 diabetics found that CoQ_{10} (200 mg/day) in combination with fenofibrate (200 mg/day) significantly improved endothelial and nonendothelial forearm vasodilatory function.[61] This effect was not found with either therapy alone or in a placebo group. An accumulating body of research demonstrates a link between mitochondrial dysfunction and type 2 diabetes. The mitochondrial enhancement offered by supplemental CoQ_{10} appears to offer some therapeutic value against a defect in cellular energy production.[62,63]

Twenty-seven patients with ventricular premature beats (VPBs) and no evidence of organic heart disease received placebo for 3 to 4 weeks, followed by 60 mg/day of CoQ_{10} for 4 to 5 weeks. The reduction in VPBs was significantly greater after CoQ_{10} than after placebo. The beneficial effect of CoQ_{10} was seen primarily in diabetics, in whom the mean reduction in VPB frequency was 85.7%. A significant reduction in VPBs also occurred in 1 (11%) of 9 otherwise healthy patients and in 4 (36%) of 11 patients with hypertension.[64]

Male Infertility

Sperm dysfunction in infertile men has been associated with lipid peroxidation and decreased antioxidant defenses in spermatozoa.[65] A statistically significant correlation between CoQ_{10} levels and sperm count was found in 32 patients with a history of infertility.

Research suggested that sperm cells with low motility and abnormal morphology have low levels of CoQ_{10}.[66] Sperm cells with low CoQ_{10} concentrations might be less capable of quenching free radicals, and might also be compromised in their ability to produce ATP in these highly metabolically active cells. Some authors suggested using the reduced-to-oxidized CoQ_{10} ratio as a diagnostic test for asthenozoospermia.[67] In a 6-month, uncontrolled open trial, in which infertile men were supplemented orally with CoQ_{10}, sperm cells demonstrated a significant increase in motility, and both seminal plasma and sperm cell quantity of CoQ_{10} increased.[68] This was supported by other studies on both sperm motility and fertilization rates.[69,70]

Parkinson's Disease

Excessive free radical production is largely responsible for dopaminergic cell death seen in Parkinson's disease (PD). Both as a cause and an effect of excessive oxidative stress, there is reduced activity of complex I of the mitochondrial electron transport chain. Given that CoQ_{10} is essential for the function of complex I and is also a powerful antioxidant, it holds therapeutic potential in the treatment of PD. Reduced levels of CoQ_{10} were demonstrated in the platelets of individuals with PD, and CoQ_{10} levels were strongly correlated with activity in complexes I and II/III. Clinically, it was demonstrated that oral CoQ_{10} increased complex I activity.[71]

A safety trial of CoQ_{10} supplementation in PD showed promising results.[19] All of the patients had the three primary features of PD—tremor, stiffness, and slowed movements—and were diagnosed with the disease within 5 years of the time they were enrolled. After initial screening and baseline blood tests, the patients were randomly divided into four groups. Three of the groups received CoQ_{10} at three different doses (300, 600, and 1200 mg/day), whereas a fourth group received a matching placebo for 16 months. The group that received the highest dose of CoQ_{10} (1200 mg/day) displayed a 44% reduction in PD progression compared to placebo,. The groups that received 300 and 600 mg/day developed slightly less disability than the placebo group, but the effects were less than those in the group that received the highest dosage of CoQ_{10}. Average plasma levels were approximately 1.8, 2.1, and 4.5 mcg/mL, respectively, for the 300, 600, and 1200 mg dosages. These results indicated that the beneficial effects of CoQ_{10} in PD might require adequate plasma levels. It is important to point out in this study that CoQ_{10} was administered along with vitamin E at a dosage of 1200 international units (IU) per day. Because high dosages of vitamin E interfere with CoQ_{10} absorption,[7] it might have prevented higher levels of CoQ_{10} from being achieved. The researchers were aware of this issue, but chose to include the vitamin E, given its apparent protective role against PD at the time (see Chapter 196 on Parkinson's Disease for more information).

Two recent studies cast doubt on the therapeutic efficacy of CoQ_{10} in PD. In a German study, a nanonized ubiquinone form of CoQ_{10} at a dosage of 100 mg three times daily or a matching placebo was given to 131 patients with PD for 3 months. Plasma levels of CoQ_{10} reached 4.6 mcg/mL in the treatment group, yet no effect on PD symptoms was shown. These results indicated that other factors might be responsible for determining the efficacy of CoQ_{10} in PD beyond achieving effective plasma levels.

On May 27, 2011, the National Institute of Neurological Diseases and Strokes (NINDS) stopped a Phase III study of CoQ_{10} for treatment of early stage PD.[72] The study enrolled 600 patients with early PD at 67 sites throughout North America. Participants were randomized to receive one of the two dosing levels of active CoQ_{10} (1200 or 2400 mg/day) or matching placebo. All subjects also received vitamin E at a dosage of 1200 IU/day. Although CoQ_{10} was shown to be safe, results of an interim analysis showed that it was futile to complete the study because longer patient follow-up was not likely to demonstrate a statistically significant difference between active treatment and placebo. However, at the time of this writing no data from the trial had been published.

Friedreich's Ataxia

Friedreich's ataxia (FRDA) is a progressive neurologic disease characterized by loss of myelin in the central nervous system. Evidence indicates that mitochondrial oxidative stress in FRDA may be responsible for the cardiomyocyte hypertrophy associated with this disease.[73] In a placebo-controlled trial, idebenone (a synthetic CoQ_{10} analog) significantly decreased heart hypertrophy (more than 20% decrease) in about 50% of study participants, with no adverse effects.[74,75]

A second study combined CoQ_{10} with vitamin E in an attempt to address two of the key features of FRDA—decreased mitochondrial respiratory chain function and increased oxidative stress. This therapy resulted in a rapid and sustained increase in the amount of energy generated by the diseased heart muscle, which

returned to near-normal levels. The improvements in skeletal muscle energy generation paralleled those of the heart but were less substantial.[76]

A 2-year intervention study of CoQ_{10} with vitamin E in 50 FRDA patients demonstrated that low baseline levels of CoQ_{10} were the single best predictor of a positive clinical response.[77]

Muscular Dystrophy

The muscular dystrophies (MDs) are a group of hereditary diseases characterized by the progressive loss of muscle cells. In some types of MD, an impairment of mitochondrial function may contribute to the pathogenesis of the disease. Several studies demonstrated a deficiency of CoQ_{10} in muscle mitochondria of humans with MD.[27] In addition, serum CoQ_{10} levels were significantly (P <0.05) inversely correlated with the degree of the genetic defect.[78] In addition to enhancing mitochondrial function, 90 days of CoQ_{10} supplementation resulted in markedly reduced inflammatory insult in animal models of MD.[79]

The first double-blind trial of CoQ_{10} in the treatment of individuals with MDs and neurogenic atrophies concluded, "Patients suffering from these muscle dystrophies and the like should be treated with vitamin CoQ_{10} indefinitely."[80] The same group conducted two studies on patients between 7 and 69 years of age who had MDs associated with cardiac diseases, including the Duchenne, Becker, and the limb-girdle dystrophies; myotonic dystrophy; Charcot-Marie-Tooth disease; and the Welander disease. Individuals were treated for 3 months with 100 mg/day CoQ_{10} or a matching placebo. In both trials, definitely improved physical performance was recorded in the groups receiving CoQ_{10}. Cardiac function was monitored by technicians who were blinded to treatment group. In each case, they correctly identified the treatment group to which the patient had been assigned on the basis of improvement or lack of improvement in cardiac function.

In a smaller double-blind study, 100 mg of CoQ_{10} was given daily for 3 months to 12 patients with progressive MD. CoQ_{10} treatment resulted in significant improvements in cardiac output and stroke volume, as well as increased physical well-being in four of eight patients.[27] Subjective improvements included increased exercise tolerance, reduced leg pain, better control of leg function, and less fatigue.

Immune Function

A number of studies demonstrated immunomodulatory effects of CoQ_{10} or its analogs.[81-83]

In a study of eight chronically ill patients, administration of 60 mg/day of CoQ_{10} was associated with significant increases in serum levels of immunoglobulin-G after 27 to 98 days of treatment.[84] In a cytokine analysis of white blood cells from 19 human volunteers, tumor necrosis factor-α levels were significantly decreased and interleukin-2 levels increased when incubated with CoQ_{10} in vitro.[85]

Acquired Immunodeficiency Syndrome

Because oxidative stress is believed to be involved in the pathogenesis of AIDS-related diseases, the antioxidant activity of CoQ_{10} may be of value for individuals with AIDS.[85,86]

Early studies suggested blood levels of CoQ_{10} were significantly lower in patients with AIDS and AIDS-related complex than in healthy controls, and that supplementation with CoQ_{10} improved ratios of lymphocytes.[87] Nucleoside reverse transcriptase inhibitor therapy, a mainstay of conventional human immunodeficiency virus management, has been associated with myopathy due to side effects on myocyte mitochondria. There is one report of CoQ_{10} alleviating this myopathy, thus permitting continuation of nucleoside reverse transcriptase inhibitor therapy.[88]

Toxicant Exposure

Many occupational and environmental toxicant exposures affect the mitochondrial respiratory chain.[89-93] Damage to the respiratory chain can decrease mitochondrial membrane potential, leading to upregulated apoptosis; CoQ_{10} demonstrated the ability to reduce this membrane-potential damage.[94,95] Although current diagnosis and treatment of environmentally related illnesses remain controversial, cytoprotection with CoQ_{10} may be an effective therapeutic method to reduce mitochondrial damage due to exposure to toxicants, both acute and chronic, and should be a focus of further research.[96]

Topical Antiaging Effects

In recent years, makers of several over-the-counter skin creams have begun advertising the addition of CoQ_{10} as an ingredient capable of curbing the aging process. In a clinical trial, topical CoQ_{10} was able to protect against ultraviolet A–mediated oxidative stress, suppress the expression of collagenase, and cause a reduction in wrinkle depth.[23]

Side Effects

CoQ_{10} appears to be safe and well tolerated in dosages up to 1200 mg/day in adults and up to 10 mg/kg body weight/day in children. Because safety during pregnancy and lactation has not been established, CoQ_{10} should not be used during these times unless the potential clinical benefit outweighs the risks. CoQ_{10} is contraindicated in cases of known hypersensitivity. In a series of 5143 patients treated with 30 mg/day of CoQ_{10}, the following incidence of side effects was reported[43]:

- Epigastric discomfort, 0.39%
- Loss of appetite, 0.23%
- Nausea, 0.16%
- Diarrhea, 0.12%

DRUG INTERACTIONS

Cholesterol-lowering statin drugs such as lovastatin, rosuvastatin, and pravastatin inhibit the enzyme 3-hydroxy-3-methylglutaryl CoA reductase, which is required for biosynthesis of both cholesterol and CoQ_{10}. Thus, administration of these drugs might compromise CoQ_{10} status by decreasing its synthesis, and statin-associated myopathy has been hypothesized to be related to a depletion of CoQ_{10}. Although some trials demonstrated that statin therapy did reduce serum or muscle levels of CoQ_{10},[97,98] whether or not this CoQ_{10} depletion caused the myopathy remains controversial.[99] Given that statins are typically prescribed to lower cholesterol, with the intention being the prevention and treatment of cardiovascular disease, the concomitant use of Q_{10} seems well-justified.

The β-blockers propranolol and metoprolol were shown to inhibit CoQ_{10}-dependent enzymes.[100] The antihypertensive effect of these drugs might therefore be compromised in the long run by the development of CoQ_{10} deficiency. In one study, administration of 60 mg/day of CoQ_{10} reduced the incidence of drug-induced malaise in patients receiving propranolol.[101]

A number of phenothiazines and tricyclic antidepressants were also shown to inhibit CoQ_{10}-dependent enzymes. It is therefore possible that CoQ_{10} deficiency might be a contributing factor to the cardiac side effects that are frequently seen with these drugs. In two clinical studies, supplementation with CoQ_{10} improved electrocardiographic changes in patients on psychotropic drugs.[102]

Several case reports describing potential interactions between CoQ_{10} and warfarin have been reported. CoQ_{10} is structurally related to menaquinone (vitamin K2) and may have procoagulant effects.[103] In each of these patients, the international normalized ratio (INR), which had been stable and therapeutic, fell below the therapeutic range within 2 weeks of beginning CoQ_{10} supplementation (as low as 30 mg/day).[104] The INR returned to the therapeutic range after CoQ_{10} was discontinued. It is recommended that the INR be monitored closely if these agents are to be used concomitantly. However, in a double-blind trial, administration of 100 mg/day of CoQ_{10} for 4 weeks had no effect on the INR in 21 patients on long-term warfarin therapy.[105] Thus, the sporadic case reports of an interaction between CoQ_{10} and warfarin might have been due to random fluctuations in INR values, rather than to CoQ_{10}.[8]

In a subchronic toxicity assessment, the no observed adverse effect level in rats was estimated to be 600 mg/kg per day for males and 200 mg/kg per day for females; in male and female dogs, the no observed adverse effect level was estimated to be more than 600 mg/kg per day.

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CHAPTER 80

Coleus forskohlii

Michael T. Murray, ND

Coleus forskohlii (family: Labiatae)
Synonyms: *Coleus barbatus*, *Plectranthus barbatus*, *P. forskohlii*
Common name: coleus

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GENERAL DESCRIPTION

Coleus forskohlii, a perennial, is a small member of the mint (Labiatae) family. It grows on sun-exposed, dry hill slopes between an altitude of 1000 and 6000 feet in subtropical, temperate climactic zones. Thus, it is found in India, Nepal, Sri Lanka, and Thailand. Its Latin name comes from the word *coleos*, which means "sheath" and refers to the fused filaments that form a sheath around the stylus of the flower. The epithet, *forskohlii*, commemorates the Finnish botanist Forskal, who traveled extensively in Egypt and Arabia in the eighteenth century.

The radially spread rootstock is the portion of the plant that is used for medicinal purposes. The rootstock is also the source of a compound of unique biological importance, forskolin. No other species of *Coleus* contains forskolin.

CHEMICAL COMPOSITION

The primary chemical of clinical interest contained in *C. forskohlii* is the diterpine forskolin (Figure 80-1). In 1974, forskolin was discovered during a large-scale screening of medicinal plants by the Indian Central Drug Research Institute. The screening revealed the presence of a hypotensive and spasmolytic component, which was initially named coleanol.[1] Additional investigation determined the exact chemical structure, and the name was changed to forskolin. From 1981 to 2010, forskolin was used in more than 15,000 in vitro and in vivo experimental studies designed to better understand the cellular processes governed by cyclic adenosine monophosphate (cAMP). Although most of these studies used this isolated constituent, there is evidence that other components within the plant extract may have biological activity, as well as enhance the absorption and action of forskolin.

HISTORY AND FOLK USE

C. forskohlii has a long history of use in Ayurvedic, Siddha, and Unani systems of medicine. Studies of the pharmacologic activity of forskolin substantiate the traditional uses of *C. forskohlii* in such conditions as[1]:

- Cardiovascular disease
- Eczema
- Abdominal colic
- Respiratory disorders
- Painful urination
- Insomnia
- Convulsions

PHARMACOLOGY

As noted in a landmark experiment in 1981, the basic mechanism of action of forskolin is the activation of adenylate cyclase, which increases cAMP in cells.[2] cAMP is perhaps the most important cell-regulating compound. Once formed, it activates many other enzymes involved in diverse cellular functions.[3]

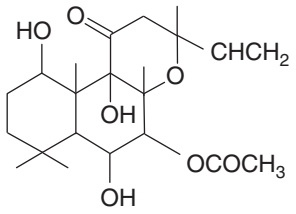


FIGURE 80-1 Forskolin.

Under normal situations, cAMP is formed when an activating hormone (e.g., epinephrine) binds to a receptor site on the cell membrane and stimulates the activation of adenylate cyclase. This enzyme is found in all cellular membranes, and only the specificity of the receptor site determines which hormone will activate it in a particular cell. In contrast, forskolin appears to directly activate adenylate cyclase, bypassing hormonal transmembrane activation of adenylate cyclase.

The physiologic and biochemical effects of a raised intracellular cAMP level include the following:

- Inhibition of platelet activation and degranulation
- Inhibition of mast cell degranulation and histamine release
- Increased force of contraction of heart muscle
- Relaxation of the arteries and other smooth muscles
- Increased insulin secretion
- Increased thyroid function
- Lipolysis

Forskolin possesses additional mechanisms of action independent of its ability to directly stimulate adenylate cyclase and cAMP-dependent physiologic responses.[4] Specifically, forskolin was shown to inhibit a number of membrane transport proteins and channel proteins through a mechanism that did not involve the production of cAMP. The result was a transmembrane signaling that resulted in activation of other cellular enzymes. Research is under way to determine the exact receptors to which forskolin binds.

Another action of forskolin is the inhibition of platelet-activating factor (PAF) by interfering with PAF binding to receptor sites.[5] PAF plays a central role in many inflammatory and allergic processes, including neutrophil activation, increased vascular permeability, smooth muscle contraction (e.g., bronchoconstriction), and reduction in coronary blood flow. Treatment of platelets with forskolin before PAF exposure results in a 30% to 40% decrease in PAF binding. This decrease in PAF binding caused by forskolin was concomitant with a decrease in the physiologic responses of platelets induced by PAF. However, this forskolin-induced decrease in PAF binding was not a consequence of cAMP formation, as the addition of a cAMP antagonist did not inhibit the action of forskolin. In addition, the inactive analog of forskolin, dideoxyforskolin, which does not activate adenyl cyclase, also reduced PAF binding to its receptor. Researchers speculated that the action of forskolin on PAF binding was due to a direct effect of this molecule and its analog on the PAF receptor itself or to components of the postreceptor signaling for PAF.

CLINICAL APPLICATIONS

The therapeutic ramifications of *C. forskohlii* based on the pharmacology of forskolin are immense. In many conditions, a decreased intracellular cAMP level is thought to be a major factor in the development of the disease process. *C. forskohlii* appears to be especially well indicated in the following types of conditions:

- Atopic dermatitis
- Asthma
- Psoriasis
- Angina
- Hypertension
- Weight Loss
- Glaucoma

Although *C. forskohlii* can be used alone, it may prove to be most useful when combined with other botanicals or measures, or both, in the treatment of these disorders.

Inflammatory Conditions

Allergic conditions such as asthma and eczema are characterized by a relative decrease in cAMP in both the bronchial smooth muscle and the skin. As a result, mast cells degranulate and smooth muscle cells contract more readily. In addition, these allergic conditions are also characterized by excessive levels of PAF.

Asthma and Eczema

Current drug therapy for allergic conditions like asthma and eczema is largely designed to increase cAMP levels by using substances that either bind to receptors to stimulate adenylate cyclase (e.g., corticosteroids) or inhibit the enzyme phosphodiesterase, which breaks down cAMP once it is formed (e.g., methylxanthines). These actions are different than forskolin's ability to increase the production of cAMP via transmembrane activation of adenylate cyclase. The cAMP-elevating action of forskolin supports the use of *C. forskohlii* extracts alone or in combination with standard drug therapy in the treatment of virtually all allergic conditions.

C. forskohlii extracts may be particularly useful in asthma, as increasing intracellular levels of cAMP results in relaxation of bronchial muscles and relief of respiratory symptoms. Forskolin was shown to have remarkable effects in relaxing constricted bronchial muscles in asthmatics.[6-8] This type of smooth muscle is also found in the gastrointestinal tract, uterus, bladder, and arteries. Forskolin was shown to have tremendous antispasmodic action on these various smooth muscles. This antispasmodic action of forskolin supports the folk medicine use of *C. forskohlii* in the treatment of not only asthma, but also intestinal colic, uterine cramps (menstrual cramps), painful urination, angina, and hypertension. In addition to forskolin's ability to relax smooth muscle, its other antiallergic activities, such as inhibiting the release of histamine and synthesis of allergic compounds, are also beneficial in treating asthma.[9]

One double-blind clinical study sought to compare the antiasthmatic effects of forskolin with the drug fenoterol. Sixteen patients with asthma were studied using three different preparations:

- Single inhalation dose of fenoterol (as a dry powder capsule [0.4 mg])
- Metered doses of fenoterol (0.4 mg)
- Forskolin dry powder capsules (10 mg)

All three preparations caused significant improvement in respiratory function and bronchodilation. However, although the fenoterol preparations caused tremors and decreased blood potassium levels, no such negative effects were seen with forskolin.

In another study, the bronchodilating effect (after 5 minutes) of forskolin was as good as that produced by fenoterol in 12 healthy volunteers (nonsmokers), as determined by whole body plethysmography.[10] Both substances were administered by metered dose inhalers. At the beginning (after 3 and 5 minutes) of the study, the protective effect of forskolin against inhaled acetylcholine was as good as that produced by fenoterol, whereas later on (after 15 and 30 minutes), fenoterol provided stronger protection.

Whether orally administered forskolin in the form of *C. forskohlii* extract would produce similar bronchodilatory effects is yet to be determined. However, based on the plant's historical use and additional mechanisms of action, it appears likely.

Psoriasis

Psoriasis is a common skin disorder that seems to be caused by a relative decrease in cAMP compared with cyclic guanosine monophosphate (cGMP). The result is a tremendous increase in cell division. Cells divide in psoriasis at a rate 1000 times greater than normal. Preliminary studies indicated that forskolin might be of great benefit in individuals with psoriasis via its ability to reestablish the normal balance between cAMP and cGMP.[1]

Cardiovascular Effects

The most useful clinical applications of *C. forskohlii* extracts will probably be for cardiovascular diseases such as hypertension, congestive heart failure, and angina. The cardiovascular effects of *C. forskohlii* and its components have been studied in great detail.[1,11,12] Its basic cardiovascular actions involve lowering of blood pressure, along with improving contractility of the heart. Again, this is related to increasing cAMP levels throughout the cardiovascular system, which results in relaxation of the arteries and increased force of contraction. The net effect is significant improvement of cardiovascular function.

Hypertension and Cardiac Failure

Several clinical and animal studies supported the use of forskolin in hypertension and cardiac failure.[11-14] In one human study involving seven patients with dilated cardiomyopathy, forskolin was shown to improve left ventricular function primarily via reduction of preload and without raising metabolic costs.[13] This study confirmed earlier animal studies showing that forskolin increased the contractile force of heart muscle.[12]

In another human study, the hemodynamic effects of intravenous (3 mcg/kg per minute) forskolin given to patients with dilated cardiomyopathy were evaluated.[14] Although systemic vascular resistance and diastolic pressure decreased, forskolin had no effect on cardiac index, ejection fraction, or myocardial oxygen consumption at this low dosage. However, when a small dosage of dobutamine was given along with the forskolin, an increase in all four parameters was observed. At a higher dosage (4 mcg/kg per minute), forskolin increased heart function by 19% and produced a 16% rise in heart rate. However, these changes were associated with symptomatic flush syndromes. These results indicated that forskolin might best be used in congestive heart failure in combination with other botanicals, such as *Crataegus* (see Chapter 82).

Forskolin was also shown to be a direct cerebral vasodilator, indicating that it might prove to be useful in cerebral vascular insufficiency and poststroke recovery.[15]

An additional mechanism of action particularly beneficial in a wide range of cardiovascular conditions is inhibition of platelet aggregation. In this area, the evidence indicated that the standardized *C. forskohlii* extract was superior to pure forskolin.[16] In an animal model evaluating in vivo inhibition of platelet aggregation, rats were divided into four groups: group 1 received *C. forskohlii* extract (480 mg/kg supplying 20 mg/kg of forskolin); group 2 received forskolin (20 mg/kg); group 3 received dipyridamole; and group 4 served as the controls. All treatments were given orally once daily. Adenosine diphosphate-induced platelet aggregation was measured on odd days 1 through 15. All three treatments produced significant inhibition of platelet aggregation. On day 15, the inhibitions were approximately 42% for group 1, 37% for group 2, and 52% for group 3. Hence, the extract of *C. forskohlii* produced greater inhibition than the pure forskolin.

Weight Loss Programs

Forskolin was shown to stimulate lipolysis, as well as inhibit the synthesis of fat in adipocytes.[17-20] Forskolin was also shown to counteract the age-related decreased response of fat cells to lipolytic hormones like epinephrine.[21] In one double-blind clinical investigation, oral ingestion of forskolin (250 mg of 10% forskolin extract twice a day) for a 12-week period was shown to favorably alter body composition while concurrently increasing bone mass and serum free testosterone levels in overweight and obese men.[22] However, a similar study in slightly overweight females showed little benefit over a placebo.[23]

Glaucoma

In clinical studies, forskolin was shown to greatly reduce intraocular pressure (IOP) when it was applied directly to the eyes.[24-27] This effect indicated that topical forskolin preparations might be of benefit in the treatment of glaucoma. Unlike current drug therapy, forskolin actually increased intraocular blood flow, had no side effects, and did not induce miosis. Oral administration might prove effective as well. In an open-label pilot study, 16 patients with glaucoma and stable IOP underwent treatment with different topical drugs and were given a supplement containing 15 mg of forskolin along with rutin (200 mg), thiamin (0.7 mg) and riboflavin (0.8 mg) for 40 days, which produced a further decrease in IOP by roughly 20% of the initial value.[28]

OTHER CLINICAL APPLICATIONS

C. forskohlii extracts concentrated and standardized for forskolin content may prove to be useful in a number of other clinical applications, including the following:

- Hypothyroidism
- Malabsorption and digestive disorders
- Depression
- Prevention of cancer metastases
- Immune system enhancement

Hypothyroidism

Forskolin was shown to increase thyroid hormone production, as well as to stimulate thyroid hormone release.[29]

Malabsorption and Digestive Disorders

Forskolin stimulated digestive secretions, including the release of hydrochloric acid, pepsin, amylase, and pancreatic enzymes.[30,31] Forskolin was shown to promote nutrient absorption in the small intestine.[32] *C. forskohlii* extracts might prove to be quite useful in treating dry mouth, since forskolin increased salivation.[33]

Depression

Forskolin was shown to exert antidepressant activity in animal studies.[34]

Cancer Metastases

Forskolin was shown to be a potent inhibitor of cancer metastasis in mice injected with malignant cells.[35] As little as 82 mcg administered to mice inhibited metastasis by over 70%.

Immune System Enhancement

Forskolin exhibited potent immune system enhancement (primarily through activation of macrophages and lymphocytes) in several models.[36-38]

DOSAGE

The recommended dosage should be based on the level of forskolin. As the forskolin content of coleus root is typically only 0.2% to 0.3%, crude coleus products may not be sufficient to produce a pharmacologic effect. The safety of the whole root at high dosages is not as well studied. It is best to use standardized extracts that have known forskolin content.

Daily dosages follow:

- Forskolin: 5 to 10 mg two to three times a day
- Standardized extract (10% forskolin): 250 mg one to two times a day
- Dried root: 2 to 5 g two to three times a day

TOXICOLOGY

The animal studies on forskolin indicated low toxicity. The pharmacology of forskolin suggests it would be wise to restrict the use of *C. forskohlii* preparations in patients with low blood pressure and peptic ulcers.

DRUG INTERACTIONS

C. forskohlii preparations should be used cautiously in patients on prescription medications, especially antiasthmatics and antihypertensives, due to its ability to potentiate these and other drugs' effects.

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CHAPTER 81

Commiphora mukul (Mukul Myrrh Tree)

Michael T. Murray, ND

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Commiphora mukul (family: Burseraceae)
Common name: mukul myrrh tree

GENERAL DESCRIPTION

Commiphora mukul, a small, thorny tree that grows 4 to 6 feet tall, is native to Saudi Arabia and India. In its natural setting, the tree remains essentially free of foliage for most of the year. Its bark is ash colored and comes off in rough flakes, exposing the under-bark, which also peels off. When injured, the tree exudes a yellowish gum resin that has a balsamic odor. This oleoresin is referred to as "gum guggul" or "guggulu." This resin is used for medicinal purposes. When tapped during the winter, the average tree yields 1.5 to 2 lb of resin.[1]

CHEMICAL COMPOSITION

Guggulu contains a mixture of diverse chemical constituents that can be separated into several fractions.[1] The first step in the fractionation process involves mixing guggulu with ethyl acetate to yield soluble and insoluble fractions (Figure 81-1). The insoluble fraction, containing the carbohydrate constituents, is regarded as toxic and is the major reason why extracts of the soluble portion are preferred to crude gum guggul for medical use. The insoluble portion has no demonstrable pharmacologic activity other than toxicity.[1]

In contrast, the soluble portion possesses significant cholesterol-lowering and antiinflammatory activity. The soluble portion can be further separated into base, acid, and neutral fractions. The neutral portion possesses almost all of the cholesterol-lowering activity, whereas the acid portion possesses the anti-inflammatory components.[1]

On further purification of the neutral portion, it was determined that the ketone fraction contains the most potent cholesterol-lowering components. The ketone fraction is composed of C_{21} or C_{27} steroids, with the major components being Z- and E-guggulsterone (Figure 81-2). These compounds are considered the major active components of gum guggul and its extracts.[1]

For medicinal purposes, a standardized extract known as guggulipid, which is standardized to contain a minimum of 50 mg of guggulsterones per gram, is regarded as the most beneficial in terms of safety and effectiveness.[1,2] In addition to guggulsterones, guggulipid contains various diterpenes, sterols, esters, and fatty alcohols. These accessory components appear to exert a synergistic effect.[1,2]

HISTORY AND FOLK USE

Guggulu is a highly valued botanical medicine in the Indian system of medicine, Ayurveda. It is included in formulas for various health conditions, including rheumatoid arthritis and lipid disorders. The classic Ayurvedic medical text, the *Sushruta Samhita*, describes in detail the usefulness of guggul in the treatment of obesity and other disorders of fat metabolism, including "coating and obstruction of channels."[1,2]

Inspired by this description, researchers began examining, in well-designed scientific studies, the clinical effectiveness of gum guggul and its extracts in disorders of lipid metabolism—specifically, its ability to lower cholesterol and triglyceride levels and promote weight loss. This research resulted in the development of a natural

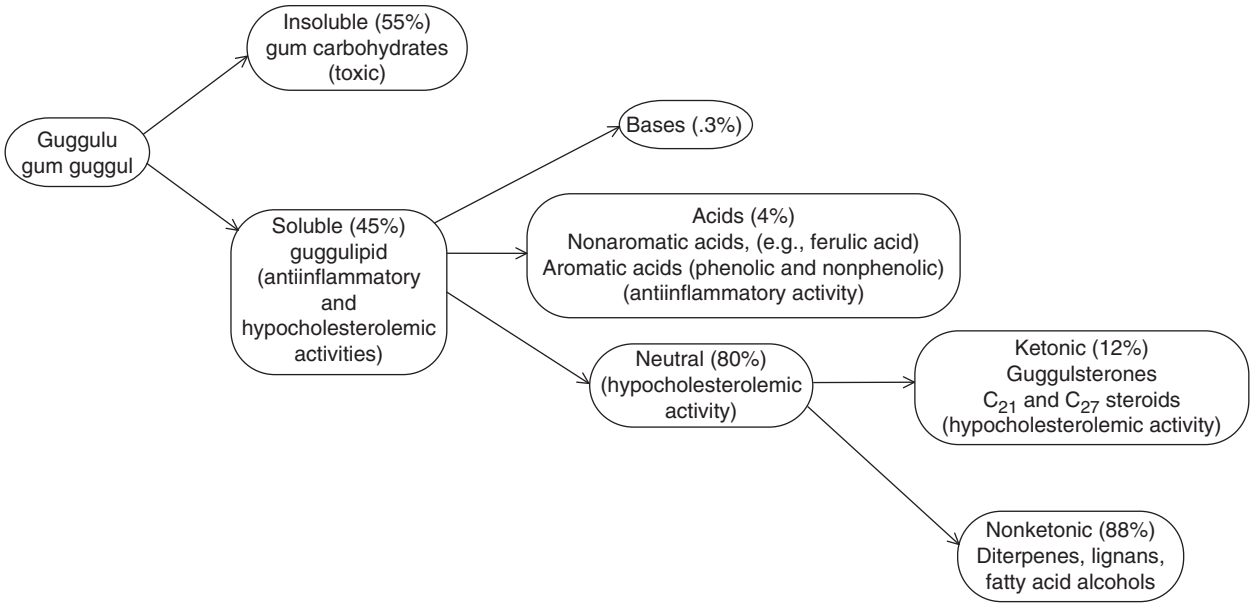


FIGURE 81-1 Chemical segregation of gum guggulu.

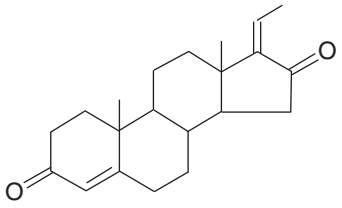


FIGURE 81-2 Guggulsterone.

cholesterol-lowering substance that is safer and more effective than many cholesterol-lowering drugs, including niacin. Guggulipid was granted approval in India for marketing as a lipid-lowering drug in 1986.[1,2]

PHARMACOLOGY

Lipid Disorders

Numerous studies in humans and animals showed that gum guggul (both crude and purified alcohol extract),[3-7] its petroleum ether extract (referred to as fraction A),[8-11] and guggulipid (standardized ethyl acetate extract)[12,13] all exert effective lipid-lowering activity. All lower both elevated cholesterol and triglyceride levels. The effect on cholesterol is particularly beneficial, as guggul lowers very low-density lipoprotein (VLDL) cholesterol and low-density lipoprotein (LDL) cholesterol, while simultaneously elevating high-density lipoprotein (HDL) cholesterol, thus offering protection against heart disease due to atherosclerosis.

Guggul preparations appear most indicated in type IIb (increased LDL, VLDL, and triglycerides) and type IV (increased VLDL and triglycerides) hyperlipidemias. Preliminary human clinical trials using guggulipid found that cholesterol levels showed typical reductions of 14% to 27% in total cholesterol levels in a 4- to 12-week period, whereas triglyceride levels dropped from 22% to 30%.[12-14] However, a larger double-blind study did not show that either of two doses of a standardized guggul extract (guggulipid, containing 2.5% guggulsterones) lowered LDL cholesterol levels in healthy adults with hyperlipidemia.[15] Subjects received either standard-dose guggulipid (1000 mg), high-dose guggulipid (2000 mg), or matching placebo three times daily for 8 weeks. LDL cholesterol levels decreased by 5% in the placebo group. Both standard-dose guggulipid and high-dose guggulipid raised levels of LDL cholesterol by 4%, respectively. There were no significant changes in levels of total cholesterol, HDL cholesterol, triglycerides, or VLDL cholesterol in response to treatment with guggulipid in the intention-to-treat analysis. Although guggulipid was generally well tolerated, six participants treated with guggulipid developed a hypersensitivity rash compared with none in the placebo group. These results call into question the clinical effectiveness of guggulipid despite plausible mechanisms of action.

In vitro studies showed that the primary mechanism of action involves guggulsterones acting as an antagonist ligand for the farnesoid X receptor (FXR) and upregulating the bile salt export pump. As a result, guggulsterones promote the conversion of cholesterol to bile acids and increase the uptake of LDL cholesterol from the blood by the liver.[14,16-19] Another possible action of guggulsterones in affecting lipid levels is their ability to stimulate thyroid function.[20,21]

Despite these noted in vitro effects, more research is needed to clarify the clinical usefulness of guggul as a lipid-lowering agent. However, guggul may have other benefits against atherosclerosis beyond lowering lipid levels. Gum guggul and its extracts, including guggulipid, have been shown to prevent the formation of atherosclerosis and aid in the regression of preexisting atherosclerotic plaques in animals. This implies that they may have similar effects in humans.

Gum guggul and guggulipid were also shown to prevent heart damage by free radicals and to improve heart metabolism.[9,14] Gum guggul and its extracts have a mild effect in inhibiting platelet aggregation and promoting fibrinolysis, implying that it may also prevent the development of a stroke or embolism.[2,14]

Antiinflammatory Effects

The guggulsterone fraction of gum guggul was shown to exhibit significant antiinflammatory action in experimental models of inflammation (e.g., raw paw edema and adjuvant arthritis

method).[22-24] Its activity in models of acute inflammation is comparable to approximately one fifth that of hydrocortisone and equal to phenylbutazone and ibuprofen.[22] In models of chronic inflammation, it was shown to be more effective than hydrocortisone, phenylbutazone, and ibuprofen in reducing the severity of secondary lesions. The antiinflammatory action is thought to be due to inhibition of delayed hypersensitivity reactions.[23,24] Guggulsterones exert a number of antiinflammatory effects, including inhibition of nuclear factor-κβ.[25]

The clinical application of these effects may include osteoarthritis. In an open trial of 30 patients with osteoarthritis of the knee, 500 mg of the concentrated extract three times daily produced significant improvements on the Western Ontario and McMaster University Osteoarthritis Index Total Score and subscales, visual analog scale, and 6-minute walk test. Western Ontario and McMaster University Osteoarthritis Index subscales were used as outcome measures.[26]

Anticancer Effects

Guggulsterone was shown to exert a wide range of anticancer effects, including an ability to modulate expression of proteins with antiapoptotic, cell survival, cell, angiogenic, and metastatic activities in tumor cells. As a result, evidence suggested that guggulsterone could suppress tumor initiation, promotion, and metastasis.[27] The clinical usefulness of these effects has not yet been determined.

DOSAGE

Although the crude oleoresin (gum guggul), alcohol extract, and petroleum ether extract all exert lipid-lowering and antiinflammatory action, they are associated with side effects (e.g., skin rashes, diarrhea) at the doses required to produce a clinical effect. Interestingly, in classic Ayurvedic texts, the purification of crude guggul in Triphala kashaya is recommended to eliminate these side effects.[2]

Guggulipid, the standardized ethyl acetate extract of the gum guggul, demonstrated not only greater clinical efficacy but also much greater patient tolerance than crude or purified gum guggul. The dosage of guggulipid is based on its guggulsterone content. The typical dosage, 25 mg of guggulsterone three times per day, is an effective treatment for elevated cholesterol levels, elevated triglyceride levels, or both. For a 2.5% guggulsterone content extract, this translates to an effective dose of 1000 mg three times/day.

For comparison, the daily dosages of the other forms follow:

- Crude gum guggul—10 g
- Alcoholic extract—4.5 g
- Petroleum ether extract—1.5 g

TOXICOLOGY

The side effects of crude gum guggul and alcoholic and petroleum ether extracts were discussed previously. In clinical studies, guggulipid did not display any untoward side effects, nor did it adversely affect liver function, blood sugar control, kidney function, or hematologic parameters.[11-13]

Safety studies in rats, rabbits, and monkeys demonstrated guggulipid to be nontoxic.[14] It does not possess any embryotoxic or fetotoxic effects and is therefore considered safe to use in pregnancy. In mice, the oral and intraperitoneal mean lethal dose values were 1600 mg/kg.[1]

DRUG INTERACTIONS

Although there are no reported guggulipid–drug interactions, one in vitro study with hepatocytes showed that guggulipid could induce the expression of CYP3A enzyme activity, suggesting that guggulipid therapy should be used cautiously in patients taking prescription medications that are metabolized by CYP3A family members, including such drugs as statins, ketoconazole (Nizoral), itraconazole (Sporanox), fexofenadine (Allegra), triazolam (Halcion), and many others.[28] In addition, guggulsterones demonstrated agonist activity against the estrogen receptor α isoform and the progesterone receptor; therefore, it should be used with caution with estrogen and/or progesterone preparations.

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CHAPTER 82

Crataegus oxyacantha (Hawthorn)

Michael T. Murray, ND

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Crataegus oxyacantha (family: Rosacea)
Synonym: *Crataegus laevigata*
Common names: hawthorn, may bush, whitethorn, haw

GENERAL DESCRIPTION

Crataegus oxyacantha is a spiny tree or shrub that is native to Europe. It may reach a height of 30 feet, but is often grown as a hedge plant. Its common name, hawthorn, is actually a corruption of "hedgethorn," because it was used in Germany to divide plots of land. Its botanical name, *C. oxyacantha,* is from the Greek kratos, meaning hardness (of the wood); oxus, meaning sharp; and akantha, meaning a thorn. The fruit and blossoms are used medicinally.[1]

Other species of crataegus (e.g., *C. monogyna, C. pentagyna*) contain similar constituents and likely have identical pharmacologic actions to *C. oxyacantha,* so they are suitable alternatives.[2,3]

CHEMICAL COMPOSITION

Hawthorn leaves, berries, and blossoms contain many biologically active flavonoid compounds, particularly anthocyanidins and proanthocyanidins (polymers of anthocyanidins, also known as biflavans or procyanidins) (Figure 82-1).[2-5] These flavonoids are responsible for the red to blue colors not only of hawthorn berries, but also of blackberries, cherries, blueberries, grapes, and many flowers as well. These compounds are highly concentrated in hawthorn berry and flower extracts.

High-performance liquid chromatography and thin-layer chromatography (of crataegus extracts) demonstrated that extracts of the flowers are particularly rich in flavonoids (e.g., quercetin, quercetin-3-galactoside, vitexin, vitexin-4′-rhamnoside), procyanidins (Figure 82-2), and oligomers of procyanidins.[5,6]

In addition to flavonoids, crataegus extracts also contain[7]:

- Cardiotonic amines (e.g., phenylethylamine, o-methoxy-phenylethylamine, tyramine, isobutylamine)
- Choline and acetylcholine
- Purine derivatives (e.g., adenosine, adenine, guanine, caffeic acid)
- Amygdalin
- Pectins
- Triterpene acids (ursolic, oleanolic, and crategolic acids)

HISTORY AND FOLK USE

Crataegus flowers and berries have been used primarily as cardiac tonics and mild diuretics in organic and functional heart disorders. They are also used for their astringent qualities to relieve sore throat pain.[1]

PHARMACOLOGY

The pharmacology of crataegus centers on its flavonoid components.[2,3] The proanthocyanidins in crataegus are largely responsible for its cardiovascular activities.

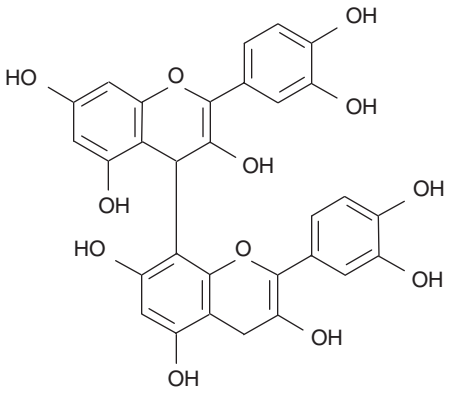


FIGURE 82-1 Proanthocyanidin B_2.

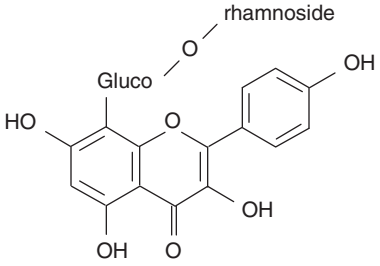


FIGURE 82-2 Vitexin-4′-rhamnoside.

Synergism with Vitamin C

As stated earlier, crataegus is particularly rich in anthocyanidins and proanthocyanidins. These flavonoids have strong "vitamin P" activity. Included in their effects are the abilities to increase intracellular vitamin C levels, stabilize vitamin C (by protecting it from oxidation), and decrease capillary permeability and fragility.[4,8,9]

Collagen-Stabilizing Action

Crataegus's flavonoid components possess significant collagen-stabilizing action. Crataegus procyanidins affect collagen metabolism in many ways, including the following:

- Reinforcement of the natural cross-linking of collagen that forms the collagen matrix of connective tissue (e.g., ground substance, cartilage, tendon)[2,4]
- Prevention of free radical damage due to potent antioxidant and free radical scavenging action[2,4,8-10]
- Inhibition of enzymatic cleavage by enzymes secreted by leukocytes during inflammation[4]
- Prevention of the release and synthesis of compounds that promote inflammation, such as histamine, serine proteases, prostaglandins, and leukotrienes[4]

Cardiovascular Effects

The beneficial effects of crataegus in the treatment of cardiovascular conditions appear to be a result of the following pharmacologic actions:

- Improvement of the blood supply to the heart by dilating the coronary vessels[2,3,11-15]
- Improvement of the metabolic processes in the heart, which results in an increase in the force of contraction of the heart muscle and elimination of some types of rhythm disturbances[2,3,11,16-18]
- Inhibition of angiotensin-converting enzyme (ACE)[19]

Crataegus's ability to dilate coronary blood vessels has been repeatedly demonstrated in experimental studies. This effect appears to be due to relaxation of vascular smooth muscle by a combination of direct effects on both the vascular endothelium and smooth muscle. In addition, various flavonoid components in crataegus have been shown to inhibit vasoconstriction by various substances, including hypophysin, histamine, and acetylcholine. In addition, procyanidins have been shown to inhibit ACE.[2,3,20]

Improvement in cardiac metabolism has been demonstrated in humans and animals who have received crataegus extracts.[2,3] The improvement is not only a result of increased blood and oxygen supply to the myocardium, but also a result of flavonoid-enzyme interactions. In particular, crataegus extracts and various flavonoid components in crataegus have been shown to inhibit cyclic adenosine monophosphate phosphodiesterase (cAMP-PDE).[21] This results in increased levels of cAMP within the myocardium, leading to a positive inotropic effect (i.e., an increase in the force of contraction). This is particularly beneficial in cases of congestive heart failure (CHF) (discussed in the section on "Congestive Heart Failure").

The procyanidins of crataegus demonstrated a specific inhibition of ACE similar to synthetic ACE inhibitors widely used in the treatment of hypertension.[20] The proanthocyanidins that appear to have the highest activity are proanthocyanidins B-5 3,3′-di-O-gallate and C-1 3,3′,3″-tri-O-gallate. It is not surprising that these proanthocyanidins are found in relatively high concentrations in hawthorn berries, flowers, and their extracts.[5,6]

CLINICAL APPLICATIONS

The clinical use of crataegus revolves around its cardiovascular effects. Its use in atherosclerosis, hypertension, and CHF, is discussed as follows.

Atherosclerosis

Crataegus preparations, although in a supplement form, should be thought of as a necessary food in the prevention and treatment of atherosclerosis. Increasing the intake of flavonoid compounds by taking crataegus extracts has numerous health-promoting effects, including reducing cholesterol levels and decreasing the size of existing atherosclerotic plaques.[22] This effect is probably a result of collagen stabilization.

A decrease in the integrity of the collagen matrix of the artery results in cholesterol deposition. Many researchers believe that if the collagen matrix of the artery remains strong, atherosclerotic plaque will never develop. Crataegus flavonoids, by increasing the integrity of collagen structures, may offer significant protection against atherosclerosis. In addition, feeding proanthocyanidin extracts to animals resulted in reversal of atherosclerotic lesions, as well as decreased serum cholesterol levels.

Flavonoids contained in hawthorn extracts appear to offer significant prevention, as well as potential reversing effects in the treatment of atherosclerotic processes, which are still the major causes of death in the United States.

Hypertension

Crataegus exerts a mild antihypertensive effect, which has been demonstrated in both experimental and clinical studies.[2] Its action in lowering blood pressure is unique in that it produces a number of diverse pharmacologic effects. Specifically, it dilates the coronary vessels, inhibits ACE, acts as an inotropic agent, and

possesses mild diuretic activity. Its clinical effects in lowering blood pressure, however, are generally mild.[19]

In one double-blind study evaluating crataegus hypotensive effects, 79 patients with type 2 diabetes were randomized to either crataegus extract (1200 mg/day) or placebo for 16 weeks. Hypotensive drugs were used by 71% of the study population, with a mean intake of 4.4 hypoglycemic and/or hypotensive drugs. Although there was no effect on systolic blood pressure, the diastolic blood pressure in the crataegus group dropped from a baseline of 85.6 mm Hg to 83.0 mm Hg compared with the placebo group (baseline: 84.5 mm Hg, outcome: 85.0 mm Hg). No herb–drug interaction was found.[23]

Crataegus's effects generally require prolonged administration, and in many instances it may take up to 2 weeks before adequate tissue concentrations are achieved. It should be kept in mind that as β-blockers lower blood pressure by reducing cardiac output, crataegus administration to patients on these drugs may produce a mild hypertensive response.

Congestive Heart Failure

Crataegus has a long history of use in the treatment of CHF, particularly in combination with digitalis or other herbs containing cardiac glycosides such as *Cereus grandiflorus,* also known as *Cactus grandiflorus,* and *Convallaria majalis.* It potentiates the action of the cardiac glycosides, presumably via its ability to inhibit cAMP-PDE and to interact with calcium channels.

Because of this enhancing effect, lower doses of cardiac glycosides can be used. In addition, magnesium has also been shown to augment digitalis action. For mild to moderate cases of CHF, crataegus extract used alone may be sufficient, but for moderate to severe CHF, it should be used in combination with other cardiac glycosides.

In early or mild stages of CHF, the effectiveness of crataegus was repeatedly demonstrated in double-blind studies.[2,3,24-31] In a meta-analysis of 10 trials including 855 patients with chronic heart failure (New York Heart Association [NYHA] classes I to III), it was concluded that hawthorn extract provided significant benefit in symptom control and physiologic outcomes as an adjunctive treatment for chronic heart failure. Exercise tolerance, the pressure–heart rate product, and symptoms (e.g., shortness of breath and fatigue) all improved significantly with hawthorn treatment compared with placebo.[32]

In one double-blind study, 30 patients with CHF (NYHA stage II) were assessed in a randomized, double-blind study.[27] Treatment consisted of a crataegus extract standardized to contain 15 mg procyanidin oligomers per 80 mg capsule. Treatment duration was 8 weeks, and the substance was administered at a dose of one capsule taken twice a day. The group receiving the crataegus extract showed a statistically significant advantage over placebo in terms of changes in heart function as determined by standard testing procedures. Systolic and diastolic blood pressures were also mildly reduced. Like all other studies with crataegus extracts, no adverse reactions occurred.

In another study, 78 patients with CHF (NYHA stage II) were given either 600 mg of extract standardized to contain 18.8% procyanidolic oligomers or placebo daily.[28] The parameter used to measure effectiveness was the patient's working capacity (W) on a bicycle ergometer. After 56 days of treatment, the crataegus group had a mean increase of 25 W compared with the placebo group's increase of only 5 W. In addition, the crataegus group also experienced a mild, but significant, reduction in systolic blood pressure (from 171 to 164 mm Hg) and heart rate (from 115 to 110 beats/min). There was no change in blood pressure or heart rate in the placebo group.

Crataegus provides a definite dose response. Individuals with more severe CHF require higher dosages to experience the most benefit. This comment is based on an important finding in a double-blind study of 209 patients with NYHA class III CHF. Although those receiving 900 mg of a crataegus extract standardized to contain 18.8% procyanidolic oligomers demonstrated improvement in all parameters tested, those receiving 1800 mg showed even better results.[30] The failure of some studies to demonstrate a therapeutic benefit with crataegus extracts may reflect inadequate dosages being administered.[33-35]

DOSAGE

Clearly, the dosage depends on the type of preparation and source material. The amount of crataegus extract used in various clinical studies on CHF was equivalent to 30 to 169 mg of epicatechin or 3.5 to 19.8 mg of flavonoids, usually administered in two or three doses. Standardized extracts are preferred, as flavonoid content in crude preparations can vary tremendously. The dosages listed for the various crataegus formulas are for use three times a day:

- Berries or flowers (dried): 3 to 5 g or as infusion
- Tincture (1:5): 4 to 5 mL (alcohol may elicit pressor response in some individuals)
- Fluid extract (1:1): 1 to 2 mL
- Freeze-dried berries: 1 to 1.5 g
- Flower extract (standardized to contain 1.8% vitexin-4′-rhamnoside or 18% procyanidolic oligomers): 200 to 600 mg

TOXICOLOGY

Crataegus was shown to have low toxicity, with an mean lethal dose of 25 mg/kg.[36] In a human study in patients with CHF, dosages at levels 100 times the typical dosage did not produce any evidence of toxicity. Although some studies showed that proanthocyanidins might be carcinogenic, more careful evaluation indicated that the carcinogenicity was probably due to nitrosamines found in the extracts used.[37] Purified proanthocyanidins were found to be nonmutagenic, according to the *Salmonella* mutagenicity assay system.

A total of 166 adverse events were reported in a review of 24 clinical studies and data from 5577 patients who received the daily dose (range, 160 to 1800 mg) and had 3 to 24 weeks of treatment with hawthorn monopreparations. Most of these adverse events were, in general, mild to moderate, with most frequent adverse events being dizziness/vertigo, gastrointestinal complaints, headache, and heart palpitation.[38] Postmarketing surveillance studies reported only mild and infrequent side effects with crataegus extract. In a study of 1011 patients, 14 adverse events (1.4%) occurred after the administration of 900 mg of hawthorn extract for 24 weeks. In two patients, a causal relation with crataegus was suspected, but was regarded by the treating doctors as unlikely. In another postmarketing surveillance study of 3664 patients who were treated with 900 mg of crataegus extract for 8 weeks, 48 patients (1.3%) reported adverse events, including hot flushes, stomach complaints, palpitations, dizziness, dyspnea, headache, and epistaxis. In 19 patients, this resulted in discontinuation of the treatment.[24]

DRUG INTERACTIONS

Hawthorn may potentiate or inhibit the actions of anticoagulants, antihypertensives, and cardiac glycosides. This concern is based primarily on theoretical grounds rather than clinical reports. Importantly, in a randomized, crossover trial with eight healthy volunteers, hawthorn did not significantly alter the pharmacokinetic parameters for digoxin. This suggests that both hawthorn and digoxin may be coadministered safely.[39]

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CHAPTER 83

Croton lechleri (Dragon's Blood)

Kathy Abascal, BS, JD RH(AHG), and Eric L. Yarnell, ND, RH(AHG)

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Croton spp. (family: Euphorbiaceae)

Synonym: Many Croton species are identified as dragon's blood, including *Croton lechleri*, *C. sordidus*, *C. urucurana*, *C. draco* (*C. draconoides*, *C. palanostigma*), *C. xalapensis*, and *C. erythrochilus*.[1-4]

Common names: dragon's blood, sangre de drago, sangre de grado, Lora sangre (sp.), sangre de perro (sp.)

GENERAL DESCRIPTION

Dragon's blood comes from the species of Euphorbiaceae trees native to Bolivia, Brazil, Colombia, Ecuador, and Peru that produce a red sap.[1] The sap ranges in color from faint to deep red, and occasionally a slight orange.

CHEMICAL COMPOSITION

The sap is used medicinally.[5] It consists primarily of proanthocyanidins (90%), including crofelemer, but also contains an important alkaloid, taspine, simple phenols, diterpenes, and phytosterols.[5-8]

HISTORY AND FOLK USE

Dragon's blood is used widely by the indigenous peoples of the Amazon basin, and the Spaniards reported that it was used widely in the Amazon region in the 1600s.[5,7] The sap is applied topically to abrasions, cuts, scratches, blisters, bites, and stings. It is taken internally in dilute form for gastrointestinal distress (e.g., gastritis, gastric ulcer, intestinal infections and inflammation, diarrhea). It is used as a gargle for sore throat; a vaginal antiseptic; a hemostatic after childbirth; a topical hemostatic for severe cuts and lacerations; and an analgesic applied directly to molar toothaches.[2] It is also taken internally for wound healing. The sap is used for various respiratory infections (tonsillitis, pharyngitis, lung infections/pneumonia, influenza, and colds).

PHARMACOLOGY

Analgesic Effect

Dragon's blood balm* had a significant analgesic effect compared with a placebo balm in a series of animal experiments.[3] Dragon's blood completely prevented hyperalgesia induced by a protease and blocked hyperalgesia induced by prostaglandin. Dragon's blood was analgesic even if the hyperalgesic stimuli were applied intradermally, suggesting that its active components can cross the skin. Dragon's blood inhibited the responses of mesenteric arteries to calcitonin generated peptide (a primary neurotransmitter of sensory afferent nerves) and attenuated the epithelial secretory response to capsaicin in guinea pigs, but not that of neurokinin-1 antagonist, suggesting a unique prejunctional and postjunctional effect on sensory afferent nerves. These pharmacologic results tend to confirm the traditional uses of dragon's blood to relieve itching, pain, edema, redness, and discomfort.

*One percent Zangrado Bute Bite Balm, Rainforest Phytoceuticals, LLC, Delmar, NY.

Antidiarrheal Effect

SP-303, a patented extract* of the procyanidolic oligomers (PCOs) from dragon's blood sap, restored intestinal fluid accumulation to near-normal levels in mice administered cholera toxin.[9]

Antimicrobial Effect

Several phenolic compounds and diterpenes isolated from dragon's blood demonstrated potent activity against *Bacillus subtilis* and *Escherichia coli* in vitro.[10] Dragon's blood sap significantly inhibited growth of gram-positive and gram-negative organisms in vitro, including *Proteus vulgaris, E. coli,* and *Staphylococcus aureus.*[11]

Antiproliferative or Cytotoxic Effect, or Both

Taspine, a dragon's blood alkaloid, was cytotoxic against KB and V-79 cells in vitro.[12] Dragon's blood induced apoptosis in human gastrointestinal cells in a dose-dependent manner, and cell proliferation decreased in all cells exposed to dragon's blood for 48 hours.[13] Overall, the effects were deemed similar to those observed with paclitaxel (Taxol). Dragon's blood significantly reduced cancer cell adhesion, with more than 85% of cells remaining in suspension. Taspine is also a topoisomerase inhibitor, but unlike other inhibitors such as doxorubicin and etoposide, taspine was cytotoxic to cells overexpressing drug efflux transporters and induced widespread apoptosis in spheroids and, to some extent, in vivo.[14]

Antiulcerogenic Effect

Dragon's blood administered at dilutions of 1:1000 and 1:10,000 in drinking water assisted the healing of ulcers in rats with acetic acid–induced gastric ulcers.[7] These doses were equivalent to doses used in traditional medicine for the treatment of gastric disorders. It healed ulcers comparably to a combination of penicillin and streptomycin and resulted in ulcers that were smaller, less inflamed, and with lower bacterial content. Whole dragon's blood sap was effective at lower doses than was SP-303. The sap contains trace amounts of compounds that are 30 times more potent than penicillin.

Antiviral Effect

Various compounds in dragon's blood showed antiviral activity against influenza, parainfluenza, herpes simplex viruses (HSVs) types I and II, and hepatitis A and B in vitro[15] A patented extract of dragon's blood sap (SP-303) showed antiviral activity against respiratory syncytial virus (RSV) and appeared to inhibit viral penetration of the host cell.[16] SP-303 also showed antiviral activity against two strains of HSV type 1, as well as a strain of HSV type 2 at a dose comparable to that of acyclovir.[17] The compound significantly reduced HSV lesion formation in the mouse vaginal model (applied topically in a 5% to 10% preparation).

At aerosol doses of 0.5 to 9.4 mg/kg per day, SP-303 increased the survival of mice lethally infected with RSV.[18] At aerosol doses of 1.3 to 9.8 mg/kg, it reduced lung titers of RSV in infected rats. SP-303 administered intraperitoneally also significantly reduced pulmonary RSV titers in infected rats with a minimum efficacious dose of 3 mg/kg.[19]

SP-303 administered once daily for 8 days beginning before or after influenza A infection in mice reduced lung consolidation, but was lethally toxic at the dose of 30 mg/kg per day. The drug administered as an aerosol (2.5, 5, and 10 mg/mL) for 1 hour twice daily also reduced lung consolidation in animals. However, when administered before virus exposure, SP-303 treatment lengthened mean day to death, but did not inhibit lung virus titer.[20]

Cicatrizant Effect

Dragon's blood precipitates proteins and other matrix elements, fostering accelerated wound healing with reduced pain, inflammation, and scarring.[3] Taspine showed a dose-related cicatrizant effect when administered in vivo to mice.[21]

CLINICAL APPLICATIONS

Analgesic

Dragon's blood sap offered rapid symptomatic relief in a placebo-controlled study of insect bites.[3] Ten Terminix workers exposed to frequent insect bites applied either dragon's blood balm* or placebo balm to bites and recorded the results over a 3-month period. When workers had multiple simultaneous bites, they used both balms on different bites and compared the results. Most of the treated bites were caused by fire ants, which elicit initial pain followed by persistent, intense itching.

Diarrhea

SP-303, a patented compound extracted from dragon's blood sap, shortened the duration of diarrhea by 21% in a double-blind, randomized, placebo-controlled study of 184 patients with travel-related diarrhea.[22] Patients were treated four times a day for 2 days with 125, 250, or 500 mg doses or placebo. The drug was most effective at the 125 and 250 mg doses. In another double-blind, randomized, placebo-controlled study, SP-303 significantly reduced stool weight and abnormal stool frequency in human immunodeficiency virus (HIV) positive patients with diarrhea.[23] Positive results were seen by day 4 in the 26 members of the active group treated with 500 mg orally of SP-303 every 6 hours compared with the 25 patients in the placebo group. Crofelemer, a proanthocyanidin in the sap, improved both pain- and discomfort-free days in a study of patients with diarrhea-predominant irritable bowel syndrome. This double-blind, randomized, placebo-controlled study of 242 patients spanned 12 weeks and tested doses of 125, 250, and 500 mg crofelemer twice daily. Crofelemer did not reduce stool frequency but acted as a nonconstipating, visceral analgesic in female patients only.[24] Crofelemer is also currently being studied in clinical trials for the treatment of secretory diarrheas associated with cholera and HIV/acquired immunodeficiency syndrome (AIDS).[25]

Herpes Simplex Viral Lesions

Virend (a topical formulation of SP-303) showed a trend toward decreased lesion pain in a double-blind, placebo-controlled study of 45 patients positive for HIV antibody with active-phase, culture-positive genital or perineal HSV lesions, or both.[9] Virend was more active in patients with smaller lesion areas. Two

*SP-303 is available as a topical drug (Virend) and an internal drug (Provir), Shaman Pharmaceuticals, South San Francisco, Calif.

*One percent Zangrado Bute Bite Balm.

patients experienced pain and burning after applying Virend, and one withdrew from the study for this reason. In another open-label study, nine AIDS patients with HSV unresponsive to acyclovir were treated with SP-303.[26] The drug showed a transient positive effect but failed to completely heal or stop virus shedding. Several patients complained that SP-303 caused pain or burning on application.

DOSAGE

In traditional medicine, the internal dose is 3 to 20 drops mixed in a beverage, 1 to 3 times daily for up to 3 weeks.[2,7] The pure sap is applied topically as needed.

Doses of 125 and 250 mg of SP-303, (procyanidolic oligomers [PCOs]) administered every 6 hours, were more effective at reducing the duration of traveler's diarrhea than the 500 mg dose.[22]

TOXICOLOGY

Dragon's blood, used topically or at low internal doses, is considered nontoxic.[27] Neither dragon's blood nor taspine showed carcinogenic or tumor-promoting effects in a 17-month long mouse study.[28] Taspine (<150 ng) was nontoxic to human foreskin fibroblasts.[21] It had no cell proliferative, carcinogenic, or tumor-promoting effects. 3′,4-0-Dimethycedrusin, isolated from dragon's blood, was nonproliferative and instead inhibited thymidine incorporation while protecting cells against degradation in a starvation medium.[13] In vitro, dragon's blood had a negligible effect on proliferation of endothelial cells and was not cytotoxic.[29] SP-303 at doses of 16 to 18.7 mg/kg per day caused weight loss and decreased survival time in mice and rats.[18] SP-303 injected intraperitoneally caused significant weight loss and death in rats at doses of 30 mg/kg per day. However, no toxicity was observed after oral administration of up to 270 mg/day of SP-303.[19]

DRUG INTERACTIONS

There are no known drug interactions.

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CHAPTER 84

Curcuma longa (Turmeric)

Michael T. Murray, ND

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Curcuma longa (family: Zingiberaceae)
Common names: turmeric, curcuma, Indian saffron

GENERAL DESCRIPTION

Curcuma longa, a perennial herb of the ginger family, is cultivated extensively in India, China, Indonesia, and other tropical countries. It has a thick rhizome from which arise large, oblong, and long-petioled leaves. The rhizome is the part used; it is usually cured (boiled, cleaned, and sun dried) and polished.

CHEMICAL COMPOSITION

Turmeric contains the following[1,2]:

- 4% to 14% of an orange-yellow volatile oil that is composed mainly of turmerone, atlantone, and zingiberone
- 0.3% to 5.4% curcumin
- Sugars (28% glucose, 12% fructose, 1% arabinose)
- Resins
- Protein
- Vitamins
- Minerals

Figure 84-1 shows the chemical structure of turmeric.

HISTORY AND FOLK USE

Turmeric is the major ingredient of curry powder and is also used in prepared mustard. It is extensively used in foods for both its color and flavor. In addition, turmeric is used in both the Chinese and Indian (Ayurvedic) systems of medicine as an antiinflammatory agent and for the treatment of numerous conditions, including flatulence, jaundice, menstrual difficulties, bloody urine, hemorrhage, toothache, bruises, chest pain, and colic.[1] Turmeric poultices are often applied locally to relieve inflammation and pain.

PHARMACOLOGY

Turmeric and its derivatives have a great deal of pharmacologic activity.[2] Although a number of components demonstrate activity, the volatile oil components and curcumin are believed to be the most active components. Turmeric has been described as follows:

- An effective antioxidant
- Anticarcinogenic
- Anti-inflammatory
- A cardiovascular protectant
- Hepatoprotective
- A gastrointestinal carminative and protectant
- Neuroprotective
- An antimicrobial agent

These beneficial effects, however, are largely based upon in vitro or experimental models. There are significant pharmacokinetic issues with curcumin, as it is poorly absorbed and rapidly metabolized and eliminated from the body. Pharmacokinetic

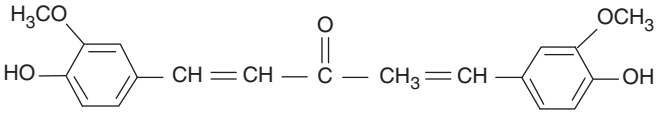


FIGURE 84-1 Curcumin.

studies in animals showed that 40% to 85% of an oral dose of curcumin passes through the gastrointestinal tract unchanged.[3,4] In humans, doses as high as 12 g of curcumin failed to significantly raise blood levels. New curcumin products with much greater bioavailability are now on the market, but significantly more clinical research is required to validate the promise of turmeric and curcumin to be to medicine what curry is to Asian cuisine.

Antioxidant Effects

Turmeric extracts exert significant antioxidant activity. Although both water- and fat-soluble extracts have been shown to be effective antioxidants in various in vitro and in vivo models, curcumin is the most potent component.[5-8] The antioxidant activity of curcumin is comparable to standard antioxidants like vitamins C and E and butylated hydroxyanisole and butylated hydroxytoluene.[5,9] Because of its bright yellow color and antioxidant properties against lipid peroxidation, curcumin is used in butter, margarine, cheese, and other food products.

For active oxygen species, curcumin is slightly weaker than vitamin C but stronger than vitamin E and superoxide dismutase. Against hydroxyl radicals, curcumin offers greater effectiveness than these vitamins.[5,6,9] Not all of the antioxidant properties of turmeric are due to curcumin alone, since the aqueous extract of turmeric is more effective against superoxide than curcumin and is much stronger in inhibiting oxidative damage to DNA.[7,8] The antioxidant activities of curcumin may in part explain the anticarcinogenic and cardioprotective capacity of this spice (see sections on "Anticarcinogenic Effects" and "Cardiovascular Effects"). In vitro and in vivo studies have also shown this antioxidant action to be neuroprotective as well.[10]

Anticarcinogenic Effects

The antineoplastic effects of turmeric and curcumin have been demonstrated at all steps of carcinogenesis: initiation, promotion, and progression. In addition to inhibiting the development of cancer, several studies suggest that curcumin can also promote cancer regression.

Turmeric and curcumin are nonmutagenic and have been shown to suppress the mutagenicity of several common mutagens (e.g., cigarette smoke condensates, benzopyrene, 7,12-dimethylbenz[a] anthracene), as do chili and capsaicin.[11-13] Turmeric and curcumin compounds have been found to induce apoptosis in lung and colon tumor cell lines.[14,15] Turmeric and curcumin have also demonstrated impressive anticancer effects against a number of chemical carcinogens on a wide range of cell types in both in vitro and in vivo studies.[16-23] Curcumin has demonstrated an impressive ability to reduce the levels of urinary mutagens.[24,25]

The protective effects of turmeric and its derivatives are only partially explained by its direct antioxidant and free radical–scavenging effects. It also inhibits nitrosamine formation, enhances the body's natural antioxidant system, increases the levels of glutathione and other nonprotein sulfhydryls, and acts directly on several enzymes and gene loci.

Curcumin's ability to protect against damage to DNA was demonstrated in a study in a community with a high content of groundwater arsenic.[26] Arsenic is extremely carcinogenic because it causes severe oxidative damage to DNA. Blood samples before curcumin supplementation showed severe DNA damage, with increased levels of free radicals and lipid peroxidation. Three months of curcumin intervention reduced the DNA damage, retarded free radical formation and lipid peroxidation, and raised the level of antioxidant activity. In another study, cigarette smokers receiving turmeric demonstrated a significant reduction in the level of urinary-excreted mutagens—an indication of the ability of the body to rid cancer-causing compounds via detoxification mechanisms. For many reasons, curcumin is emerging as a very important agent in the battle against cancer.[27]

Data also suggest that curcumin causes cancer to regress. Some of curcumin's benefits come from its antioxidant activity, but it also:

- Inhibits the formation of cancer-causing nitrosamines
- Enhances the body's production of cancer-fighting compounds, such as glutathione
- Promotes the liver's proper detoxification of cancer-causing compounds
- Prevents overproduction of cyclooxygenase-2, an enzyme that may contribute to the development of tumors

In addition to these preventative actions, curcumin has also been shown to inhibit tumor growth in several ways by:

- Inhibiting epidermal growth factor (EGF) receptor sites: EGF stimulates cells to proliferate by connecting to a receptor on the cell surface. About two thirds of all cancers produce an abundance of these receptors, which makes them highly sensitive to EGF. By reducing the number of EGF receptors, curcumin decreases the cell's tendency to proliferate.
- Inhibiting angiogenesis: Fibroblast growth factor is a protein that promotes the formation of new blood vessels to feed the growing tumor. Curcumin inhibits production of this growth factor.
- Inhibiting nuclear factor-κβ: This is a protein that many cancer cells produce to block the signals commanding them to stop proliferating.
- Increasing the expression of the nuclear p53 protein: This protein is essential for apoptosis, the normal process of cell "suicide."
- Inhibiting enzymes that promote cancer cell growth.

Antiinflammatory Effects

The volatile oil fraction of *C. longa* has been demonstrated to possess antiinflammatory activity in various experimental models (e.g., Freund's adjuvant-induced arthritis, formaldehyde- and carrageenan-induced paw edema, and cotton pellet and granuloma pouch tests).[28,29] Its effects in these studies were comparable to cortisone and phenylbutazone.

Even more potent in acute inflammation is curcumin.[30-33] Curcumin is as effective as cortisone or phenylbutazone in models of acute inflammation but only half as effective in chronic models. However, although phenylbutazone and cortisone are associated with significant toxicity, curcumin displays virtually no toxicity (see later discussion on "Toxicology").

The rank in order of potency of curcumin analogs, cortisone, and phenylbutazone in carrageenan-induced paw edema is as follows:[31,32]

sodium curcuminate > tetrahydrocurcumin > curcumin > cortisone > phenylbutazone > triethylcurcumin

Sodium curcuminate can be produced by mixing turmeric with slaked lime. This mixture, applied as a poultice, is an

ancient household remedy for sprains, muscular pain, and inflamed joints.[32]

Curcumin's counterirritant effect may also be a major factor in its topical antiinflammatory action.[31] Capsaicin, a similar pungent principle from *Capsicum frutescens* (cayenne pepper), has been shown to be quite effective as a topical pain reliever in cases of postherpetic neuralgia and arthritis. Both capsaicin and curcumin deplete nerve endings of the neurotransmitter of pain, substance P.[34]

Based upon in vitro studies, curcumin exhibits many direct antiinflammatory effects including*:

- Inhibition of leukotriene formation
- Inhibition of platelet aggregation
- Promotion of fibrinolysis
- Inhibition of neutrophil response to various stimuli involved in the inflammatory process
- Stabilization of lysosomal membranes

In addition to its direct antiinflammatory effects, curcumin also appears to exert some indirect effects. In models of chronic inflammation, curcumin was much less active in adrenalectomized animals. Possible mechanisms of action include the following:

- Stimulation of the release of adrenal corticosteroids
- "Sensitizing" or priming cortisol receptor sites, thereby potentiating cortisol action
- Increasing the half-life of endogenous cortisol through alteration of hepatic degradation

Cardiovascular Effects

The effects of turmeric and curcumin on the cardiovascular system include prevention of oxidative damage to low-density lipoprotein cholesterol, inhibiting platelet aggregation, and reducing fibrinogen levels.[38-43] These effects are of great significance in preventing atherosclerosis and its complications.

In animal studies, adding as little as 0.1% curcumin to a high-cholesterol rat diet decreased cholesterol levels to one half of those found in rats fed cholesterol but no curcumin.[38] Curcumin's cholesterol-lowering actions include interfering with intestinal cholesterol uptake; increasing the conversion of cholesterol into bile acids by increasing the activity of hepatic cholesterol-7-α-hydroxylase, the rate-limiting enzyme of bile acid synthesis; and increasing the excretion of bile acids via its choleretic effects.[38,39,44]

Effects on blood lipids from human studies are equivocable. In one small study, 10 healthy volunteers received 500 mg/day of curcumin for 7 days.[40] A significant decrease in the level of serum lipid peroxides of 33%, an increase in high-density lipoprotein cholesterol of 29%, and a decrease in total serum cholesterol of 11.63% were observed. However, two other studies failed to show any effect on blood lipids. One study used escalating doses (15, 30, and 60 mg three times daily)[45] and another used dosages up to 4 g/day for 6 months, but these studies only raised the plasma curcumin concentration to 490 nmol/L.[46]

Curcumin's effect on fibrinogen and platelet aggregation, which are known predictors of future coronary heart disease, may be more significant than its effects on cholesterol.[47] In a preliminary study of 30 apparently healthy volunteers, baseline levels of fibrinogen were recorded, and 8 subjects were found to have high plasma fibrinogen (above 350 ng/mL).[48] These subjects were given a hydroalcoholic extract of *C. longa* containing 20 mg of curcumin for 15 days. Impressively, curcumin administration decreased the fibrinogen levels to the 240 to 290 mg/dL range (Table 84-1).

TABLE 84-1 **Lowering Effects of the Treatment with a Curcuma Extract (Turmeric) on Abnormally High Plasma Fibrinogen Levels (Values in Milligrams Per Deciliter Before and After a 15-Day Treatment)**

SUBJECT NUMBER	SEX	AGE (YR)	BEFORE	AFTER
1	M	68	809	241
2	M	31	476	272
3	M	64	584	290
4	F	54	351	282
5	F	59	480	268
6	F	62	690	240
7	F	69	490	272
8	F	66	402	251
Means ± SD			535.6 ± 151.4*	271.1 ± 31

Modified from Ramirez Bosca A, Soler A, Carrion-Gutierrez MA, et al. Mech Ageing Dev 2000;114:207-210.

*As shown by the analysis of variance test, the decrease had a statistical significance of $\alpha = 0.05$.

Turmeric's and curcumin's action on inhibiting platelet aggregation appears to be mediated by inhibiting the formation of thromboxanes (a promoter of aggregation) while simultaneously increasing prostacyclin (an inhibitor of aggregation).[41,42]

Hepatic Effects

Curcumin exhibited hepatoprotection similar to that of glycyrrhizin and silymarin (see Chapters 96 and 123, respectively, for further discussion) against carbon tetrachloride and galactosamine-induced liver injury.[2,49] This protection was largely a result of its potent antioxidant activity. Similar results were seen with Javanese turmeric *(Curcuma xanthorrhiza).* Mice given intraperitoneal injections of the hepatoxic drugs carbon tetrachloride (32 mg/kg) and acetaminophen (600 mg/kg) experienced significantly decreased liver damage, as measured by serum glutamate oxaloacetate and serum glutamate pyruvate transaminase when treated with 100 mg/kg of turmeric.[50]

The antioxidant and hepatoprotective effects alone support turmeric's historical use in liver disorders; however, turmeric and curcumin also exert antiinflammatory and choleretic effects. The increases of serum glutamate oxaloacetate and serum glutamate pyruvate transaminase commonly seen in experimental models of inflammation were prevented by curcumin.[30]

Curcumin is an active choleretic, increasing bile acid output by more than 100%.[2] In addition to increasing biliary excretion of bile salts, cholesterol, and bilirubin, curcumin also increases the solubility of bile.[44] This suggests a benefit in the prevention and treatment of cholelithiasis.

Gastrointestinal Effects

Turmeric and its components exert a number of beneficial effects on the gastrointestinal system. Turmeric's long use as a carminative has significant research support.[2] Specifically, curcumin was shown to inhibit gas formation by *Clostridium perfringens* and in rats given diets rich in flatulence-producing foods. In addition,

*References 2, 30, 31, 33, 35-37.

sodium curcuminate was shown to inhibit intestinal spasm, and another compound from turmeric, *p*-tolymethylcarbinol, was shown to increase the secretion of secretin, gastrin, bicarbonate, and pancreatic enzymes.[2]

As a component of curries and spicy foods, there is some concern that turmeric may be irritating to the stomach. However, several studies showed turmeric to be beneficial to gastric integrity. Turmeric and curcumin were shown to increase the mucin content of the stomach and exert gastroprotective effects against ulcer formation induced by stress, alcohol, indomethacin, pyloric ligation, and reserpine.[2,51] However, at high doses, curcumin or turmeric may be ulcerogenic (see later discussion on "Toxicology").

Antiaging and Neuroprotective Effects

As far as slowing down the aging process, in addition to the effects discussed previously, there is considerable evidence that curcumin protects against age-related brain damage and in particular, Alzheimer's disease. Researchers began exploring this effect after noting that elderly (aged 70 to 79) residents of rural India, who eat large amounts of turmeric, were shown to have the lowest incidence of Alzheimer's disease in the world, 4.4 times lower than that of Americans. In addition, researchers also demonstrated that curcumin was able to prevent the development of amyloid plaque and the neurofibrillary tangles that are the hallmark features of the brain lesions in mice specifically bred to develop the disease.[52,53]

Studies also suggested a neuroprotective role of curcumin in stroke models.[10] Curcumin was shown to reduce plaque burden in models of Alzheimer's disease. Curcumin was also shown to decrease naphthalene and 4-hydroxy-2-nonenal–induced cataract formation on the lens by decreasing the rate of apoptosis and subsequent opacification resistance of the lens.[54,55] The authors postulated that induction of the enzyme glutathione S-transferase, which acts to decrease lipid peroxidation, was probably responsible for the cataractogenesis-inhibiting effects.

Antimicrobial Effects

Alcohol extracts and the essential oil of *C. longa* were shown in one study to inhibit the growth of most organisms occurring in cholecystitis (i.e., *Sarcina*, *Gaffkya*, *Corynebacterium*, and *Clostridium*).[2] Other microorganisms that were inhibited include *Staphylococcus, Streptococcus, Bacillus, Entamoeba histolytica,* and several pathogenic fungi.[2,56] The concentrations used in these studies were relatively high: 0.5 to 5 mg/mL of the alcohol extract and essential oil, and 5 to 100 mg/mL of curcumin.

CLINICAL APPLICATIONS

Turmeric and curcumin have several clinical applications. However, the most popular uses of curcumin are for three primary purposes: (1) as a general antioxidant to prevent heart disease and slow down the aging process; (2) as a chemoprotector against cancer and as a treatment adjunct; and (3) to reduce inflammation, particularly in osteoarthritis and inflammatory bowel disease.

General Antioxidant

The benefits of curcumin as a general antioxidant and in the prevention of atherosclerosis and slowing down the aging process have been previously discussed. Curcumin's antioxidant activity may be particularly helpful in preventing low-density lipoprotein cholesterol from becoming oxidized and damaging arteries. In addition, it exerts other beneficial effects in preventing atherosclerosis, including possibly lowering cholesterol levels, preventing plaque formation, inhibiting platelet aggregation, and reducing fibrinogen levels (see previous discussion "Cardiovascular Effects").

Cancer Prevention and Treatment Adjunct

As discussed earlier, turmeric and curcumin demonstrated significant protective effects against cancer development in experimental studies in animals. Human research is limited, but shows promising results.

In one human study, 16 long-term smokers were given 1.5 g of turmeric daily, whereas a group of 6 nonsmokers served as a control group.[24] At the end of the 30-day trial, the smokers receiving the turmeric demonstrated significant reduction in the level of mutagens excreted in the urine. These results are quite significant, because the level of urinary mutagens is thought to correlate with the systemic load of carcinogens and the efficacy of detoxification mechanisms. Due to widespread exposure to smoke, aromatic hydrocarbons, and other environmental carcinogens, the frequent use of turmeric as a spice appears warranted.

Turmeric extracts and curcumin demonstrated direct antitumor results in a number of experimental models of skin, epithelial, stomach, lung, and liver cancers.[14,20,57-60] This effect was also substantiated in a human study.[61] Sixty-two patients with either ulcerating oral or cutaneous squamous cell carcinomas who failed to respond to the standard treatments of surgery, radiation, and chemotherapy were given either an ethanol extract of turmeric (for oral cancers) or an ointment containing 0.5% curcumin in Vaseline. The ointment or extract was applied topically three times daily. At the end of the 18-month study, the treatment was found to be effective in reducing the smell of the lesion (90%), itching and exudate (70%), pain (50%), and size of the lesion (10%). Although these were not spectacular results, it must be pointed out that this patient population failed to respond to standard medical treatment.

Although more human studies are needed on the use of curcumin in cancer treatment, the experimental and preliminary clinical evidence is quite encouraging. However, the clinical studies in cancer patients showed that curcumin was poorly absorbed, and rapidly metabolized and eliminated from the body.[62] Doses as high as 12 g of curcumin failed to significantly raise blood levels. Fortunately, new curcumin products now exist, with much greater bioavailability that may allow for delivery of effective doses of curcumin.

Inflammation

C. longa has been used in Ayurvedic medicine, both locally and internally, in the treatment of sprains and inflammation. This use seems to be substantiated not only by the experimental studies described earlier, but also by clinical investigations.[33,63,64] For example, in one double-blind crossover clinical trial in patients with rheumatoid arthritis, curcumin (1200 mg/day) was compared with phenylbutazone (300 mg/day). The improvements in the duration of morning stiffness, walking time, and joint swelling were comparable in both groups.[63] However, although phenylbutazone is associated with significant adverse effects, curcumin has not been shown to produce any side effects at the recommended dosage level.

In another study that used the postoperative inflammation model for evaluating nonsteroidal antiinflammatory drugs (NSAIDs), curcumin was again shown to exert comparable antiinflammatory

action to phenylbutazone.[64] Although curcumin has an anti-inflammatory effect similar to phenylbutazone and various NSAIDs, it does not possess direct analgesic action. Most likely due to its antiinflammatory effects, topical application appears to be of benefit in wound healing.[65]

The results of these studies indicate that turmeric or curcumin may provide benefit in the treatment of inflammation. However, as previously mentioned, the bioavailability of curcumin is quite poor.[33,62] A number of methods now exist that enhance the absorption of curcumin. One of those methods is complexing the curcumin with soy phospholipids to form a phytosome. This product, Meriva, has significant research behind it, including human clinical research. Absorption studies in animals indicated that peak plasma levels of curcumin after administration of Meriva were fivefold higher than those after administration of regular curcumin.[66]

Meriva was used in two studies in patients with osteoarthritis. In the first study, 50 patients were given 1000 mg Meriva (providing 200 mg of curcumin) for 3 months, after which symptom scores decreased by 58%, walking distance in the treadmill test was prolonged from 76 to 332 meters, and the level of an inflammatory marker (C-reactive protein) in the blood decreased from 168 to 11.3 mg/L in the subpopulation with high C-reactive protein.[67] In the second study, 100 patients with osteoarthritis were given the same dosage of Meriva for 8 months. Just as in the previous study, symptom scores, walking distance, and blood measurements of inflammation were all significantly improved.[68]

A third study involved a rather interesting condition, chronic inflammation of the uvea—the front portion of the eye including the iris.[69] The study group consisted of 106 patients divided into three main groups of different uveitis origin: group 1 (autoimmune uveitis), group 2 (uveitis due to herpes), and group 3 (different causes of uveitis). The patients were given 1200 mg of Meriva for 1 year. In the previous year, there were a total of 275 relapses. In the 1-year treatment group with Meriva, there were only 36 relapses at the end of the 12-month follow-up, an 88% improvement.

Absorption of curcumin may not be as significant of a factor when dealing with gastrointestinal inflammation. In one double-blind study in patients with quiescent ulcerative colitis, 43 patients received curcumin, 1 g after breakfast and 1 g after the evening meal, plus sulfasalazine or mesalamine, and 39 patients received placebo plus sulfasalazine or mesalamine for 6 months. Of the patients who received curcumin, 2 relapsed during 6 months of therapy (4.65%), whereas 8 of 39 patients (20.51%) in the placebo group relapsed. Furthermore, curcumin improved both clinical signs and symptoms with ulcerative colitis via standard activity indexes.[70]

DOSAGE

On the basis of the evidence presented earlier, turmeric should be consumed liberally in the diet. When specific medicinal effects are desired, higher doses of turmeric can be given or extracts of *C. longa* or curcumin can be used. Because curcumin is so poorly absorbed, its clinical use should include something that may increase its absorption. Historically, this suggestion has meant using it in a lipid base, such as lecithin, fish oils, or essential fatty acids (with meals), or formulated in conjunction with piperine or bromelain (on an empty stomach).

A number of new methods now exist to enhance the absorption of curcumin. Of these, Meriva is establishing itself as a leading form of curcumin as a result of a growing body of clinical research at doses of 1000 to 1200 mg providing 200 to 240 mg of curcumin.

Another preparation, Theracurmin, is a surface controlled particle dispersion, with an average particle size of curcumin of 0.19 μm compared with an average particle size of 22.75 μm in curcumin powder. This represents a reduction of over 100 times, and its absorption rate is 27 times greater than regular curcumin. This is a superior absorption compared with all other commercial forms tested, including other enhanced forms of curcumin, including phosphatidylcholine-bound curcumin (Meriva).[71] Based upon a limited number of clinical studies, the dosage of Theracurmin is 300 mg/day (providing 30 mg of curcumin).

TOXICOLOGY

Toxicity has not been reported at standard dosage levels. The oral mean lethal dose levels for turmeric, its alcohol extracts, and curcumin have not been determined, because 2.5 g/kg fed to mice, rats, guinea pigs, and monkeys, and 3 g/kg sodium curcuminate fed to rats resulted in neither mortality nor chromosomal aberrations in teratology tests.[2,3,4,72] At high doses, curcumin or turmeric may damage the gastrointestinal system, since curcumin, with doses of 100 mg/kg body weight, was ulcerogenic in rats.[2] Some studies found sensitivity of mice to turmeric that resulted in hepatotoxicity.[73,74] Curcumin toxicity has not been found in rats or other mammals, even at very high doses (5% to 10% by weight of diet).[15] Human studies suggest that curcumin is nontoxic to humans up to 8000 mg/day when taken by mouth for 3 months.[75]

DRUG INTERACTIONS

Curcumin has several possible drug interactions, only a few of which have been confirmed. In one human study, 300 mg of curcumin reduced the absorption of the β-blocker talinolol by roughly 35%.[76]

In rabbits, pretreatment with curcumin resulted in increased plasma elimination half-life, thereby reducing the dosage of norfloxacin.[77]

In an experimental model, curcumin was shown to inhibit apoptosis produced by a number of chemotherapy agents, including camptothecin, mechlorethamine, and doxorubicin.[78]

Based upon in vitro studies, curcumin may inhibit the following drug metabolizing enzymes: CYP3A4, CYP1A2, and CYP2A6.[79,80]

Curcumin was also shown to downregulate intestinal P-glycoprotein levels, thereby increasing the concentrations of Celiprolol and midazolam. This action may have significance for other drugs influenced by intestinal P-glycoprotein downregulation, including colchicine; various chemotherapy agents including etoposide, doxorubicin, and vinblastine; digoxin; and immunosuppressive agents.[80]

Some theoretic concern has been raised that curcumin might increase the risk of bleeding of anticoagulant drugs due to its ability to decrease platelet aggregation.[81]

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CHAPTER 85

Dehydroepiandrosterone (DHEA)

Laurie K. Mischley, ND, Paul J. Nicolai, ND, and Alan R. Gaby, MD

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INTRODUCTION

Dehydroepiandrosterone (DHEA) is a steroid hormone secreted primarily by the adrenal glands and to a lesser extent by the testes and ovaries. Circulating levels of DHEA and its ester, DHEA sulfate (DHEAS) are 20 times higher than those of any other adrenal steroid. Due primarily to the fact that no DHEA-specific receptors have been found, this hormone has long been considered to function as a reservoir from which the body could draw as a precursor for the formation of other hormones. Thus, the attempt to elucidate a physiologic role for DHEA and possible clinical applications for DHEA are an ongoing topic of exploration in human medical research.

Although DHEA was first identified in 1934, its clinical use did not achieve prominence until 1993 when French scientists claimed it was a "cure" for aging[1] based on the observation that human DHEA levels peak in the late 20s and decline steadily thereafter. Epidemiologic evidence suggests that higher DHEA levels are associated with increased life expectancy[2] and enhanced well-being.[3,4] Persons with a steeper decline and greater variability in DHEAS levels over time have been shown to have a higher death rate, regardless of baseline DHEAS levels.[5] It has therefore been postulated that some of the manifestations of aging may be caused by a decline in DHEA production. DHEA has often been and continues to be used as part of an "antiaging" treatment program.

DHEA production varies profoundly throughout life. Levels begin to increase in children at 8 to 10 years of age (adrenarche) and peak in the second decade of life. Beginning in the early 30s, levels typically decline by 10% per decade and then plateau around the age of 80 years.[3,4] This decline in DHEA production, often referred to as adrenopause, ultimately results in an 80% loss of total DHEA production compared with that of a young adult. Interestingly, this age-related decline does not occur with other adrenal hormones such as glucocorticoids or mineralocorticoids.[6] In addition to the normal decline associated with aging, other possible causes for a decline in DHEA production include inflammation, many illnesses, and both chronic and subchronic stress.[7]

DHEA BIOCHEMISTRY

DHEA and its sulfate, DHEAS, are the most abundant steroid hormones in the human body and can be found in blood, saliva, urine, and cerebrospinal fluid (CSF).[7] Most DHEAS synthesis occurs in the adrenals via the action of hydroxysteroid sulfotransferase, otherwise known as DHEA sulfotransferase. It is this sulfated form of DHEA that has the longest half-life and is found in the bloodstream in the highest amount, thus leading to the commonly-accepted theory that DHEAS serves as a precursor or "buffer" reservoir of DHEA to be used for the intracellular synthesis of various estrogens and androgens throughout the human body. DHEA and DHEAS undergo continuous interconversion, but because DHEAS represents approximately 80% of the total DHEA pool, has a longer half-life, and lacks the circadian fluctuation seen with DHEA, it is more reliably used in clinical laboratory assessment.[8,9]

Despite DHEA being the major secretory product of the human adrenals, an understanding of DHEA's physiologic roles remains elusive. Assessing whether the effects of DHEA are a direct result of the hormone, its metabolites, or a combination of the two has been difficult.[10] Although often chemically classified as a weak androgen, little evidence of direct androgenic activity exists, so any androgenic activity is most likely mediated through its conversion to other more potent androgens. As a

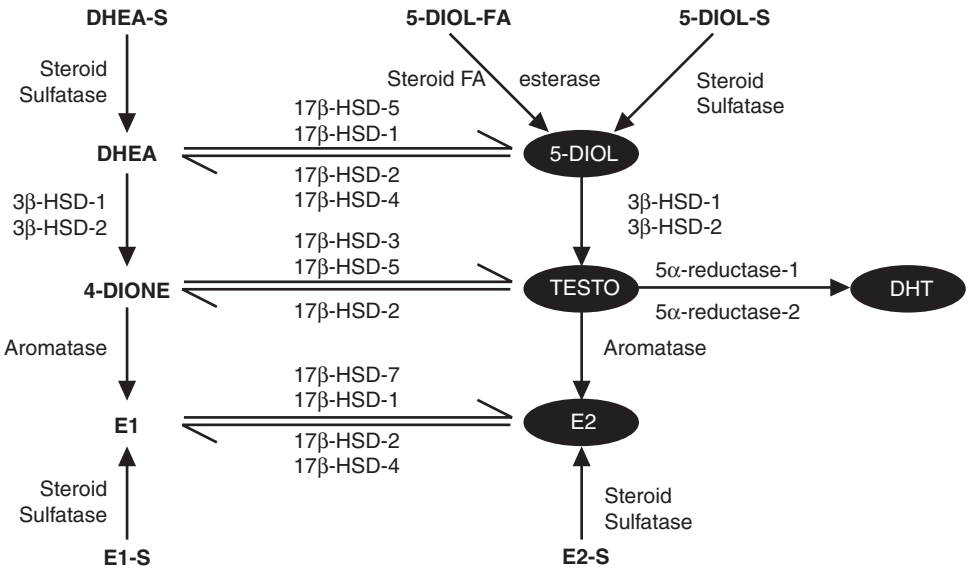


FIGURE 85-1 Dehydroepiandrosterone metabolism to other steroid molecules in peripheral tissues. (From Labrie F, Luu-The V, Labrie C, Simard J. DHEA and its transformation into androgens and estrogens in peripheral target tissues: Intracrinology. Frontiers Neuroendocrinology 2001;22:185-212.)

person ages and both ovarian and testicular production of hormones declines, this peripheral conversion of DHEA/DHEAS becomes increasingly more important as a source of these androgens.[7] In women, about two thirds of circulating testosterone is produced from peripheral conversion of ovarian and/or adrenal precursors. This percentage is higher in women who have had bilateral oophorectomy.[11]

The biosynthesis of all sex steroids in humans proceeds through DHEA.[12] As a steroid precursor, DHEA is converted to both estrogens and androgens, depending on the requirements of the target tissue. The majority of DHEA conversion to metabolites occurs within peripheral cells via the enzymes aromatase and steroid sulfatase (STS), both of which are present in the majority of human cells (Figure 85-1).

The effect of endogenous DHEA in humans varies significantly depending on the individual's age, gender, menopausal status, and DHEA levels. On a cellular level, both the target tissue and intracellular enzyme availability shape the fate of the molecule.[13] This process, often referred to as intracrinology, allows for local action of the various hormonal metabolites of DHEA on target tissues such as the brain, bones, breasts, and ovaries without either a specific DHEA receptor or a significant increase in the circulating levels of these metabolites. A specific high-affinity DHEA receptor has not yet been discovered, and there is little evidence that DHEA is able to exert any physiologic action without either modulating another receptor type or being converted into an active metabolite or another hormone.[14,15] In the brain, for example, endogenous DHEA's effects appear to be mediated via a combination of sex steroids, metabolites such as 7 α-hydroxy-DHEA, γ-aminobutyric acid, *N*-methyl-D-asparate, or other receptors.[7] In vitro studies demonstrated that DHEA has the ability to activate estrogen receptors in the prostate at reasonable physiologic concentrations, as well as demonstrating an inhibitory effect of DHEA on androgen receptors at much higher concentrations.[14]

DHEA IMMUNOLOGY

There is a fairly large body of work demonstrating an immune modulatory effect of DHEA or DHEAS and numerous possible mechanisms by which this might occur. Most of this information must be approached with caution in terms of a clinical perspective, however, due primarily to the fact that a preponderance of the data are from either in vitro studies or in vivo murine studies.

DHEA appears to have a significant regulatory effect on cytokine production in the form of increasing interleukin-2 (IL-2) secretion from TH-1 cells and decreasing production of IL-6 and IL-10 from TH-2 cells.[16] IL-6 stimulates hepatocytes to produce acute-phase reactants and B-lymphocytes to produce immunoglobulin. In rheumatoid arthritis, levels of IL-6 correlated strongly with both erythrocyte sedimentation rate and rheumatoid factor titers.[17] Both IL-6 and IL-10 were shown to be mediators of inflammatory- and age-related diseases, such as polymyalgia rheumatica, rheumatoid arthritis, inflammatory bowel disease, osteoporosis, and atherosclerosis. These same mediators were implicated as possible contributors to the pathophysiology of Alzheimer's disease, Parkinson's disease, and β-cell malignancies.[18]

It has been theorized that the increase in IL-6 production during the process of aging might be due in part to diminished DHEA secretion.[18] This theory is based on research demonstrating that serum DHEA levels correlated negatively with serum IL-6. Exogenously administered DHEA inhibits IL-6 secretion in a U-shaped fashion, with serum concentrations equaling that of healthy controls exerting the greatest effect.[18]

In one double-blind study, administration of 50 mg/day of DHEA to postmenopausal women produced a twofold increase in natural killer cell activity and a 6% decrease in the proportion of T-helper cells.[19] The significance of these changes is not entirely clear. Although the increase in natural killer cell activity might be expected to enhance immune surveillance against cancer and viral infections, the decline in T-helper cells could have adverse consequences. In contrast, because DHEA is known to mediate T-cell responses,[20] the decline in T-helper cells could merely be a reflection of enhanced T-cell function. Activation of immune function by DHEA was also demonstrated in elderly men.[21]

DHEA was also shown to have a measurable positive effect in terms of mitigating the immune-suppressive effects of both endogenously-produced and exogenously-administered glucocorticoids.[16]

CLINICAL APPLICATIONS

Previous studies hinted at a wide variety of beneficial effects in conditions such as diabetes, obesity, decreased immune function, atherosclerosis, and many of the disorders typically associated with normal aging. Although promising, the clinical utility of many DHEA studies may be limited in that they have been conducted using rodent models. Rodents have little endogenous DHEA, and their DHEA levels do not decrease with age. DHEA in rodent studies is often administered at supraphysiologic doses, which may also make it difficult to determine the clinical relevance of using physiologic doses of DHEA in humans. It is the intention of this chapter to base recommendations for the clinical use of DHEA on human studies to the greatest extent possible.

Adrenal Hypofunction/Addison's Disease

Despite the well-documented decline in DHEA levels seen in true adrenal hypofunction, adrenal hormone replacement protocols do not routinely recommend the administration of DHEA.[22-24] Even in the context of adequate glucocorticoid replacement, individuals with reduced adrenal function commonly report symptoms of depression and dysthymia, as well as a general reduction in overall quality of life. Several studies in patients with adrenal insufficiency demonstrated that DHEA replacement might result in an improvement in mood and fatigue, an increase in sexual satisfaction, and a better overall sense of well-being.[25-28]

Aging

Preliminary data suggested that DHEA might retard the aging process. For example, in a study of 75 healthy subjects, aged 90 to 106 years, men with the highest DHEAS levels had the highest level of functioning.[29] Several other studies in elderly humans supported an inverse correlation between DHEA levels and the degree of dependence in activities of daily living and mobility. In one study, plasma DHEA levels were low in 80% of male nursing home residents who required total care compared with 40% in other nursing home residents and 6% in independently living men of comparable age.[4,30]

In men older than 90 years of age, higher DHEAS levels were associated with a higher body mass index and waist-to-hip ratio, taken as indices of the body's energy (fat) reserves. In women older than 90 years of age, DHEAS levels were positively correlated with serum-free triiodothyronine and inversely with triglycerides.[29]

In an attempt to determine whether DHEA supplementation would counteract defects associated with aging, 280 healthy individuals between the ages of 60 and 79 years old were given 50 mg/day of DHEA or placebo for a year. In women older than 70 years of age, there was a reduction in the amount of bone loss and an increase in most libido parameters. Women also showed improvements of skin status, including greater hydration, epidermal thickness, sebum production, and pigmentation.[31]

Although DHEA levels do not appear to correlate significantly with cognitive function,[3,4,32] low serum DHEAS was associated with decreased psychological well-being and symptoms of depression.[4]

Depression

Elevated cortisol levels are well documented in depression, occurring in approximately 50% of cases.[33] Hypercortisolemia has also been shown to impair learning and memory in humans, and prolonged exposure to excess glucocorticoids leads to neuronal atrophy.[34,35] Therefore, the neurocognitive deficits observed in depressive disorders may be partially attributable to glucocorticoid hypersecretion. DHEA possesses significant antiglucocorticoid activity,[36] and it may be via this mechanism that administration of DHEA reduces neurocognitive deficits in major depression.[37,38]

An extensive study of depression in adolescents showed approximately 30% had abnormally low DHEA levels,[39] and mean levels of DHEA in the saliva of depressed adults were lower than those in normal control subjects.[33] Improvements in cognition were observed after oral administration of DHEA to middle-aged and elderly depressed patients,[40] and the antidepressant actions of DHEA were demonstrated in several randomized controlled trials.[41,42] The ability of DHEA to affect depressive symptomatology seems to be most substantial where DHEA levels are low or in those with an elevated cortisol-to-DHEA ratio.

CSF DHEAS levels are highly correlated with serum levels,[4] and DHEA easily crosses the blood–brain barrier. Evidence also suggests the brain synthesizes DHEA from cholesterol.[43] The ability of DHEA to enhance mood may be related to its role in the central nervous system. Research suggests the hormone may play a vital role as a neurosteroid in regulation of neuronal excitability. DHEA supplementation was shown to increase levels of β-endorphins, bind *N*-methyl-D-asparate receptors, act as an antagonist of γ-aminobutyric acid receptors, and protect against the deleterious effects of glucocorticoids.[41,42,44] In rats, DHEA was shown to increase hypothalamic serotonin levels.[45] These pharmacologic properties might help explain the efficacy of DHEA in mood disorders.

Few studies have attempted to treat depression with DHEA. In 2006, researchers conducted a double-blind, placebo-controlled trial of nonmajor depression in patients with human immunodeficiency virus/acquired immunodeficiency syndrome. The authors concluded that DHEA was superior to placebo, with a 62% response rate for the DHEA group compared with a 33% response rate for placebo patients among participants completing the trial. That few adverse events were reported suggests this readily available intervention might have clinical utility in some populations.[46]

Alzheimer's Disease

Unlike peripheral DHEA, which is predominantly converted to estrogens and testosterone, DHEA metabolism in the central nervous system appears to be somewhat unique.[47] A decreased concentration of plasma DHEAS in patients with Alzheimer's disease was reported,[48-50] and low plasma DHEAS levels appeared to be a risk factor for the development of Alzheimer's disease.[48] In contrast, elevated brain tissue and CSF levels of this steroid also appeared to be a risk factor for the development of Alzheimer's disease.[51] Reduced plasma DHEAS levels did not appear to be associated with the degree of cognitive decline or risk of mortality.[52]

Several small studies using DHEA in the treatment of Alzheimer's disease produced unimpressive results,[53-55] and it remains unclear as to whether different study designs might produce positive results. For instance, one proposed mechanism was that DHEA's antiglucocorticoid effects might offset hippocampal damage associated with elevated basal cortisol levels.[53] Despite its unlikely role in cognitive improvement, there continues to be a substantial amount of enthusiasm for the potential role of DHEA as a neuroprotective agent.

Menopause

Practitioners of complementary and alternative medicine (CAM) often recommend including DHEA as part of a postmenopausal

hormone therapy regimen to promote well-being, mental acuity, and enhance sexual function. A closer look at the current medical literature revealed that low sexual function in women was associated with low DHEAS more than any other androgen[56] and suggested several possible uses for DHEA in this population.

That said, any discussion pertaining to the use of DHEA in menopausal patients is likely handicapped by the fact that there is often great disparity between the way CAM practitioners prescribe DHEA and the way it is used in studies. CAM practitioners typically recommend smaller daily doses of 5 to 25 mg rather than the 50 mg/day (or more) that is often used in clinical research. Most clinical research also uses DHEA as the sole intervention, something most CAM practitioners would be unlikely to do with actual patients, as they would often employ some combination of estrogens, progesterone, DHEA, and testosterone, while attempting to help a patient improve their diet, exercise patterns, and other aspects of their lifestyle. One study that attempted to explore the use of DHEA in this type of combined manner demonstrated that oral dosing of DHEA at 10 mg/day for 12 months, either alone or in combination with estradiol and micronized progesterone, produced a significant rise in both androgens and β-endorphins, as well as a decrease in cortisol levels. Although intellectually promising and noteworthy, the researchers' decision to measure only biochemical outcomes instead of the physiologic outcomes that are useful in clinical practice leaves much still to be determined.[6]

Topical application of 1% DHEA for 4 months resulted in an improvement in several parameters of skin health compared with topical application of the same formulation without the DHEA.[57]

Although evidence regarding the oral administration of DHEA does not tend to demonstrate consistent efficacy in terms of improving libido in postmenopausal women,[58,59] there is promising evidence regarding the use of vaginal DHEA for this purpose. Clinical trial data on DHEA vaginal suppositories demonstrated significant positive effects on libido, arousal, pleasure, and orgasm, as well as improvement in measures of vaginal atrophy and a lowering of vaginal pH. Also of potential clinical significance is the fact that 3 months of intravaginal DHEA administration did not affect endometrial histology and did not increase serum levels of estradiol, testosterone, or DHEA over those found in normal postmenopausal women.[60-63]

Osteoporosis

A possible relationship between DHEA deficiency and osteoporosis was suggested by a study of women with Addison's disease in whom the onset of menopause was followed by an unusually rapid rate of bone loss. This accelerated bone loss was associated with marked reductions in plasma concentrations of both DHEA and testosterone.[64] A study examining women aged 45 to 69 years determined that 55 of 105 women had low bone mineral density (BMD), and that the average serum DHEAS level was 60% lower in women with low BMD compared with those with normal bones. Also of note is the fact that, although there was no relationship between estrogen levels and BMD in this study, women with low DHEAS values were 40 times more likely to have osteoporosis than were women with normal DHEAS levels.[65] Another study of 29 postmenopausal women demonstrated significant positive correlation between bone mineral content in the distal radius and ulna and age-adjusted serum DHEA levels.[66] More recent studies continue to expand upon these findings by documenting the positive correlation between androgen levels and BMD in postmenopausal women who do not have Addison's disease, thus suggesting an essential role for DHEA, testosterone, or both, in the maintenance of bone mass in postmenopausal women. It appears that free testosterone levels are more significantly correlated with increased bone mass in the lumbar spine, whereas DHEAS levels tend to correlate with increased bone mass in the femoral neck, both notable areas of concern in terms of the prevention and treatment of osteoporosis.[63]

Although testosterone was shown to have receptor sites on osteoblasts, the lack of an analogous receptor for DHEA leaves the mechanism by which DHEA contributes to bone production and maintenance as a matter of some speculation. Possible theories include functioning as a precursor molecule for the formation of estradiol and various androgens in systemic circulation, a direct promotion of bone formation by increasing levels of insulin-like growth factor-1 (IGF-1),[67] or possibly an intracrine mechanism involving an interaction with vitamin D3 to enhance the conversion of DHEA to estrone in osteoblasts.[68]

Recommendations pertaining to the clinical use of DHEA for the prevention and treatment of osteoporosis are less clear due to mixed results in controlled trials and a lack of both long-term studies and good data in terms of fracture risk reduction. One double-blind, placebo-controlled study of 50 mg/day DHEA supplementation demonstrated improved bone turnover and decreased osteoclastic activity in women older than 70 years.[31] In another, treatment using transdermal DHEA cream for 1 year in postmenopausal women demonstrated significantly increased serum osteocalcin levels and BMD of the femur, while simultaneously demonstrating a decrease in bone alkaline phosphatase levels.[69] A recent randomized, placebo-controlled trial in 225 healthy adults age 55 to 85 years showed that oral dosing of 50 mg/day DHEA for a year increased lumbar spine BMD in women only. There was no effect on femoral neck or total body BMD in women and no significant changes in BMD were noted at any site in the men studied.[70] A study that selected exclusively men and women with lower levels of DHEA demonstrated a notably different result using the same 50 mg/day dose, in that BMD in the lumbar spine was improved in both men and women compared with placebo, as was hip BMD in women.[71] Unfortunately, neither of these studies looked at or directly mentioned fractures or fracture risk in their subjects, although there was one indirect mention of DHEA supplementation leading to increased serum IGF-1 levels and the positive correlation between lower IGF-1 levels and risk of hip fracture in postmenopausal women.[72]

Erectile Dysfunction

The Massachusetts Male Aging Study, conducted from 1987 to 1989, was the first to describe an inverse correlation between DHEAS levels and the incidence of erectile dysfunction. More than half of the men in this study had minimal, moderate, or complete impotence,[73] and the degree of impotence was directly correlated with lower serum DHEAS levels. Follow-up research suggested that this was especially true for men younger than 60 years old.[74]

One double-blind, placebo-controlled study demonstrated that oral DHEA supplementation at 50 mg/day for 6 months resulted in improvement in all five domains of the International Index of Erectile Function, which quantitatively describes an individual's ability to achieve or maintain an erection sufficient for satisfactory sexual performance.[75,76] Response was most substantial in individuals with hypertension or lack of an organic etiology for their condition.[75] There was no impact of DHEA treatment on serum prostate specific antigen, prolactin, testosterone, mean prostate volume, or mean

postvoid residual urine volume.[76] A more recent placebo-controlled randomized trial of 50 mg DHEA twice a day demonstrated no benefit compared with either testosterone or placebo.[77]

Cardiovascular Disease

Administration of DHEA reduced the severity of atherosclerosis in cholesterol-fed rabbits.[49] In another rabbit model, low-dose DHEA mitigated the damaging biochemical and structural effects of a high-fat diet.[78] DHEAS was also shown to have digitalis-like activity, accounting for 62% to 100% of the total plasma digitalis-like factors in 11 healthy adults.[53]

Mean plasma DHEAS levels are significantly lower in men with a history of heart disease than in men without such a history. One study found that in men with no history of heart disease at baseline, a low plasma DHEAS level (<140 mcg/dL) was associated with a more than threefold increase in the age-adjusted risk of death from cardiovascular disease.[79] Similar findings were reported by others,[80-82] although other investigators described only a modest protective effect of DHEA.[83,84]

The association between DHEAS and cardiovascular disease in women is less clear.[85] Cardiovascular death rates might actually be greatest in women with both low and high DHEAS compared with those with intermediate levels.[86,87] Although studies exploring the relationship between endogenous DHEA levels and cardiovascular risk factors have been encouraging in terms of demonstrating decreased carotid intima-media thickness[88] and less atherogenic lipid profiles,[89] recent randomized double-blind trials in hypoadrenal women did not demonstrate this benefit with the administration of oral DHEA. Several studies actually showed a tendency toward more atherogenic lipid profiles in terms of statistically significant decreases in the participant's high-density lipoprotein levels,[84,90] whereas another randomized, double-blind, placebo-controlled study of longer duration found no significant changes in the lipid values of postmenopausal women who took 50 mg/day of oral DHEA for an entire year.[91]

There appear to be numerous reasons to continue the study of DHEA administration for the prevention and treatment of cardiovascular disease, but there is currently little clinical data that support the routine use of DHEA, particularly when given the myriad of both pharmaceutical and complementary and alternative options that are available for this purpose.

Cancer

Premenopausal women with breast cancer had significantly lower plasma levels of DHEA than age-matched controls without breast cancer, whereas postmenopausal women had significantly higher DHEA levels than age-matched controls.[92] In another study, women with DHEA levels in the highest tertile were 60% less likely to develop breast cancer than were women in the lowest tertile.[93] In a prospective case–control study, serum DHEA and DHEAS levels were significantly lower in individuals who subsequently developed bladder cancer than in those who did not.[94]

These findings suggest that DHEA has anticancer activity and that low DHEA levels may be a risk factor for cancer, except in postmenopausal women. However, it is obvious that further research is required before guidelines can be developed regarding DHEA therapy and cancer. The observation that some postmenopausal women with breast cancer have elevated DHEA levels, as well as the fact that DHEA is converted in part to estrogen and testosterone, should be cause for concern. It is unknown whether the anticancer effects of DHEA are stronger than the potential prostate cancer–promoting effects of additional testosterone or the breast cancer–promoting effects of additional estrogen. This is a complicated issue, because the metabolism of DHEA is usually "cross-gender" (i.e., women get an increase in testosterone, whereas estrogen levels often do not change, and vice versa for men). Until these questions can be answered, DHEA therapy should be approached with caution in patients who have either been diagnosed with or who are at risk for developing hormone-dependent cancers.

Rheumatoid Arthritis

Although a 2009 case–control study demonstrated no significant correlation between serum DHEAS levels and the future likelihood of developing rheumatoid arthritis (RA), decreased serum DHEAS concentrations were demonstrated in patients with RA,[95-97] possibly due to increased aromatase activity in the synovial tissue and the subsequent conversion of DHEA into estrogens, which may in turn stimulate the inflammatory process in patients with RA.[98-100] From a clinical perspective, the real issue at hand continues to be whether these low DHEA levels are a consequence of RA rather than a predisposing factor to the disease and whether or not DHEA administration is beneficial in patients with RA.[96]

It is worth noting that several studies on RA demonstrated protective or even therapeutic effects of DHEA in rodents with experimentally-induced arthritis.[101,102] One study noted a clear benefit from the administration of about 10 mg/day, an amount roughly equivalent to 2500 mg/day for a 75 kg human being.[102] Despite these potentially encouraging results and the fact that some practitioners have observed patients with RA who exhibited clinical improvement after treatment with DHEA, there are no controlled trials in humans demonstrating either a lack of efficacy or the same positive effects on disease activity that have been shown in murine models of RA.[103]

Although it does not appear that any large clinical trial of DHEA is imminent, there is some promising research being done in mice using oral dosing of DHEA metabolites, one of which, HE3286, has demonstrated clinical benefits on several measures of disease activity without being otherwise immune suppressive. It also appears that this compound is both orally available and is effective in much lower doses than DHEA, which could lead to the possibility of using it in human RA patients at reasonable doses.[103]

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic inflammatory connective tissue disorder that occurs predominantly in women. A positive effect of DHEA administration in autoimmune conditions such as SLE is likely due to a decrease in the production of proinflammatory cytokines, such as IL-6 and cytokine-mediated antibody, thus DHEA has the potential for a positive effect on the clinical manifestations of antibody-mediated diseases.[18,104]

Several studies demonstrated efficacy in patients with SLE when treated with 50 to 200 mg/day DHEA.[105-109] A double-blind, placebo-controlled trial of women with SLE demonstrated that the group receiving DHEA had a significant reduction in the number of disease flares and serious lupus-related adverse events, as well as improvement in the person's global assessment.[108] That being said, a recent review of randomized controlled trials comparing DHEA with placebo in persons with SLE demonstrated little to no effect on measures of disease activity, but did demonstrate an improvement in quality of life measures. It was also noted that DHEA-treated

subjects reported twice the rate of androgenic side effects compared with those given placebo.[110]

Inflammatory Bowel Disease

DHEAS concentrations are decreased in patients with both Crohn's disease and ulcerative colitis (UC).[111] In one study, 200 mg/day DHEA was given orally for 56 days to 7 patients with active Crohn's disease and 13 patients with active UC, all of whom were refractory to other drugs. Some patients went into remission: 6 of 7 Crohn's patients and 6 of 13 UC patients. The treatment response rate was 85.7% for Crohn's disease and 61.5% for UC. No patient withdrew from the study because of side effects.[112]

The mechanism of action may result from the ability of DHEA to decrease mediators of inflammation. It was shown that DHEA inhibits the activation of nuclear factor-κβ and the secretion of IL-6 and IL-12.[18]

DOSAGE

Although DHEA appears to be safe, the long-term effects of moderate to high dosages are unknown. In the elderly, 50 mg/day will increase DHEA levels into the reference range of young adults.[3] Although some practitioners routinely prescribe 50 mg/day for healthy women and 100 mg/day for healthy men, such doses may be supraphysiologic. Dosages of 5 to 50 mg/day for women and 10 to 50 mg/day for men appear to be safe.[27] Patients with SLE or other autoimmune diseases sometimes need as much as 200 mg/day or more to obtain benefit. Large doses should be split into twice daily dosing, usually morning and evening.

Studies show that orally-administered DHEA is well-absorbed,[113] and that, once in circulation, DHEA readily penetrates the blood–brain barrier.[114,115]

TOXICITY

With some exceptions, both oral and topical administration of DHEA appears to be relatively safe for clinical use.[27] In one study, administration of 1600 mg/day for 28 days to healthy volunteers resulted in some degree of insulin resistance, but no other significant side effects. A 2009 study giving postmenopausal women 50 mg/day of oral DHEA for a year demonstrated no significant effects on either insulin glucose or lipid values.[91] The same study also documented no significant difference in endometrial proliferation compared with placebo. In several SLE studies, 200 mg/day given for a number of months was generally well tolerated, with the exception of mild to moderate acne and occasional mild hirsutism. Another study reported intermittent nausea, perioral dermatitis, subjective feelings of aggressiveness, and intermittent hoarseness.[112] According to several reports, there is a possibility that cardiac arrhythmias and anxiety may be exacerbated by DHEA supplementation.[116,117] A positive association was reported between adrenal androgen levels and breast cancer risk in premenopausal women, particularly those over age 45.[118] Because DHEA is a known precursor to more potent sex hormones, its use should probably be avoided in individuals with hormone-sensitive cancers.

DRUG INTERACTIONS

Estrogen (oral contraception pills, hormone replacement therapy), free testosterone, and DHEA levels were reduced in women taking estrogen.[119]

Aromatase inhibitors—These drugs are used to interrupt the growth of hormone-dependent cancers. Aromatase is the enzyme responsible for many of the conversions in the steroid pathway.

STS inhibitors are currently being developed for use in breast cancer therapy. STS controls the hydrolysis of DHEAS.[120]

DHEA may potentiate the action of thyroid hormones.[121]

SUMMARY

In conclusion, DHEA appears to have potential as a therapy for numerous conditions. However, much still remains to be clarified in terms of human applications, so it would seem appropriate to treat this powerful hormone with caution and respect to maximize its benefits and minimize its risks.

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CHAPTER 86

Echinacea Species (Narrow-Leafed Purple Coneflower)

Michael T. Murray, ND

CHAPTER CONTENTS

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Echinacea spp. (family: Asteraceae)
Echinacea angustifolia
Common names: narrow-leafed purple coneflower, black sampson, snakeroot
Echinacea purpurea
Common name: purple coneflower
Echinacea pallida
Common name: pale purple coneflower

GENERAL DESCRIPTION

Echinacea spp. are perennial herbs native to Midwestern North America, from Saskatchewan to Texas. The genus derives its name from the Greek *echinos,* meaning sea urchin. This refers to the prickly scales of the dried seed head portion of the flower. Nine species of echinacea have been taxonomically classified by McGregor on the basis of comparative anatomy and morphology (Table 86-1).[1]

Of the nine species, *Echinacea angustifolia*, *E. purpurea*, and *E. pallida* are the most commonly used clinically.[2] *E. angustifolia*, with a typical height of up to 2 ft, is shorter than *E. purpurea* (1.5 to 5 ft) and *E. pallida* (1 to 3 ft). Another key to species identification is that *E. angustifolia* and *E. purpurea* have yellow pollen, whereas *E. pallida* is noticeably paler and has white pollen. The portions of the plant used for medicinal purposes include the aerial portion, the whole plant including the root, and the root itself. The tap root of *E. angustifolia* can reach a length of 3 to 4 ft.[3]

E. angustifolia has thick, hairy, 1- to 3-inch-long leaves found at the base of a purple seed head shaped like a cone. The only exception to the family of "purple" coneflower is *Echinacea paradoxa,* which has a yellow flower.

CHEMICAL COMPOSITION

Analysis of *Echinacea* spp. has yielded a wide assortment of chemical constituents with pharmacologic activities. From a pharmacologic perspective, the important constituents of *Echinacea* spp. can be divided into seven categories:

- Polysaccharides
- Alkylamides
- Caffeic acid derivatives
- Flavonoids
- Essential oils
- Polyacetylenes
- Miscellaneous chemicals

In the case of echinacea, it appears that although individual immune-enhancing compounds produce significant effects when they are combined in meaningful amounts, there is an additive effect. The immune-enhancing components of echinacea work together in a harmonious fashion to produce the phenomena of synergy. A key manner in which echinacea affects immune function is via enhancing the ability of macrophages to engulf and destroy particulate matter. The specific components of echinacea that possess this action are the polysaccharides, alkylamides, and cichoric acid. Although each component is effective alone, the greatest degree of enhancement was noted when the three active components were used in a specific ratio (0.25, 2.5, and 25 mg/mL).[4] This phenomena of synergy was noted with a clear dose-dependent effect. In other words, the effects with the

TABLE 86-1 **Taxonomic Formation of the Genus *Echinacea***

SPECIES	SYNONYMS
Echinacea angustifolia	*Brauneria angustifolia*
E. atrorubens	*Rudbeckia atrorubens*
E. laevigata	*B. laevigata*
E. pallida	*R. pallida, B. pallida*
E. paradoxa	*B. paradoxa*
E. purpurea	*R. purpurea*
R. hispida	
R. serotina	
E. speciosa	*E. simulata*
E. intermedia	
E. sanguinea	
E. tennesseensis	*B. tennesseensis*

Modified from McGregor RL. The taxonomy of the genus Echinacea (Compositae). Univ Kansas Sci Bull. 1968;48:113-142.

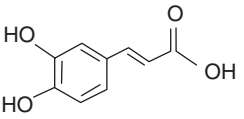
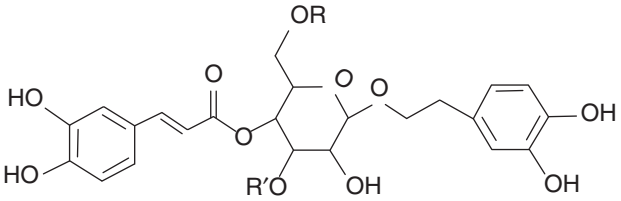


FIGURE 86-1 Caffeic acid.



Compound	R	R′
Echinacoside	Glucose (1,6-)	Rhamnose (1,3-)
6-O-Caffeoyl-echinacoside	6-O-Caffeoyl-glucose	Rhamnose (1,3-)
Verbascoside	H	Rhamnose (1,3-)
Desrhamnosyl-verbascoside	H	H

FIGURE 86-2 Echinacoside and similar compounds.

three actives were greater than any individual active and the higher the dosage, the greater the effect on enhancing macrophage function. A similar effect was noted in the ability of macrophages to detect the presence of foreign matter in the blood and signal the other components of the immune system to mount an attack via interleukin-1 (IL-1) and granulocyte colony-stimulating factor.

Because echinacea contains a wide assortment of chemical constituents with confirmed immune-enhancing effects, this is important for manufacturers to recognize to ensure sufficient levels of all these active compounds. Unfortunately, most echinacea products on the market do not specify the levels of active compounds because they have not been analyzed for them. In addition, when manufacturers do state the level of a particular marker compound, most consumers fail to realize that concentrating only for one particular active compound of echinacea results in loss of other constituents and, as a result, all of the synergistic effects. For example, some manufacturers standardize for "total phenolic content" or the compound echinacoside.[5] Although these types of echinacea extracts were found to have some antioxidant properties, recent studies found them to have no effect on enhancing immune function in experimental animal studies.[6,7]

Growing understanding of the chemical composition of echinacea requires manufacturers to perform quality control tests not only on the finished product, but also on the plant to ensure that it is being grown properly and harvested at the exact time for maximal levels of all active compounds. It is imperative that echinacea be treated properly after harvesting. In addition, studies indicate that a significant amount of the active ingredients are destroyed in the drying process. If the fresh plant material is not processed immediately, the content of several key components—especially cichoric acid and alkylamides—will be low (as much as 80% will be lost).[8-10] Chemical analysis of commercial echinacea preparations demonstrated tremendous variation in the levels of key compounds. For example, one analysis of various commercial echinacea products found that there was not only tremendous variation in the level of cichoric acid, with most products containing either none or little, but even within the same product there was tremendous interbatch variation.[11]

Polysaccharides

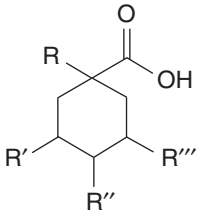
A number of immunostimulatory and mild anti-inflammatory polysaccharides have been isolated from *Echinacea* spp.[2,3,12-15] Most notable are inulin, which is found in a high concentration (5.9%) in *E. angustifolia* root, and the high-molecular-weight (25,000 to 50,000) polysaccharides found in the aerial part of *E. purpurea*. These components possess significant immune-enhancing properties. Typically, the most potent immune-enhancing polysaccharides are the water-soluble, acidic, branched-chain heteroglycans composed of many types of sugars rather than the polyfructose content of inulin.

Alkylamides

Alkylamides typically exert a tingling sensation on the tongue, which is representative of their mild anesthetic effect. These compounds are found in highest concentrations in the roots. The roots of *E. angustifolia* contain higher concentrations (0.004% to 0.039%) than *E. purpurea* (0.009% to 0.151%) and *E. pallida* (0.001%).[16,17] Alkylamides are among the most active constituents of echinacea on macrophage function.[18] In a human pharmacokinetic study, alkylamides were detected in plasma 20 minutes after ingestion of an echinacea preparation, and indicated that dosing at least three times a day was required to maintain plasma concentrations.[19]

Caffeic Acid Derivatives

Caffeic acid serves as the backbone for a number of important medicinal plant compounds in other plants, as well as *Echinacea* spp. (Figure 86-1). The first compound believed to be unique to *Echinacea* was echinacoside, a compound eventually shown to be composed of caffeic acid, a caffeic acid derivative (similar to catechol), glucose, and rhamnose, all attached to a central glucose molecule (Figures 86-2 and 86-3).[20] Echinacoside accumulates in the roots but is also found in smaller concentrations in the flowers. The roots *of E. angustifolia* contain 0.3% to 1.3%, whereas the roots of *E. pallida* contain a similar concentration of 0.4% to 1.7%.[12] It is assumed that *E. purpurea* has similar echinacoside levels as well.



Compound	R	R′	R″	R‴
3-O-Caffeoyl-quinic acid (chlorogenic acid)	OH	Caffeic acid	OH	OH
Isochlorogenic acids	OH	Caffeic acid	Caffeic acid	OH
	OH	Caffeic acid	OH	Caffeic acid
	OH	Caffeic acid	Caffeic acid	Caffeic acid
Cynarin	Caffeic acid	Caffeic acid	OH	Caffeic acid

FIGURE 86-3 Other caffeic acid derivatives.

Other caffeic acid derivatives important in the pharmacology of *Echinacea* include cichoric acid, chlorogenic acid, and cynarin.[3] Cichoric acid was originally isolated from *E. purpurea* and is found in much higher concentrations in this species compared with *E. angustifolia* and *E. pallida*.[3,21] However, *E. angustifolia* and *E. pallida* have higher amounts of other types of caffeic acid derivatives. These differences are not thought to have much clinical significance; rather, they may prove to be valuable in quick chemical differentiation of species.

Flavonoids

The leaves and stems of *E. angustifolia* and *E. purpurea* have been shown to contain numerous flavonoids, with rutoside being the most abundant.[3] The total flavonoid content (calculated as quercetin) for *E. angustifolia* and *E. purpurea* was 0.48% and 0.38%, respectively.[3]

Essential Oils

The essential oil content varies among the three common species[22]:

- *E. angustifolia* root and leaves contain less than 0.1%.
- *E. purpurea* root contains 0.2%, and flowers and leaves contain 0.6%.
- *E. pallida* root contains up to 2%, and the leaves contain less than 1%.

Interestingly, in one study, the essential oil content of *E. pallida* root was found to rise to 3.5% to 4% in April and May but fall to 1% to 1.5% for the rest of the year.[23] The major essential oil components are sesquiterpene derivatives, borneol, α-pinine, and related aromatic compounds.[3]

Polyacetylenes

A number of polyacetylenes have been identified from the roots of all three commercial species.[24] The difference in the type of polyacetylene and susceptibility to breakdown may help to differentiate which species is best for commercial use. Because the polyacetylenes of *E. pallida* are quite susceptible to autoxidation, *E. angustifolia* may be better for commercial products.[25] Research showed that long-term storage greatly decreases the content of polyacetylenes to only trace levels at best. However, the polyacetylene derivatives of autoxidation of *E. pallida* are quite characteristic and useful in differentiating *E. pallida* from *E. angustifolia*.

Miscellaneous

Undoubtedly, other constituents contribute to the pharmacology of echinacea. The occurrence of a "colorless alkaloid" was first reported by the great John Uri Lloyd in 1897 and substantiated recently by the isolation of the alkaloids tussilagine and isotussilagine.[26] Other compounds isolated from *Echinacea* spp. include the following[3]:

- Resins
- Glycoproteins
- Sterols
- Minerals
- Fatty acids

HISTORY AND FOLK USE

Echinacea was used extensively by the Native Americans living in areas where it grew. American Indians used echinacea against more illnesses than any other plant. The root was used externally for the healing of wounds, burns, abscesses, and insect bites; internally for infections, toothache, and joint pains; and as an antidote for rattlesnake bites.[27]

H.C.F. Meyer, a German lay healer, introduced a commercial product containing echinacea to Americans around 1870. He recommended "Meyer's blood purifier"[3] as a wonder cure for almost every conceivable malady, and there were numerous case reports of successful treatments for snakebites, typhus, diphtheria, and other infections.

E. angustifolia became a favorite with eclectic physicians, since it was thought to be greater in activity than other species. Eclectics used it externally as a local antiseptic, stimulant, deodorant, and anesthetic, and internally for "bad blood" (i.e., to correct "fluid depravation with tendency to sepsis and malignancy").[28,29]

Although many physicians began to investigate and use echinacea as a serious medicine, in 1909 the Council on Pharmacy and Chemistry of the American Medical Association refused to recognize echinacea as an active drug, stating: "In view of the lack of any scientific scrutiny of the claims made for it, *Echinacea* is deemed unworthy of further consideration until more reliable evidence is presented in its favor." Despite this opposition, echinacea was included in the National Formulary of the United States and remained there until 1950.[3]

With the demise of the eclectic movement, the popularity of echinacea in the United States waned except among naturopathic physicians until around 1980, when it was rediscovered due to increased consumer interest in immune system disorders such as candidiasis, chronic fatigue syndrome, acquired immunodeficiency syndrome (AIDS), and cancer. Although interest in echinacea decreased in America between the 1930s and 1980s, European physicians continued research. Much of this research was initiated by a 1932 study by Gerhard Madaus, who demonstrated immune-enhancing effects of a preparation from the fresh juice of the aerial portion of *E. purpurea*. This was followed by development of a commercial product (Echinacin) and a great deal of scientific study. Thus, *E. purpurea* began to be as respected as *E. angustifolia* among herbal practitioners in Europe.[3]

PHARMACOLOGY

The chemistry, pharmacology, and clinical applications of echinacea have been the subject of more than 300 scientific studies.[2,3,30]

This section summarizes some of the pharmacologic information on *Echinacea* with attention to the species used, part of the plant used, solvent used for extraction, and other relevant features. When no species delineation is made, the activity described is similar in all species.

Tissue Regeneration and Antiinflammatory Properties

Echinacin (a commercial product consisting of the freshly pressed juice of *E. purpurea* stabilized in ethanol) as well as polysaccharide components of echinacea have been shown to promote tissue regeneration and reduce inflammation in experimental studies.[31] This effect is apparently largely due to inhibition of the enzyme hyaluronidase via formation of a polysaccharide complex with hyaluronic acid, thereby maintaining the structure and integrity of the collagen matrix in connective tissue and ground substance. In addition to increased hyaluronic acid stabilization, echinacea also stimulates fibroblast growth and manufacture of glycosaminoglycans, a critical goal in wound healing. Echinacea exerts a mild, direct cortisone-like effect and enhances the secretion of adrenal cortex hormones.[3] The polysaccharide portion appears to be responsible for the direct anti-inflammatory effects, although the alkylamide fraction has also demonstrated some activity.[32]

Immunostimulatory Properties

Echinacea possesses a broad spectrum of effects on the immune system as a result of its content of a diverse range of active components affecting different aspects of immune function.[2,3] For example, inulin, the major component in the root of *E. angustifolia*, activates the alternative complement pathway and thus promotes chemotaxis of neutrophils, monocytes, and eosinophils; solubilization of immune complexes; neutralization of viruses; and bacteriolysis. Echinacea also increases the levels of properdin, the normal serum globulin that stimulates the alternative complement pathway.[2,3,33] Another nonspecific immune enhancement is echinacea's enhancement of serum leukocyte and granulocyte counts.[2,3,30-34]

The high-molecular-weight heteroglycan polysaccharide components of echinacea have profound immunostimulatory effects. The majority of these effects appear to be mediated by the binding of active echinacea polysaccharides to carbohydrate receptors on the cell surface of macrophages and T-lymphocytes. However, some of the T-cell activation found in early studies is now thought to be due to a contaminant protein. Later studies using a purer polysaccharide fraction did not show significant results.[3]

Echinacea promotes nonspecific T-cell activation (i.e., transformation, production of interferon, and secretion of lymphokines). The resultant effect is enhanced T-cell mitogenesis, macrophage phagocytosis, antibody binding, natural killer cell activity, and increased numbers of circulating neutrophils.[3,30]

Echinacea polysaccharides were also shown to enhance macrophage phagocytosis and to stimulate macrophages to produce increased amounts of tumor necrosis factor (TNF), interferon, and IL-1; destroy tumor cells in tissue culture; and inhibit *Candida albicans* infection in rats infected intravenously with a lethal dose (3×10^5 cells) of *C. albicans*.[3,34] The interactions with macrophages were most likely responsible for much of the immune system enhancement of echinacea polysaccharides.

In addition to the polysaccharides, lipophilic alkylamides and caffeic acid derivatives like cichoric acid are thought to contribute to the immunostimulatory aspects of echinacea, especially alcoholic extracts.[2,3,30] Although most research has been devoted to the water-soluble components such as polysaccharides, the lipophilic fraction yields the most potent enhancement of macrophage phagocytosis.[3,4]

The carbon clearance test is often used to measure systemic macrophage activation. The method involves measuring the rate of disappearance of carbon granules from the blood at varying intervals after administration of the test substance. Root extracts of echinacea administered orally tend to yield greater effects on phagocytic activity than the aerial portion, with *E. purpurea* greater than *E. angustifolia,* which is greater than *E. pallida*.[3]

Many studies used injectable preparations, but oral preparations are generally thought to yield similar or even better results, although direct comparisons are apparently not available. For example, intramuscular Echinacin administered to healthy males on 4 successive days was shown to increase granulocytic phagocytosis by nearly 50%, whereas the oral administration of an *E. purpurea* root extract at a dose of 30 drops three times a day to healthy males for 5 consecutive days resulted in an increase of 120%.[3] However, this difference might be due to the differing constituents of the forms used. The expressed juice of the aerial portion *E. purpurea*, as found in Echinacin, has lower concentrations of several of the phagocytosis-stimulating compounds characteristic to echinacea, including polysaccharides, alkylamides, and caffeic acid derivatives like cichoric acid compared with alcoholic extract.[3]

In general, echinacea appears to offer benefits for all infectious conditions. An exception to this statement may be AIDS. It is unclear at this time if echinacea should be recommended for AIDS. Although this condition is associated with widespread depression of the immune system, presumably due to the human immunodeficiency virus, stimulation of T-cell replication may also stimulate replication of the virus as well. In addition, echinacea was shown to lower T-helper cells and decrease T-helper cell–to–suppressor cell ratios.[2,3] Although there are anecdotal reports of echinacea's efficacy in human immunodeficiency virus-infected individuals, more research is necessary.

Antiviral Properties

The juice of the aerial portion of *E. purpurea,* along with alcoholic and aqueous extracts of the roots, were shown to possess antiviral activity. Some of the viruses inhibited in cell cultures include influenza, herpes, and vesicular stomatitis viruses.[3,35] Although certain echinacea components (e.g., echinacoside, other caffeic acid derivatives, polysaccharides) might block virus receptors on the cell surface, the antiviral effects might also be due to inhibition of hyaluronidases. The viral-inhibiting action of echinacea was significantly diminished when hyaluronidase was added to the cell cultures.[3] Many organisms secrete hyaluronidase, which increases connective tissue permeability and allows the organism to become more invasive.[36]

Clinically, the inhibition of hyaluronidase coupled with general immunostimulation of echinacea is probably more important than direct antiviral activity. The nonspecific antiviral action of echinacea enhances cytotoxic killing of virus-infected cells and the release of interferon. Interferons bind to cell surfaces, where they stimulate synthesis of intracellular proteins that block the transcription of viral RNA.

Antibacterial Properties

The direct antibacterial activity of echinacea is quite mild. This is somewhat surprising, since echinacea has a long history of effective use in both internal and external bacterial infections. Possibly,

it possesses anti-infective properties that prevent bacterial adherence, although this has yet to be determined. Clearly, its clinical efficacy is due to its strong immune-potentiating actions.

Echinacea possesses mild antibacterial action due largely to echinacoside, the complex caffeic acid derivative, found in highest concentrations in the root of *E. angustifolia*. Echinacoside and caffeic acid were shown to have antibacterial action against *Staphylococcus aureus, Corynebacterium diphtheriae*, and *Proteus vulgaris*. Approximately 6.3 mg of echinacoside is equivalent to 10 Oxford units of penicillin.[3,20]

Antineoplastic Activity

Obviously, echinacea possesses indirect, antineoplastic activity via its general immuno-enhancing effects. Specifically important is its stimulation of macrophages to greater cytotoxic activity against tumor cells. (Z)-1,8-pentadecadiene, a lipid-soluble component found in the roots of *E. angustifolia* and *E. pallida*, was shown in vivo to possess significant direct antineoplastic activity.[37]

CLINICAL APPLICATIONS

At present, although the results from clinical research are mixed, given the long history, safety, and confirmed immune-enhancing effects in experimental modes, as well as the numerous clinical studies that showed positive results, the clinical applications of echinacea include the following:

- Treatment of the common cold and other viral respiratory tract infections
- Possible prevention of the common cold and viral respiratory tract infections
- Treatment of temporary immune deficiency and increased susceptibility to infections
- Children attending daycare
- Adults experiencing undue stress
- Sport-induced immunodeficiency
- Supportive therapy to enhance the effectiveness of antibiotics in bacterial infections
- Chemotherapy and radiation-induced immune suppression
- Herpes simplex infections

Mixed results from clinical studies with echinacea were most likely due to lack of or insufficient quantity of active compounds. The axiom for effectiveness of any herbal product is its ability to deliver an effective dose of active compounds. If the product, by chance, had sufficient levels of active compounds, it would be effective. If not, it would likely be no more effective than a placebo. For example, in one double-blind study, 160 subjects were given either echinacea or placebo and then exposed to a common cold virus. Infection occurred in 44 (57%) and illness occurred in 36 (43%) of the echinacea- and placebo-treated subjects, respectively. However, the preparation contained no echinacosides or alkamides and contained only 0.16% cichoric acid.[38] In contrast, in a clinical trial using a well-defined echinacea extract containing alkamides, cichoric acid, and polysaccharides at concentrations of 0.25, 2.5, and 25 mg/mL, respectively, prepared from freshly harvested *E. purpurea* plants (commercially available as Echinilin or Echinamide), showed excellent results.[39] In this randomized, double-blind, placebo-controlled trial, 282 subjects, 18 to 65 years old, with a history of two or more colds in the previous year, but otherwise in good health, were randomized to receive either echinacea extract or placebo. They were instructed to start the echinacea or placebo at the onset of the first symptom related to a cold, consuming 10 doses the first day and four doses per day on subsequent days for 7 days. Severity of symptoms (10-point scale: 0, minimum; 9, maximum) and dosing were recorded daily. A nurse examined the subjects on the mornings of days 3 and 8 of their cold. A total of 128 subjects contracted a common cold (59 echinacea, 69 placebo).

The total daily symptom scores were found to be 23.1% lower in the echinacea group than in the placebo group. Throughout the treatment, the response rate to treatments was greater in the echinacea group. This study indicated that early intervention with a standardized formulation of echinacea resulted in reduced symptom severity in subjects with naturally acquired upper respiratory tract infection.

Again, to highlight the issue of quality control and source of preparation, several studies with less well-defined echinacea products showed little benefit, especially in experimentally induced rhinovirus infections. In another double-blind study, 302 volunteers from four military institutions and one industrial plant in Germany were given either a placebo or alcohol-based tinctures from either *E. purpurea* or *E. angustifolia* dried root for 12 weeks.[40] The main outcome measure was time until the first upper respiratory tract infection. The secondary outcome measures were the number of participants with at least one infection, global assessment, and adverse effects. The time until occurrence of the first upper respiratory tract infection was 66 days in the *E. angustifolia* group, 69 days in the *E. purpurea* group, and 65 days in the placebo group. In the placebo group, 36.7% had an infection, whereas in the *E. angustifolia* group it was 32%, and in the *E. purpurea* group it was 29.3%. These results indicated that there was no significant benefit with either form of echinacea, although there was an approximately 20% reduced risk of infection in the echinacea groups. In addition, 70% of the *E. purpurea* and 78% of the *E. angustifolia* group felt they had benefited from treatment compared with 56% in the placebo group. The *E. angustifolia* had a slightly higher percentage of subjects experiencing side effects (18%) compared with the *E. purpurea* (10%) and placebo (11%) groups.

In one of the most detailed clinical trials, 719 patients were assigned to 1 of 4 parallel groups: no pills, placebo pills (blinded), echinacea pills (blinded), or echinacea pills (unblinded, open-label). Echinacea groups received 8 tablets on the first day and on the subsequent 4 days 4 tablets per day, each containing the equivalent of 675 mg of alcoholic extract of *E. purpurea* root (of dried roots) and 600 mg of alcoholic extract *E. angustifolia* root; the placebo group received the same number of tablets. The primary end point was defined as the "area under the curve" for global severity with duration and severity. Severity was assessed by the Wisconsin Upper Respiratory Symptom Survey-21 questionnaire and the duration by the participants' impression of having a cold. The results showed only a statistically insignificant trend in reduction of the cold duration by half a day and a reduction of severity of approximately 10%.[41]

The result from this trial indicated that a major issue with some of the echinacea research might be the echinacea preparations used (i.e., weak ethanol-based tinctures derived from dried root). Clinical studies in upper respiratory tract infections done on extracts of fresh *E. purpurea* whole plant or aerial plant, especially in liquid form, are consistently positive compared with those using dried echinacea species extracts (or powdered herbs), especially in solid forms (tablets or capsules). It is possible that echinacea may exert direct local effects and that its contact with the oropharyngeal lymphatic tissue is extremely important in acute upper respiratory tract infection conditions. Reasonably large and well-designed, double-blind, placebo-controlled studies found

that preparations of echinacea from the aerial portion of the plant produced modest effects in aborting, as well as reducing, the symptoms and duration of colds.[30,40,42]

In addition to the previously described study with a well-defined echinacea preparation from the aerial portion of *E. purpurea*, another study showed good results when 108 patients with the initial symptoms suggesting a cold received either EchinaGuard—an extract of the fresh-pressed juice of *E. purpurea*—at a dosage of 4 mL twice daily or placebo for 8 weeks.[43] The percentages of patients who remained healthy were 35.2% of the echinacea group and 25.9% of the placebo group. The length of time between infections was 40 days for the echinacea group and 25 days for the placebo group. When infections did occur in patients receiving echinacea, they were less severe and resolved more quickly. Patients showing evidence of a weakened immune system (CD4/CD8 ratio <1.5) benefited the most from echinacea.

The results from another trial were especially encouraging, since it also suggested that echinacea could not only make colds shorter and less severe, it could sometimes stop a cold that was just starting.[44] In this study, 120 people were given a preparation from the fresh-pressed juice of *E. purpurea* or a placebo as soon as they started showing signs of getting a cold. Participants took either echinacea or placebo at a dosage of 20 drops every 2 hours for 1 day, then 20 drops 3 times a day for 9 more days. Fewer people in the echinacea group felt that their initial symptoms actually developed into "real" colds (40% of those taking echinacea vs 60% taking the placebo actually became ill). Also, among those who did come down with "real" colds, improvement in the symptoms started sooner in the echinacea group (4 days instead of 8 days). Both results were statistically significant. However, echinacea's ability to shorten the duration of colds was more dramatic.

Not all studies of the fresh-pressed juice of *E. purpurea* or EchinaGuard showed positive effects in reducing the duration or severity, or both, of upper respiratory infections. For example, a study in children 2 to 11 years old was particularly disappointing, because the results indicated that it was not only ineffective, but its use was associated with an increased risk of rash.[45]

In another double-blind trial, 128 patients received 100 mg of the freeze-dried pressed juice from the aerial portion of *E. purpurea* or a placebo three times daily until cold symptoms were relieved or until the end of 14 days, whichever came first.[46] Symptoms (sneezing, nasal discharge, nasal congestion, headache, sore or scratchy throat, hoarseness, muscle aches, and cough) were scored subjectively by the patient and recorded daily in a diary. No statistically significant difference was observed between treatment groups for either total symptom scores or mean individual symptom scores. The time to resolution of symptoms was also not statistically different. The failure in this trial might have been due to the previously mentioned lack of direct contact with the oropharyngeal lymphatic system.

Clearly, more research using well-characterized echinacea preparations at appropriate dosages is necessary in well-designed trials. Currently, the "gold standard" for evaluating cold remedies involves inoculating healthy individuals with rhinovirus. Although the concentration of viral assault is much greater than what one might encounter in the real world, any substance showing efficacy in this model is regarded as being highly efficacious. In one study, 48 healthy adults received the fresh-pressed juice of *E. purpurea* (EchinaGuard) or placebo, 2.5 mL 3 times per day, for 7 days before and 7 days after intranasal inoculation with rhinovirus (RV-39).[47] A total of 92% of echinacea recipients and 95% of placebo recipients were infected. However, colds developed in 58% of echinacea recipients compared with 82% of placebo recipients. Although administration of echinacea before and after exposure to rhinovirus did not decrease the rate of infection, it did appear to reduce the clinical development of a cold. However, because of the small sample size, statistical hypothesis testing had relatively poor power to detect statistically significant differences in the frequency and severity of illness. As mentioned previously, the only other experimental rhinovirus infection and echinacea study was seriously marred, because the preparation used contained no active components.[38]

TABLE 86-2 **Treatment of Recurrent Candidiasis with Echinacin—Rate of Reoccurrence at 6 Months**

THERAPEUTIC SCHEME	NO. OF PATIENTS	RECURRENCE RATE (%)
Topical antimycotic alone	43	60.5
Topical antimycotic + subcutaneous Echinacin	20	15
Topical antimycotic + intramuscular Echinacin	60	5
Topical antimycotic intravenous Echinacin	20	15
Topical antimycotic oral Echinacin	60	16.7

Modified from Coeugniet EG, Kuhnast R. Recurrent candidiasis: adjuvant immunotherapy with different formulations of echinacin. Therapiewoche 1986;36:3352-3358.

Candidiasis

Echinacea's effect against *C. albicans* noted in animal studies was confirmed in several human clinical studies.[3] A study featured in Table 86-2 demonstrated that Echinacin greatly accentuated the efficacy of a topical antimycotic agent (econazole nitrate), decreasing reoccurrence from 60.5% to 5% to 16.7%. The researchers used standardized skin tests to show that this enhancement was due to echinacea's boosting of cell-mediated immunity.[48] Also of interest was the similarity in the efficacies of both the oral and injectable forms.

Snakebites

Echinacea has quite a reputation among naturopathic physicians and native American healers for the treatment of snakebites. No studies of this use have been carried out, but echinacea's inhibition of hyaluronidase might account for much of its reputed efficacy, because most snake venoms permeate the system as a result of hyaluronidase in the venom breaking down connective tissue of the ground substance.

Wound Healing

Several uncontrolled clinical studies substantiated echinacea's wound-healing activities.[3,37,49,50] The largest (4598 patients) demonstrated that a salve of the juice of the aerial portion of *E. purpurea* had an 85% overall success rate in the treatment of inflammatory skin conditions, such as abscesses, folliculitis, wounds of all kinds, eczema, burns, herpes, and varicose ulcers of the leg.[3]

Arthritis

Echinacea's anti-inflammatory activity was shown in uncontrolled studies to be useful in rheumatoid arthritis. In one study, 15

drops of Echinacin three times daily resulted in a 21.8% decrease in inflammation. Although this improvement was less than cortisone (42%) and prednisone (49.2%), no side effects were associated with Echinacin, whereas both of these drugs have well-known side effects.[51]

Cancer

Several studies noted a stimulatory effect of echinacea on leukocyte counts in patients receiving radiation for cancer therapy.[49,52] A study using the commercial preparation Esberitox demonstrated that 85% of 55 patients showed a stabilization of leukocyte counts compared with the control group, which showed a steady decline in levels (starting at 6000 and decreasing to 2500 after 45 days).[49] This strongly supports the recommendation of echinacea to patients undergoing orthodox cancer treatments. In an open prospective study with matched historical controls, an injection of polysaccharide fraction isolated from the herb *E. purpurea* was shown to counteract the undesired effects of chemotherapy.[53] Fifteen patients with advanced gastric cancer, who underwent palliative chemotherapy with etoposide, leucovorin, and 5-fluorouracil, received daily intravenous injections of 2 mg of a polysaccharide fraction isolated from *E. purpurea* herb cell cultures for 10 days (beginning 3 days before chemotherapy). The median number of leukocytes 14 to 16 days after chemotherapy was 3630/mL in the patients who received echinacea polysaccharide compared with 2370/mL (870 to 3950) in the patients of the historical control group. These results suggested that echinacea might be effective in reducing chemotherapy-induced leukopenia.

COMMERCIAL PREPARATIONS

As evident from the previous information, determining which echinacea preparation is best is difficult. It is not only difficult to determine which species is most effective, but also the portion of the plant used and how it is prepared are serious issues. Dosage recommendations for all currently available forms follow, along with a few observations regarding the "preparations controversy."

Another problem that needs to be addressed is quality control. Since as early as 1904, many commercial sources of echinacea have contained adulterants and no echinacea. For example, it was estimated that due to supplier errors in collection, more than 50% (and possibly as high as 90% at times) of the echinacea sold in the United States from 1908 to 1991 was actually *Parthenium integrifolium,* or Missouri snakeroot.[54] Some suggested that this adulteration was due to confusion of the common names. Others pointed out that although the *P. integrifolium* plant looks quite different "… once the root is cut and sifted it has an uncanny resemblance to *E. angustifolia* or *E. pallida* roots, though it possesses its own characteristic flavor and fragrance."[54] From practical and clinical viewpoints, physicians should require adequate documentation from suppliers that they are, in fact, supplying echinacea, as well as its species.

Species

Although studies have shown various echinacea species, or components found in higher concentrations in one species, to be more effective than others, each commercial species has its advantages and disadvantages. No "best" species can be recommended at this time, since differing experimental models have yielded inconsistent results. Rather, the clinician must recognize the unique value of each species. Although *E. angustifolia* has long been considered the best species and to possess the greatest activity, some studies dispute this. For example, several studies showed *E. purpurea* to demonstrate greater enhancement of phagocytosis. In one study, an aqueous extract of *E. angustifolia* did not demonstrate any impact on phagocytic function in rats, whether it was administered orally, intraperitoneally, or intravenously.[55] As *E. purpurea* is the easiest to grow commercially, it may become the most used in the United States, as it is in Europe.

Part of the Plant to Use

The portion of the plant that possesses the greatest immune-enhancing properties depends on the experimental model. The key points, as described earlier, are that various echinacea components exert immune-enhancing effects and there is clearly a synergistic effect among these constituents.

Preparations

Echinacea products are available in many different forms:

- Crude plant in either ground or powdered form
- Freeze-dried
- Alcohol-based tinctures and liquid extracts
- Aqueous tinctures and liquid extracts
- Dry, powdered alcoholic or aqueous

It is popular to standardize hydro/alcoholic extracts for echinacoside (for *E. angustifolia*) or cichoric acid (for *E. purpurea*). Although these extracts are thought by their proponents to be the most potent, it must be noted that even 4 to 10 times homeopathic preparations have been shown to produce activity.[32]

Solvents

Which solvent is best to use? Again, this question is extremely difficult to answer, since both hydrophilic and lipophilic components have been shown to possess immune-enhancing activities. Even a small amount of ethanol results in precipitation or breakdown of the immuno-active polysaccharides, suggesting that aqueous extracts may be best. However, an aqueous extract would leave behind valuable lipophilic immune-enhancing alkylamides and caffeic acid derivatives. To optimize an extract's immune-enhancing effects, many manufacturers use low ethanol (10% to 20%) hydro/alcoholic mixtures or combine a low ethanol extract with a high ethanol extract. Both products typically contain both polar and lipophilic compounds.

DOSAGE

Box 86-1 lists dosages of echinacea as a general immune stimulant during infection. The question of whether echinacea should be used on a long-term or continual basis really depends on the need. In a healthy individual with no apparent depression of the immune system, continual administration is certainly not indicated. However, as recent studies showed, patients with impaired immune function experience long-term benefit.[56] The usual recommendation with long-term use is 8 weeks on, followed by 1 week off.

TOXICOLOGY

When used at the recommended doses, there is no danger of toxicity, since no studies have reported acute or chronic toxicity reactions due to echinacea extracts. Echinacin, given intravenously,

BOX 86-1 Dosages (Three Times/Day) as a General Immune Stimulant During Infection

Dried root (or as tea): 0.5-1 g
Freeze-dried plant: 325-650 mg
Juice of aerial portion of *Echinacea purpurea* stabilized in 22% ethanol: 2-3 mL (0.5-0.75 tsp)
Tincture (1:5):2-4 mL (1-2 tsp)
Fluid extract (1:1):1-2 mL (½-1 tsp)
Solid (dry-powdered) extract (6.5:1 or 3.5% echinacoside): 150-300 mg

resulted in fever (0.5° C to 1° C elevation in body temperature) on occasion. This was presumably a result of secretion of interferon-α and IL-1 by activated macrophages.[3]

The median lethal dose (LD_{50}) of intravenous Echinacin was determined to be 50 mL/kg body weight in mice and rats. The polysaccharides in *E. purpurea* (aerial portion) were shown to have an LD_{50} of 1000 to 2500 mg/kg when given peritoneally to mice. Long-term administration of Echinacin to rats at doses many times the human therapeutic doses gave no evidence of any toxic effects.[55] Mutagenic tests with Echinacin demonstrated no mutagenic activity.[2,3]

Modern reviews of the safety and efficacy of *Echinacea* spp. found no toxicity in both adults and children in cases of both acute and long-term administration.[2,30,57-60] Given the number of echinacea doses consumed yearly (>10 million) and the number of adverse events (<100), echinacea appears extremely safe. Reported side effects are also uncommon and usually limited to minor gastrointestinal symptoms, increased urination, and mild allergic reactions. However, severe allergic reactions have occurred occasionally, some of them life threatening. Allergic reactions were often reported in people who were also allergic to other members of plants in the daisy (Compositae) family (e.g., daisy, ragweed, marigolds).[61]

The German Commission E warns against using echinacea in cases of autoimmune disorders, such as multiple sclerosis, lupus, and rheumatoid arthritis. These warnings are theoretical, since there is no evidence that echinacea use has actually harmed anyone with these diseases.

Echinacea appears to be safe even for pregnant or lactating women based on both animal studies and evaluation studies in women using echinacea during pregnancy showing no harmful effects.[62]

DRUG INTERACTIONS

Echinacea preparations appear to have a low potential for drug interactions.[60] Currently, there are no verifiable reports of drug–herb interactions with any echinacea product. Theoretically, echinacea may interfere with drugs that are purposely used to suppress the immune system. These include cyclophosporin, which is used in patients who have had organ transplants to prevent the immune system from rejecting the transplanted organ.

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CHAPTER 87

Eleutherococcus senticosus (Siberian Ginseng)

Michael T. Murray, ND

Eleutherococcus or *Acanthopanax senticosus* (family: Araliaceae)
Common names: Siberian ginseng, touch-me-not, devil's shrub, eleuthero ginseng

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GENERAL DESCRIPTION

Eleutherococcus senticosus, or Siberian ginseng, is a shrub that grows 5 to 8.5 ft high. Its erect, spiny shoots, 1.5 to 2.5 inches in diameter, are covered with a light gray or brownish bark. The leaves are long petioled in a compound, palmate configuration. The five leaflets are elliptic and finely serrated at the margins on both sides, with scattered, minute spinules along the veins.[1]

Eleuthero grows abundantly in parts of Russia, the Far East, Korea, China, and Japan, north of latitude 38. Its distribution is much greater than that of *Panax ginseng* (see Chapter 110).[1]

The root is the most widely used component, with the highest concentration of biologically active substances occurring in the fall, just before defoliation. The leaves are also used medicinally, with their highest concentration of biologically active substances occurring in July, just before flowering.

CHEMICAL COMPOSITION

The initial phytochemical report on eleuthero was published in 1965 by members of the Institute of Biologically Active Substances in Vladivostok, Russia.[1] Seven compounds, termed eleutherosides A–G, were isolated from a physiologically active fraction of the methanol extract of eleuthero. The total eleutheroside content of the root ranges from 0.6% to 0.9%, and content of the stems ranges from 0.6% to 1.5%. The ratio of the eleutherosides A–G obtained is approximately 8:30:10:12:4:2:1, respectively. Figure 87-1 illustrates the structure of a key type of constituent. Table 87-1, modified from reviews of eleuthero, summarizes what is currently known about the components of *E. senticosus*.[1] It is important to recognize that thin-layer chromatographic analysis showed that the ginsenosides characteristic of *Panax* sp. (American, Chinese, Korean, Japanese ginsengs) are not present in the roots of *E. senticosus*.

HISTORY AND FOLK USE

Ginseng plants, members of the family Araliaceae, including *E. senticosus*, are among the most ancient and esteemed of all medicinal herbs. Their use in Chinese herbal medicine dates back more than 4000 years.[1,2] References in ancient documents to members of the Araliaceae family are imprecise, giving rise to some confusion in modern interpretation. Nonetheless, the Chinese have long believed that the regular use of eleuthero increases longevity, improves general health and appetite, and restores memory.

The Russians have a separate history of eleuthero and even claimed, despite a long history of use by Chinese herbalists (references date back to 2000 BC), that "Eleutherococcus was not known in Oriental folk medicine." The Russian history of eleuthero begins in 1855 when a pair of Russian scientists, C.I. Maximovich and L.I. Shrenk, traveled from St. Petersburg to the Ussuri region of Russia on the Amur River. It was in this area that Maximovich observed a vast thicket of unusual plants, with leaves resembling horse chestnut and young shoots resembling ginseng. Unable

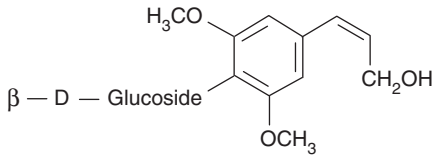


FIGURE 87-1 Eleutheroside B.

TABLE 87-1 **Compounds Found in *Eleutherococcus Senticosus***

COMPOUND	TYPE	LOCATION
Eleutheroside A (daucosterol)	Sterol	Roots, stems
Eleutheroside B (syringin)	Phenylpropanoid	Roots, stems
Eleutheroside B_1 (isofraxidin-7-0-α-L-glucoside; also known as β-calycanthoside)	Coumarin	Roots
Eleutheroside B_2	Unknown	Roots
Eleutheroside B_3	Unknown	Roots
Eleutheroside B_4 [(–)-sesamin]	Lignan	Roots
Eleutheroside C (methyl-α-D-galactoside)	Sugar	Roots, stems
Eleutheroside D [(–)-Syringaresinol di-0-β-D-glucoside]	Lignan	Roots, stems
Eleutheroside E (different crystalline form of D; also known as acanthoside D)	Lignan	Roots, stems
Eleutheroside F	Unknown	Roots
Eleutheroside G	Unknown	Roots
Eleutheroside I (=mussenin B)	Triterpene	Leaves
Eleutheroside K	Triterpene	Leaves
Eleutheroside L	Triterpene	Leaves
Eleutheroside M (=hederasaponin B)	Triterpene	Leaves
Senticosides A–D (may be identical to eleutherosides I, K, L, and M)	Triterpene	Leaves
Vitamin E	Benzofuran	Roots
Beta-carotene	Carotenoid	Roots
Isofraxidin	Coumarin	Roots
Coumarin X	Coumarin	Roots
Complex mixture	Essential oil	Roots
Copper	Mineral	Roots
(–)-Syringaresinol	Lignan	Roots
Caffeic acid	Phenylpropanoid	Roots
Caffeic acid ethyl ester	Phenylpropanoid	Roots
Coniferyl aldehyde	Phenylpropanoid	Roots
Synapyl alcohol	Phenylpropanoid	Roots
Beta-sitosterol	Sterol	Roots
Polysaccharides	Sugar	Roots, fruit
Galactose	Sugar	Roots
Glucose (α and β)	Sugar	Roots
Maltose (α and β)	Sugar	Roots
Sucrose	Sugar	Roots
Oleanolic acid	Triterpene	Roots

Modified from Davydov M, Krikorian AD. Eleutherococcus senticosus (Rupr. & Maxim.) Maxim. (Araliaceae) as an adaptogen: a closer look. J Ethnopharmacol 2000;72:345-393.

to identify the plant, the two scientists brought back samples to St. Petersburg for classification. The plant was given the genus name of *Eleuthero*, or "free-berried shrub," and the species name of *senticosus*, which means "thorny" in Latin.

Not until the middle of the twentieth century was eleuthero again "discovered," when Russian scientists began investigating substances that produce a "state of nonspecific resistance" in the body. Substances with this effect were termed adaptogens. In 1958, Brekhman described an adaptogen as follows[1,3]:

- It must be innocuous and cause minimal disorders in the physiologic functions of an organism.
- It must have a nonspecific action (i.e., it should increase the resistance to adverse influences by a wide range of physical, chemical, and biochemical factors).
- It usually has a normalizing action irrespective of the direction of the pathologic state (alterative action).

Brekhman's research with adaptogens began with *P. ginseng*, because this was the best-known natural adaptogen. After confirming the adaptogenic action of panax in human studies, Brekhman began searching for an alternative to this plant because of the difficulty and expense in obtaining panax. Initially, all six species of Araliaceae native to Russia were investigated, and eleuthero was found to be the most promising. Numerous studies (in vivo, in vitro, and human studies) have been conducted since the late 1950s, nearly all in the Soviet Union. They are not referenced here because they are not translated and not widely available. Instead, review articles and original articles in English are cited.[1-7]

PHARMACOLOGY

As mentioned earlier, a number of experimental and clinical studies demonstrated that eleuthero possesses adaptogenic properties (i.e., the ability to increase nonspecific body resistance to stress, fatigue, and disease). Additional experimental and clinical research supports other therapeutic applications of *E. senticosus*.

Adaptogenic Activity

An important characteristic of an adaptogen is its ability to "normalize," irrespective of the direction of pathology. *E. senticosus* was found to do the following in experimental models:

- Impede the adrenal hypertrophy induced by adrenocorticotropic hormone and the adrenal atrophy induced by cortisone
- Impede the thyroid hypertrophy induced by thyroidin and thyroid gland atrophy induced by 6-methylthiouracil
- Reduce blood glucose levels in alimentary and adrenal hyperglycemia and increase glucose levels in insulin-induced hypoglycemia
- Reduce leukocytosis induced by the parenteral administration of milk, as well as leukopenia induced by endotoxins
- Reduce erythrocytosis induced by cobaltous nitrate and erythropenia induced by phenylhydrazine

These are summarized in Table 87-2. Similar results were obtained with *P. ginseng* (see Chapter 110). As is evident from the discussion of eleuthero's adaptogenic activities, it shares many features with *P. ginseng*. In addition to adaptogenic activities, eleuthero, like panax, has been shown to do the following[1]:

- Increase resistance to infection in animals
- Reduce hepatic cholesterol biosynthesis
- Increase reproductive capacity and sperm counts in bulls
- Possess significant antioxidant activity
- Stimulate DNA synthesis and cellular repair enzymes

TABLE 87-2 **Abnormalities Normalized by *Eleutherococcus senticosus***

FUNCTION	NORMALIZATION ACTION OF *ELEUTHEROCOCCUS SENTICOSUS*
Adrenal	Impedes hypertrophy induced by ACTH Impedes atrophy induced by cortisone
Thyroid	Impedes hypertrophy induced by thyroidin Impedes atrophy induced by 6-methylthiouracil
Kidney	Increases renal capacity in pyelonephritis
Blood pressure	Decreases high blood pressure through pressure improvement of atherosclerosis Increases pressure in hypotension
Blood glucose	Reduces alimentary and adrenal hyperglycemia glucose Increases blood sugar in insulin-induced hypoglycemia
Leukocyte	Reduces leukocytosis induced by the administration of milk Reduces leukopenia induced by endotoxins
Erythrocyte	Reduces erythrocytosis induced by cobaltous nitrate Reduces erythropenia induced by phenylhydrazine
Stress	Reduces activation of the adrenal cortex in response to stress Prevents stress-induced thymic and lymphatic involution
Radiation	Protects against radiation exposure
Cancer	Inhibits carcinogenesis from urethane, 6-methylthiouracil indole
Cholesterol	Reduces hepatic biosynthesis
DNA	Stimulates synthesis

ACTH, Adrenocorticotropic hormone.

Stress Control

Another important action of adaptogens is the inhibition of the alarm phase of the stress reaction. Eleuthero showed similar action to *P. ginseng* in experiments designed to demonstrate an antialarm action. Specifically, eleuthero was shown to increase the swimming time of rats, reduce activation of the adrenal cortex in response to stress (alarm phase reaction), and prevent stress-induced thymic and lymphatic involution.[1-6]

Radiation Protection

In addition to its confirmed adaptogenic activity, eleuthero also demonstrated both protective and therapeutic actions in animals exposed to both single and prolonged x-ray radiation. In one study, both *E. senticosus* and *P. ginseng* were found to double the life span of rats exposed to prolonged radiation (total doses of 1620 to 7000 rads). When eleuthero was combined with antibiotics, the lifetime of irradiated rats (total dose of 3000 rads over 60 days) increased threefold.[7]

These results suggest that eleuthero may be of benefit in protecting against harmful radiation and as an adjunctive aid in radiation therapy in oncology. The latter suggestion is further supported by studies of eleuthero that demonstrated an inhibition of carcinogenesis.

Carcinogenesis Inhibition

Eleuthero preparations were shown to inhibit a number of cancer types in experimental studies in animals.[1,3] Part of eleuthero's anticancer effects may be due to its immune-stimulating effects. In vitro, it increased phagocytosis of *Candida albicans* by granulocytes and monocytes from healthy donors by 30% to 45%.[8,9] In vitro studies showed that whole ethanolic fluid extract of *E. senticosus* could induce and enhance interleukin-1 and interleukin-6 but not interleukin-2 production.[10]

CLINICAL APPLICATIONS

Adaptogenic Activity in Healthy Individuals

A fluid extract (33% ethanol) of *E. senticosus* root was administered to more than 2200 human subjects in clinical trials conducted in Russia designed to evaluate the "adaptogenic" effects of eleuthero. The data indicated that eleuthero had the following effects:

- Increased the ability of humans to withstand many adverse physical conditions (e.g., heat, noise, motion, workload increase, exercise, decompression)
- Increased mental alertness and work output
- Improved the quality of work under stressful conditions and improved athletic performance

The male and female subjects ranged in age from 19 to 72 years. Dosages of the fluid extract (33% ethanol) ranged from 2 to 16 mL, one to three times a day, for periods of up to 60 consecutive days.

Results from research outside of Russia were mixed, with little evidence to support that eleuthero improves physical performance in athletes.[11-13]

Adaptogenic Activity in Disease States

A fluid extract (33% ethanol) of *E. senticosus* root was administered to more than 2200 human subjects with various illnesses, including angina, hypertension, hypotension, acute pyelonephritis, various types of neuroses, acute craniocerebral trauma, rheumatic heart disease, chronic bronchitis, and cancer.[1]

Eleuthero appeared to be effective in atherosclerotic conditions, as evidenced by its ability to lower elevated serum cholesterol and prothrombin levels, reduce blood pressure, and eliminate anginal symptoms in human subjects. Its action on blood pressure was truly adaptogenic, since eleuthero was also shown to increase blood pressure in subjects with hypotension.[1]

Its effect in regulating blood pressure might be indicative of improved renal function; it was demonstrated that patients with acute pyelonephritis given eleuthero extract had increased renal capacity, as measured by an increased secretion of phenol red.[1]

Eleuthero appears to have some psychotropic action, because it was proven effective in the treatment of various psychological disturbances. Eleuthero consistently demonstrated an ability to increase one's sense of well-being, regardless of the psychological complaint (e.g., insomnia, hypochondriasis, various neuroses). A possible explanation of this effect is improved balance of the biogenic amines, including serotonin, dopamine, norepinephrine, and epinephrine, since eleuthero extract administered to rats was shown to increase biogenic amine content in the brain, adrenals, and urine.[1]

Data are insufficient to fully evaluate eleuthero's action in other disease states. However, it must be kept in mind that an adaptogen is nonspecific in its action and possesses a normalizing action irrespective of the direction of the changes from physiologic norms.

DOSAGE

The standard dosage of the fluid extract (33% ethanol) of *E. senticosus* roots used in the majority of studies ranged from 2 to 4 mL (up to 16 mL), one to three times a day, for periods of up to 60 consecutive days. In multiple dosing regimens, there is usually a 2- to 3-week interval between courses.[1,4]

Dosages are as follows:

- Dried root: 2 to 4 g
- Tincture (1:5): 10 to 20 mL
- Fluid extract (1:1): 2 to 4 mL
- Solid (dry-powdered) extract (20:1): 100 to 200 mg

TOXICOLOGY

Toxicity studies in animals demonstrated that eleuthero extracts are virtually nontoxic. The median lethal dose of the 33% ethanol extract of eleuthero is 14.5 mL/kg in mice and greater than 20 mL/kg in rats. No long-term toxicity was observed when a daily dose of 5 mL/kg of the fluid extract was administered to rats. Teratogenicity was studied in three species (rats, rabbits, and minks), with no adverse effects observed.[1]

In human clinical studies, it was demonstrated that eleuthero extracts (33% ethanol) in the recommended dosage range were well tolerated, and side effects were infrequent. A few studies found mild side effects at higher dosages (4.5 to 6 mL three times daily) when used for long periods (60 days). The symptoms included insomnia, irritability, melancholy, and anxiety. Pericardial pain, headaches, palpitations, and elevations in blood pressure were reported in individuals with rheumatic heart disease.[1] These symptoms were probably due to the mild stimulating effects of eleuthero and, although not serious, indicated the need to decrease the dosage or allow a washout period, or both.

DRUG INTERACTIONS

A clinical study in healthy humans indicated that extracts of eleuthero at generally recommended doses are unlikely to alter the levels of drugs primarily dependent on the CYP2D6 or CYP3A4 pathways for elimination.[14] However, in one case report, although a clear relationship could not be established, a person taking eleuthero with digoxin (Lanoxin) developed dangerously high serum digoxin levels.[15] Therefore, simultaneous use with digoxin requires close medical supervision and regular monitoring of blood digoxin levels.

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CHAPTER 88

Ephedra Species*

Michael T. Murray, ND and Joseph E. Pizzorno, ND

Ephedra sinica (family: Ephedraceae)
Common names: Chinese ephedra, Ma Huang, Chinese joint fir
Related species:
Ephedra distachya (European ephedra)
Ephedra trifurca or *Ephedra viridis* (desert tea)
Ephedra nevadensis (Mormon tea, cay note, canutillo, whorehouse tea, tapopote, teamster's tea)
Ephedra americana (American ephedra)
Ephedra gerardiana (Pakistani ephedra)

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GENERAL DESCRIPTION

Ephedra spp. are erect, branching shrubs found in desert or arid regions throughout the world. The 1.5- to 4-ft shrubs typically grow on dry, rocky, or sandy slopes. The many slender, yellow-green branches of ephedra have two small leaf scales at each node. The mature, double-seeded cones are visible in the fall.

CHEMICAL COMPOSITION

The chemical analysis of the stems and branches of *Ephedra* spp. focused on their alkaloid content. In *Ephedrea sinica*, the total alkaloid content can be up to 3.3%, with 40% to 90% of this being ephedrine. The remaining alkaloids are primarily pseudoephedrine and norpseudoephedrine.[1,2] In *E. gerardiana*, the alkaloid content usually varies from 0.8% to 1.4%, about half ephedrine and half other alkaloids (e.g., pseudoephedrine, *N*-methylephedrine, norephedrine).[2,3] *E. nevadensis* contains little or no ephedrine.

Depending on species, parts used (aerial, stem, leaf, or a combination of stem and leaf), harvesting, and extraction techniques, the alkaloid content of commercially available ephedra products varies considerably. In a series of studies, the alkaloid content in ephedra-based products varied by as much as fivefold, with different brands exhibiting lot-to-lot differences ranging from 44% to 260%. Although some products listed the ephedrine content on the label, many did not. In addition to the variations in alkaloid content, commercial ephedra products usually contained other highly active botanicals, including kola nut, guarana, and St. John's wort, as well as many contaminants (e.g., heavy metals).[3,4]

HISTORY AND FOLK USE

E. sinica has been used for medicinal purposes in China since approximately 2800 BC. Ma Huang (the stem and branch) was used primarily in the treatment of the

*On February 6, 2004, the U.S. Food and Drug Administration (FDA) issued a ban on the sale of dietary supplements containing ephedra. This ban was finalized on April 12, 2004. The FDA made this decision on the basis of clinical studies and adverse events. Dietary supplements containing ephedrine alkaloids, like other sympathomimetics, raise blood pressure and increase heart rate. The FDA thought ephedrine-based products exposed users to several risks, including the consequences of a sustained increase in blood pressure (e.g., serious illnesses or injuries including stroke and heart attack that can result in death). There was also a risk of increased morbidity and mortality from worsened heart failure and proarrhythmic effects in susceptible individuals.

common cold, asthma, hay fever, bronchitis, edema, arthritis, fever, hypotension, and urticaria.[1]

The Chinese believed the effect of the root and rhizome (Ma Huanggen) to be the opposite of the stem and branches and limited its use to the treatment of profuse night sweating.[1] Two hypotensive principles (ephedradine A and B) have since been isolated from ephedra root, along with a hypertensive compound (1-tyrosine betaine or maokine).[1]

Western medicine's interest in ephedra began in 1923 with the demonstration that the isolated alkaloid ephedrine possessed a number of pharmacologic effects. Ephedrine was synthesized in 1927 and has since been used extensively for clinical conditions in which sympathomimetic effects are desired.[3]

After ephedra-containing dietary supplements were linked to a high rate of serious side effects and a number of deaths, the U.S. Food and Drug Administration (FDA) banned the sale of ephedra-containing supplements on April 12, 2004. However, this ban is not without controversy (see the "Toxicology" section).

PHARMACOLOGY

The pharmacology of ephedra centers around its ephedrine content. Ephedrine and pseudoephedrine have been extensively investigated and are widely used in both prescription and over-the-counter (OTC) medications for asthma, hay fever, and rhinitis. In 1973, more than 20 million prescriptions contained one of these alkaloids. In 2000, ephedra was found in at least 200 OTC products, and it was estimated that as many as two to three billion doses were consumed that year in the United States.

Ephedrine

Ephedrine's basic pharmacologic action is that of a sympathomimetic. Ephedrine stimulates both α- and β-adrenergic receptors, as well as the release of norepinephrine. Ephedrine shares many pharmacologic actions with epinephrine, although ephedrine is much less active. Ephedrine also differs from epinephrine in its ability to be absorbed orally, its longer duration of action, and its more pronounced effect upon the central nervous system (CNS). The CNS effects of ephedrine are similar to those of amphetamines but, again, are much less potent.[1-4] Figure 88-1 illustrates its chemical structure.

The cardiovascular effects of ephedrine are also similar to those of epinephrine. It increases both diastolic and systolic blood pressure, cardiac output, and heart rate, but for a longer (about 10 times) period. Like epinephrine, ephedrine increases coronary, cerebral, and muscle blood flow at the expense of renal and splanchnic blood flow.[1-5]

The bronchial muscle relaxation induced by ephedrine is much less than epinephrine, but, again, the duration of action is much longer. Other smooth muscles, with the exception of the human uterus, are generally affected by ephedrine in the same manner (mild relaxation) as epinephrine. Ephedrine relaxes the human uterus, where the effects of epinephrine are more complex.[1-4]

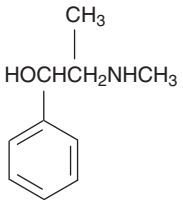


FIGURE 88-1 Ephedrine.

Extracts of ephedra were shown to inhibit complement in vitro, and a Chinese herbal medicinal prescription, Makyo-kanseki-to, was found to inhibit cyclic adenosine monophosphate activity.[6,7]

The principle adverse effects of ephedrine are CNS stimulation, nausea, tremors, tachycardia, and urinary retention.[1,2]

The major route of elimination of ephedrine is as the unchanged drug in the urine. The average half-life is 6 hours, although acidifying the urine decreases the half-life considerably. Alkalinization increases the half-life.[8,9]

Pseudoephedrine

Pseudoephedrine exhibits bronchodilating activity similar to ephedrine but has weaker pressor, cardiac, and CNS effects. Pseudoephedrine is often recommended over ephedrine in the treatment of chronic asthma, because it has fewer side effects.

Pseudoephedrine also demonstrated significant anti-inflammatory effects in various experimental models.[8-10] Other ephedra alkaloids, including ephedrine, also exhibited anti-inflammatory activity, although at much lower potency. Because the anti-inflammatory effect of pseudoephedrine is essentially identical in normal and adrenalectomized mice, the anti-inflammatory activity is not exerted via the adrenal glands. Instead, it appears that the anti-inflammatory activity of pseudoephedrine and other ephedra alkaloids is due to inhibition of prostaglandin E_2 synthesis.

CLINICAL APPLICATIONS

Asthma and Hay Fever

Ephedra and its alkaloids have proven effective as bronchodilators for the treatment of mild to moderate asthma and hay fever. The peak bronchodilation effect occurs in 1 hour and lasts about 5 hours after administration.

The therapeutic effect of ephedra diminishes if used over a long period of time due to the weakening of the adrenal gland caused by ephedrine. Therefore, it is often necessary to use ephedra in combination with herbs such as *Glycyrrhiza glabra* and *Panax ginseng* and nutrients such as vitamin C, magnesium, zinc, vitamin B_6, and pantothenic acid, which all support the adrenal glands.

The folklore herbal treatment of asthma involved the use of ephedra in combination with herbal expectorants. (Expectorants are herbs that modify the quality and quantity of secretions of the respiratory tract, resulting in the expulsion of the secretions and an improvement in respiratory tract function.) Commonly used expectorants include the following:

- *Glycyrrhiza glabra* (licorice)
- *Grindelia camporum* (grindelia)
- *Euphorbia hirta* (euphorbia)
- *Drosera rotundifolia* (sundew)
- *Polygala senega* (senega)

Common Cold

Ephedrine and pseudoephedrine are components of many OTC products for the self-treatment of the common cold. In China, ephedra, in combination with various other herbs, was found to be clinically effective in the treatment of cold symptoms, as well as those of influenza, pneumonia, whooping cough, and bronchitis.[1]

Weight-Loss Aid

In both human and animal studies, ephedrine was shown to promote weight loss.[2,11-19] Although ephedrine demonstrated an anorectic effect,[11] its main mechanism for promoting weight loss appeared to be increasing the metabolic rate of adipose tissue.[11-16] Therefore, ephedra's weight-reducing effects are most significant in those individuals with a low basal metabolic rate.[13] These effects can be greatly enhanced when used in combination with methylxanthines, caffeine, and theophylline, as well as aspirin,[13-18,20] which potentiates the action of ephedrine and other ephedra compounds.

In one animal study, when ephedrine was used alone, it resulted in a 14% decrease in body weight and a 42% decrease in body fat. However, when used in combination with caffeine or theophylline, the decreases were 25% and 75%, respectively.[14] However, when either caffeine or theophylline was used alone, there was no significant loss in body weight. The reason for the greater decrease in body weight is the increased metabolic rate and fat cell breakdown promoted by ephedrine and enhanced by caffeine and theophylline.

It is recommended that, for methylxanthines, *Camellia sinensis* (green tea) or extracts of *Cola* sp. be used rather than coffee or black tea.

One of the better designed studies on the use of an ephedrine/caffeine combination determined the safety and efficacy of an herbal supplement containing Ma Huang (90 mg/day ephedrine) and kola nut (192 mg/day caffeine) given to subjects for 6 months for weight loss. A total of 167 subjects were randomized to receive either a placebo or ephedrine/caffeine combination. The subjects were monitored primarily for changes in blood pressure, heart function, and body weight. In addition to these parameters, body composition and metabolic changes were studied. The results of this study demonstrated significant beneficial effects on body weight, body fat, and blood lipids of the herbal supplement in overweight men and women who were otherwise healthy. Herbal versus placebo treatment decreased body weight (−5.3 vs −2.6 kg), body fat (−4.3 vs −2.7 kg), and low-density lipoprotein cholesterol (−8 vs 0 mg/dL), and increased high-density lipoprotein cholesterol (+2.7 vs −0.3 mg/dL; $P = 0.004$). The ephedrine/caffeine mixture produced small changes in blood pressure variables (+3 to −5 mm Hg) and increased heart rate (4 ± 9 beats/min), but cardiac arrhythmias were not increased. Compared with placebo treatment, the herbal supplement produced no adverse events and only minimal side effects consistent with the known stimulant action of ephedrine and caffeine (e.g., dry mouth, insomnia).[19]

DOSAGE

The optimum dosage of ephedra depends on the alkaloid content in the form used (note that there is substantial variation in concentration of active constituents in plants). The average total alkaloid content of *E. sinica* is 1% to 3%. When used in the treatment of asthma or as a weight-loss aid, the ephedra dose should have an ephedrine content of 12.5 to 25 mg and be taken two to three times daily. For the crude herb, an equal dose would be approximately 500 to 1000 mg three times a day. Standardized preparations are often preferred, because they have more dependable therapeutic activity.

TOXICOLOGY

Ephedra can obviously produce the same side effects as ephedrine (e.g., increased blood pressure and heart rate, insomnia, anxiety).

The FDA advisory review panel on nonprescription drugs recommended that ephedrine not be taken by patients with heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland. Nor should ephedrine be used in patients on antihypertensive or antidepressant drugs.

Pregnant women should also avoid the use of ephedra and ephedrine. Ephedrine administered to chick embryos resulted in cardiovascular teratogenicity and embryotoxicity at doses as low as 1 µmol/egg.[21] The teratogenic effect of ephedrine is potentiated by caffeine.[22] Presumably, this activity of ephedrine is the result of the production of nitrosamines.[23] Simultaneous vitamin C administration might reduce the formation of nitrosamines from ephedra alkaloids.[24,25]

A key reason that the FDA issued the ban on ephedra products was the tremendous amount (more than 2000) of adverse event reports (AERs) filed with the FDA related to the use of supplements containing ephedra alkaloids.[26,27] However, when the Council of Responsible Nutrition studied the AERs filed with the FDA, it found that 98% of the AERs did not contain complete information, and in 81% of the reports, information on total daily intake of ephedra was not provided.[28] Of the 1173 reports, 121 were selected for further evaluation. Of the 121 selected cases, 47 were considered to contain serious adverse events, including 15 cases of stroke and stroke-like symptoms, 13 cases of seizures, 15 cases of cardiac arrest, and 2 cases of individuals who collapsed.

From the selected 121 cases, there were 8 reports of death: 6 were cardiovascular, 1 occurred in an automobile accident, and 1 was a spontaneous abortion. Among the six cardiovascular-related deaths, five were males and one was female. All five males who died from cardiovascular problems were using dietary supplements containing ephedra as an athletic performance enhancer. Additionally, four of the five were simultaneously using other performance-enhancing products such as caffeine; therefore, their deaths cannot be directly attributed to the use of ephedra. The report concluded that after extensive examination of these AERs, it was not possible to conclusively determine if there were any unexpected toxicologic effects due to the ephedra contained in the dietary supplements solely on the basis of the information presented in the AERs.

DRUG INTERACTIONS

As mentioned earlier, ephedrine should not be taken by patients with heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland. Nor should ephedrine be used in patients on antihypertensive or antidepressant drugs. Ephedrine will potentiate other stimulant/sympathomimetic drugs and will likely counteract antihypertensives.

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CHAPTER 89

Epilobium Species (Fireweed)

Kathy Abascal, BS, JD, RH(AHG), and Eric L. Yarnell, ND, RH(AHG)

Epilobium spp. (family: Onagraceae)
Synonym: *Chamaenerion* spp.
Common names: fireweed, willow herb, great willow herb *(Epilobium angustifolium)*, rose-bay *(Epilobium angustifolium)*, wickup *(Epilobium angustifolium)*; small-flowered willow herb *(Epilobium parviflorum)*; marsh epilobium *(Epilobium palustre)*, wickop *(Epilobium palustre)*, swamp willow herb *(Epilobium palustre)*

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GENERAL DESCRIPTION

Epilobium is a genus of some 200 species that typically grow at relatively high latitudes or high altitudes.[1] This perennial is found in all parts of the world. It has tall, erect, and somewhat woody stems, from 2 to 7 ft tall, crowded with long, narrow, alternate leaves that are from 2 to 6 in long. Its flowers range from lavender to pink to carmine-purple, and its pods are long, narrow, and filled with feathery seeds.[2] Most species have small flowers (e.g., *Epilobium parviflorum,* known as small-flowered willow herb). A few have large flowers (e.g., *E. angustifolium,* known as great willow herb). Despite the use of the term "willow," there is no relationship between *Epilobium* spp. and *Salix* spp. (willow).

CHEMICAL COMPOSITION

The aerial parts are rich in flavonoids[3] and flavonol glycosides based on kaempferol, quercetin, and myricetin skeletons.[4] The plants contain complex tannins such as ellagitannins (oenothein A and B) and gallotannins[5]; β-sitosterol; triterpenes[6]; and gallic, chlorogenic, and ellagic acids.[7] In the small-flowered species, myricetin is the predominant flavonoid. The large-flowered species have a completely different flavonoid pattern, with isoquercitrin being predominant. The plant contains the highest content of the flavonoid myricetin 3-0-β-D-glucuronide shortly after flowering (Figure 89-1).

HISTORY AND FOLK USE

Fireweed has been widely used as a medicine and as a food in many parts of the world. Native Americans used it for burning urination, male urination problems, coughs and sore throats, stomachaches and intestinal discomfort, bowel hemorrhages, gastritis, tuberculosis, and as a panacea for pain.[8] It was used as a poultice for boils; abscesses; carbuncles; bruises; infected sores, cuts, and wounds; and other skin ailments. Various Eskimo and Siberian tribes also used the plant to treat sores.[9] Young shoots were widely consumed as food and fodder, as were the roots and leaves. The seed fluff was used for weaving cloth, making thread, and starting fires. Fireweed is named *mjoelke* in Scandinavia, a derivation of the word milk, because of centuries of observation that cows grazing on the plant produce more milk.

Eclectic physicians considered fireweed unequaled as a treatment for summer bowel troubles and also used it in other types of diarrhea, including cholera infantum and typhoid dysentery.[10] The Eclectics often administered fireweed as an infusion, using frequent small doses (up to every 10 minutes). *E. hirsutum* was used in Egyptian and European folk medicine to treat inflammation, adenoma, and prostate tumors.[11] Europeans also used the plant to treat eczema, seborrhea, other skin conditions, and menstrual disorders.[12] The plant was also used for the treatment of benign prostatic hyperplasia.[13]

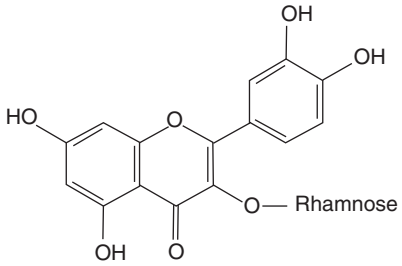


FIGURE 89-1 Quercitrin.

PHARMACOLOGY

Analysis of studies on fireweed is complex, given the subtle differences among species and differences in the actions of aqueous and alcoholic extracts. Overall, most fireweed species appear to have analgesic, antidiarrheal, antiinflammatory, antimicrobial, antineoplastic, and prostate-related activities.

Analgesic Effect

Ethanolic extracts of *E. angustifolium* injected subcutaneously had a weak analgesic effect on mice in the hot plate test, whereas its analgesic effect was greater than that of acetylsalicylate in the acetic acid test.[14] In mice, an extract of *E. hirsutum* had an analgesic effect comparable to morphine and diclofenac.[15]

Antidiarrheal Effect

Fireweed showed significant antidiarrheal and antimotility effects in a variety of animal models.[16]

Antiinflammatory Effect

Aqueous extracts of *E. angustifolium* (40 mg/kg orally) strongly reduced the release of prostaglandins and depressed edema in vivo.[17] Its effect on edema was equivalent to indomethacin (2 mg/kg). *E. parviflorum* did not suppress edema and had about 20% of the effect on prostaglandin release. Isolated myricetin-3-0-β-D-glucuronide was 10 times more effective than indomethacin at inhibiting edema in rats, was equally effective at inhibiting prostaglandin biosynthesis, and had a dose-related antiarthritic effect.[18,19] It inhibited both cyclooxygenase-1 and -2 nearly equivalently and inhibited 5-lipooxygenase comparably to nordihydroguaiaretic acid. It dose-dependently inhibited platelet aggregation equivalently to indomethacin, but in contrast to indomethacin, induced no gastric ulcers. The compound may be safer than nonsteroidal antiinflammatory drugs, since it prevents the arachidonic shunting that results in the formation of leukotrienes.

Antimicrobial Effect

Dilute extracts of fireweed are antimicrobial in vitro.[20] *E. angustifolium* and *E. rosmarinifolium* have the broadest spectrum of action, inhibiting bacteria, yeast, and fungi. *E. angustifolium* and *E. hirsutum* inhibited *Microsporum canis* at concentrations as low as 10 mcg/mL. In another study, *E. angustifolium* failed to inhibit *Aspergillus niger* but somewhat inhibited *Candida albicans* while strongly inhibiting *Staphylococcus aureus* and *Escherichia coli*.[21]

Antitumor Effect

Oenothein B, isolated from fireweed, showed some antitumor activity against sarcoma 180 in mice and some selectivity against lung cancer cells and two colon cancer lines, but did not have a noticeable effect on the prostate cancer lines tested.[22] In other studies, *E. angustifolium* had a specific and significant antiproliferative effect on human prostate epithelial cells.[23] In addition, several of its flavonoids were potent growth inhibitors when tested on various hormone-sensitive and hormone-nonsensitive cell lines.

Effect on Prostate and Prostatic Enzymes

Extracts of various fireweed species inhibited aromatase in vitro.[24] This action was primarily attributed to oenothein A and B, but other fireweed flavonoids also inhibited aromatase. Both oenothein A and B had a considerably greater inhibitory action on 5-α-reductase in vitro than the reference drug finasteride. The aqueous extract and ultrafiltrate of *E. angustifolium* had an antiandrogenic effect in intact rats, and the aqueous extract had a proandrogenic effect in castrated rats.[25] In another study, alcoholic extracts of fireweed failed to inhibit 5-α-reductase, whereas the aqueous extract showed significant inhibition.[26] This action was attributed to the compound oenothein B.

CLINICAL APPLICATIONS

No clinical studies were found on any of the fireweed species. This is unfortunate, since preliminary studies indicated that fireweed might be more effective than drugs such as finasteride and indomethacin, as discussed earlier. The existing pharmacologic research supports fireweed's well-established use in traditional medicine as a treatment for prostate disorders and as a topical medicine in various skin conditions.

DOSAGE

Dosages for fireweed are not well established. Fireweed is traditionally administered as a standard infusion using 2 to 3 teaspoons of herb to 1 cup of boiling water, taken as needed.[27] The suggested dose for an aqueous/alcoholic tincture is 2 to 6 mL three times a day.

Aqueous/alcoholic tinctures appear to be more effective than tinctures with a high alcohol concentration.[28,29] No widely accepted standardization exists to ensure quality fireweed extracts, although flavonoid profiles can be used to distinguish the various species.[30,31] Species grown in Africa appear to have a significantly higher content of oenothein B than the same species grown in Europe.[32]

TOXICOLOGY

Fireweed has no known toxic effects, and its lack of toxicity is underscored by a worldwide use as both food and fodder. The median lethal dose for injected ethanol extract in mice is 1.4 g/kg.[33]

DRUG INTERACTIONS

There are no documented drug interactions with fireweed.

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CHAPTER 90

Fatty Acid Metabolism

Richard S. Lord, PhD, and J. Alexander Bralley, PhD

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Although a growing body of research documents the critical importance of fatty acids for maintaining health, common food choices in modern society do not lead to appropriate levels or balances of these nutrients. Years of negative associations of dietary fat with calories, cholesterol, and cancer have resulted in a general public attitude that foods containing fats should simply be avoided. Many food manufacturers have taken advantage of this attitude by modifying fat content and labeling, wherever possible, to tout "low-fat" foods. Advertisements for such foods further instill the notion that dietary fat is bad. Amid the clamor over the largely mistaken problems associated with dietary fats, many problems have been created by the large-scale use of modified fats by food suppliers. Individuals do not feel the effects of abusing dietary fats for the short term because of the presence of many protective mechanisms that make health threats from fat abuse an insidious process.

Modern diets of fast foods and packaged dinners tend to be rich in saturated fats and hydrogenated oils and lacking in essential fatty acids (EFAs). We now know that the amount and type of dietary fat play major roles in maintaining health. Some saturated fatty acids stimulate cholesterol formation, but most do not.

The old concept of three EFAs has been replaced by recognition of critical roles for multiple polyunsaturated fatty acids (PUFAs). Dietary fats simultaneously provide the major cellular energy source, control the passage of compounds into and out of cells, determine the integrity of nerve tissue, and serve to form powerful hormones.

The essential hormone function is mediated by some special fatty acids that affect energy flow, cell division, immune responses, and many other body controls. These critical fatty acids are used to make powerful tissue-specific compounds called eicosanoids. Figure 90-1 illustrates the various roles of fatty acids. This chapter discusses more about these functions after some basic fatty acid relationships are explained.

FATTY ACID STRUCTURE AND METABOLISM

About 30 structural isomers and homologs of fatty acids occur in human tissues. They are named in various ways, including those with Latin prefixes such as *penta-* and *hexa-* for the number of carbon atoms. These are the chemical names approved by the International Union of Pure and Applied Chemists. Many also have common names. Because common names are in widest use among clinicians, they are used here. Table 90-1 provides a lexicon of fatty acid terms.

Fatty acids containing the maximum number of carbon–hydrogen bonds are called saturated. They have a higher energy or caloric yield than corresponding unsaturated fatty acids (UFAs). They are present as major components of most foods and are high in manufactured foods such as candy bars. The most abundant members in human tissues are those that are 14 (myristic), 16 (palmitic), or 18 (stearic) carbons long. The elongation process can be repeated to yield members that are 20, 22, and 24 carbons long.

Three major families of UFAs are found in human tissues: the ω-9, ω-6, and ω-3 UFAs (or n-9, n-6, and n-3). The ω-6 and ω-3 PUFAs are defined by the position of the double bond closest to the terminal methyl group of the fatty acid molecule. In the ω-6 family, the first double bond occurs between the sixth and seventh carbons from the methyl group end of the molecule, whereas in the ω-3 family, the first double bond occurs between the third and fourth carbons (Figure 90-2 provides naming conventions).

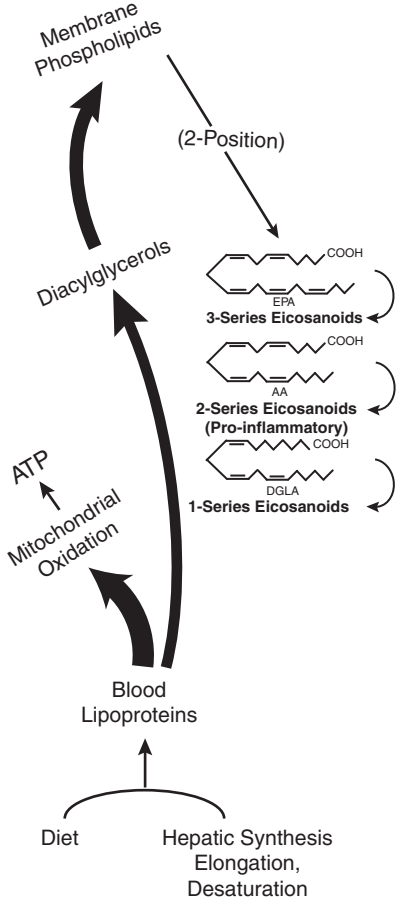


FIGURE 90-1 Metabolic roles of fatty acids.

The older δ naming scheme gives the positions of all double bonds, counting from the carboxyl or number 1 carbon. The ω scheme takes advantage of the fact that the double bonds are always separated by three carbons and simply gives the total length and number of double bonds separated by a colon. The number after the ω symbol gives the position of the first double bond counting from the ω-1 carbon.

Fatty acids can be synthesized from acetyl coenzyme A (CoA) derived from carbohydrate, protein, and other nonlipid sources. This pathway produces saturated fatty acids, predominantly palmitic acid (16:0). Palmitic acid can be desaturated, forming palmitoleic acid of the ω-7 class of UFAs. Palmitic acid can also be lengthened to stearic acid (18:0) and desaturated to form oleic acid of the ω-9 class. The ω-6 and ω-3 classes of UFAs are derived from dietary PUFAs. These classes can be further lengthened and desaturated. None of the four ω classes of UFAs, however, is interconvertible. These reactions can be repeated in various combinations, giving an array of saturated and UFAs for use in the essential functions of tissue maintenance.

The desaturase enzymes function to place double bonds at positions up to nine carbons from the carboxyl end of the molecules. When you count from the other end, the position varies, depending on the length of the fatty acid. Thus, for stearic acid with 18 carbons, a desaturase can form a double bond nine carbons from the carboxyl end, which is also nine carbons from the methyl end (18 – 9 = 9). These differences become important because the type of eicosanoid hormones that can be formed later depends on the position of the first double bond from the methyl end.

The geometry of desaturase enzymes will not allow insertion farther than nine carbons (δ-9) from the carboxyl group. Thus, linoleic acid (LA; δ-9, 12) cannot be synthesized in humans. Fatty acids of various chain lengths can act as desaturase substrates, as well as those that already possess double bonds at other positions.

TABLE 90-1 **Lexicon of Fatty Acid Terms**

TERM OR ABBREVIATION	DEFINITION OR EXPLANATION
AA	Arachidonic acid
ALA	Alpha-linolenic acid
Alpha-linolenic acid	Delta 9,12,15 octadecatrienoic acid; 18:3 ω-3
Arachidonic acid	Delta 5,8,11,14 eicosatetraenoic acid; 20:4 ω-6
Beta-oxidation	The mitochondrial metabolic pathway whereby fatty acids are converted into acetyl CoA, which enters the citric acid cycle to ultimately yield adenosine triphosphate. The carbon atoms of the fatty acid are oxidized to carbon dioxide.
Carnitine	The molecule to which fatty acids are attached in the process of their enzyme-mediated entry into the mitochondrial matrix. This enzyme is inhibited by malonyl CoA formed during fatty acid synthesis from carbohydrates.
Cerebronic acid	The 2-hydroxy derivative of lignoceric acid (24:0); found in glycosphingolipids in the brain
Cervonic acid	Another name for docosahexaenoic acid
cis	Geometrical isomer in which two groups are on the same side of a double bond
Clupanodonic acid	Another name for δ-7,10,13,16,19-docosapentaenoic acid (DPA3), an ω-3 series, long-chain, highly unsaturated fatty acid; found in fish oils and phospholipids in the brain
Delta	Used to describe the position of double bonds relative to the carboxyl end of a fatty acid
Desaturase	Tightly bound to the endoplasmic reticulum membrane, this enzyme, in association with cytochrome b5 and cytochrome b5 reductase, uses reduced nicotinamide adenine dinucleotide and oxygen to introduce double bonds into fatty acids. There are at least four separate desaturases, named according to the position of inserted double bonds. Delta-9-desaturase, δ-6-desaturase, and δ-5(4) desaturase act on fatty acetyl CoA thioesters, always inserting double bonds between the thioester bond (carboxylate group) and the double bond closest to it, leaving a three-carbon gap. Activities of these enzymes fluctuate according to dietary fat intake to maintain optimal fluidity state of the membrane lipids. Their concentrations decrease in starvation and increase greatly on refeeding carbohydrates. They are suppressed when dietary unsaturated fatty acid intake (including trans isomers) is high.

TABLE 90-1 **Lexicon of Fatty Acid Terms—cont'd**

TERM OR ABBREVIATION	DEFINITION OR EXPLANATION
DGLA	Dihomogammalinolenic acid
Dihomogammalinolenic acid	Delta 8,11,4 eicosatrienoic acid; 20:3 ω-6
DHA	Delta 4,7,10,13,16,19 docosahexaenoic acid; 22:6; an ω-3 series long-chain, highly unsaturated fatty acid; found in fish oils and the phospholipids in the brain (also known as cervonic acid)
Dienoic	Contains two double bonds
EFA	Essential fatty acid
Eicosanoid	A product of the specific, enzyme-directed oxidation of polyunsaturated fatty acids containing 20 (eicosa)carbons. This term encompasses the prostaglandins, thromboxanes, and leukotrienes.
Eicosapentaenoic acid	Delta 5,8,11,14,17 eicosapentaenoic acid; 20:5 ω-3; one of the most abundant fatty acids in fish oils
Elongase	An enzyme that adds 2-carbon units (acetate) to the carboxyl end of an existing saturated or unsaturated fatty acid. Mitochondrial form uses acetyl CoA, whereas endoplasmic form has malonyl CoA as substrate.
EPA	Eicosapentaenoic acid
Gamma linolenic acid	Delta 6,9,12 octadecatrienoic acid; 18:3 ω-6
GLA	Gamma-linolenic acid
HUFA	Highly unsaturated fatty acid; generally having five or six double bonds
LA	Linoleic acid
Lauric acid	Tetradecanoic acid; C12:0; first isolated and identified from the laurel plant
LCP	Long-chain polyunsaturated fatty acid
Linoleic acid	Delta 9,12 octadecadienoic acid; 18:2 ω-6
Meads acid	Delta 5,8,11 eicosatrienoic acid; 20:3 ω-9. This compound is not normally produced in appreciable amounts due to the preferential loading of the desaturase enzymes with the more strongly binding essential fatty acids and their metabolic products. It accumulates, however, in essential fatty acid deficiency, making it a marker for this condition.
Monoenoic	Containing one double bond
MUFA	Monounsaturated fatty acid
Omega	Used to describe the position of double bonds relative to the methyl end of a fatty acid
P + M/S ratio	Polyunsaturated + monounsaturated to saturated fatty acid ratio
P/S ratio	Polyunsaturated-to-saturated fatty acid ratio
Phospholipase A_2	An enzyme that catalyzes the hydrolysis of the fatty acid ester from position 2 of phosphoglycerides. Dependent on calcium, this enzyme is responsive to intracellular calcium, calmodulin, etc. It releases primarily polyenoic fatty acids (arachidonic acid, etc.) from membranes for eicosanoid synthesis.
PUFA	Polyunsaturated fatty acid
Phosphatide	Diacylglycerol phosphate, to which various groups may be attached through phosphoester linkage; the principal components of cell membranes
Polyenoic	Containing two or more double bonds
Saturated fatty acid	A fatty acid in which all of the carbon atoms except for the carboxyl carbon are fully hydrogenated as $–CH_2–$ (and $–CH_3$)
Stearidonic acid	Delta 6,9,12,15 octadecatetraenoic acid; 18:4 ω-3; a product of elongation of ALA and a precursor to EPA. A good source is black currant seed oil.
Timnodonic acid	Another name for EPA or 20:4 ω-6
Trans	Geometrical isomer in which two groups are on opposite sides of a double bond
Unsaturated fatty acid	A fatty acid in which two or more adjacent pairs of carbon atoms are lacking hydrogen atoms, having instead an additional carbon–carbon bond or double bond
δ	The Greek letter delta
ω	The Greek letter omega

CoA, coenzyme A.

Figure 90-3 shows the products of the δ-9 desaturase acting on three saturated fatty acids.

The activity of the desaturase enzymes is critical for maintaining the ratio of saturated and unsaturated components in cell membranes. Tumor tissue and virus-transformed cells have a higher content of UFAs, especially oleic acid, which increases relative to the amount of stearic acid. Such shifts increase the metabolic rates of many lipid-dependent enzymes and are associated with a higher capacity for cell division.[1] Individuals with recurrent tumors may already have too much oleic acid relative to stearic acid, and encouraging a diet high in olive oil or other highly UFAs may be contraindicated.

In the tissues of plants and higher animals, the insertion of double bonds always results in the cis geometry. The phrase "partially hydrogenated vegetable oil" on food labels indicates that a natural oil has been chemically modified in a process that converts some

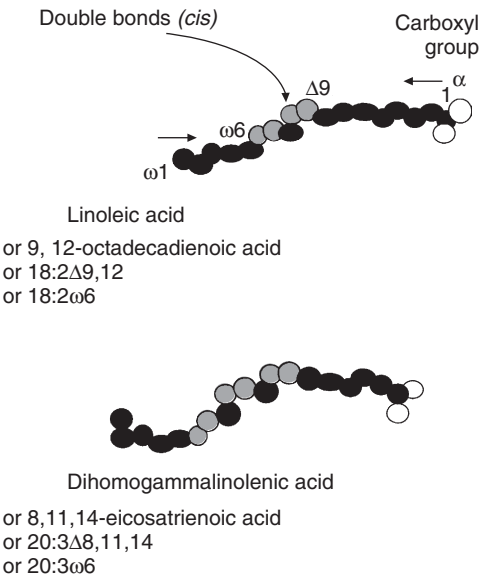


FIGURE 90-2 Naming conventions for unsaturated fatty acids.

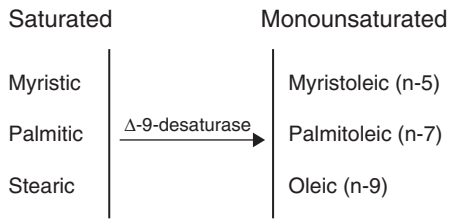


FIGURE 90-3 Formation of monounsaturated fatty acids.

of the cis UFAs to the trans form. Oleic acid is changed into its trans isomer, elaidic acid, which is the most abundant trans fatty acid in most hydrogenated oils. In human metabolism, trans unsaturated fat behaves similar to saturated fat, meaning that their accumulation tends to increase the risk of heart disease. Adverse effects of trans fatty acids on high-density lipoprotein or low-density lipoprotein cholesterol are well documented in medical research literature.[2-4]

Interference with eicosanoid production is also suspected, and research in the area of health risks of trans fatty acids is accelerating. Trans fatty acid levels in cell membranes are determined by dietary intake of hydrogenated oils.[5] A person eating a doughnut for breakfast (3.19 g of trans fatty acids), a small order of French fries with lunch (3.43 g), two teaspoons of margarine on bread with dinner (1.24 g), and two cookies for a snack (1.72 g) would ingest a total of 9.58 g of trans fatty acids, enough to negate the serum cholesterol-lowering effects of a decrease in saturated fat of 10% of total energy intake.[6]

Dietary PUFAs are largely composed of the ω-6 family (e.g., linolenic acid [LA]), which is abundant in vegetable seed oils, and the ω-3 family (e.g., α-linolenic acid [ALA]), which is high in vegetable leaves, flaxseeds, walnuts, canola, and modest in soybean oil.[7] Table 90-2 lists other members of these classes. When the diet supplies adequate LA and ALA, they may be used to form the other members in their classes by desaturation and elongation reactions.

The δ-6 desaturase enzyme acts as a gateway for the flow of fatty acids through the desaturation and elongation pathway. Although it can act on any long-chain fatty acid, the substrate binding affinity increases greatly with the number of double bonds already present. Thus, 18:3 binds stronger than 18:2, which binds stronger than 18:1. The result is that ALA is quickly converted to eicosapentaenoic acid (EPA), whereas oleic acid is slowly converted into 20:3ω9 in the presence of appreciable amounts of either LA or ALA. When the two EFAs are absent, however, 20:3ω9 accumulates because the desaturase is free to act on oleic acid. Elevated 20:3ω9 (Mead or eicosatrienoic acid) is a marker that can be used to detect EFA deficiency.

TABLE 90-2 **Polyunsaturated Fatty Acid Families**

FAMILY	CONFIGURATION	NAME
Omega-6	18:2	Linoleic acid (LA)
	18:3	Gamma linolenic acid (GLA)
	20:3	Dihomogammalinolenic acid (DGLA)
	20:4	Arachidonic acid (AA)
Omega-3	18:3	Alpha-linolenic acid (ALA)
	20:5	Eicosapentaenoic acid (EPA)
	22:5	Docosapentaenoic acid (DPA-3)
	22:6	Docosahexaenoic acid (DHA)

The δ-6 desaturase enzyme requires a zinc ion for activity. For this reason, supplementing a patient with sources of LA and ALA does little good if zinc deficiency is present. The changes in body growth, organ weights, and lipid concentrations in plasma and liver produced by zinc deficiency are reversed by the addition of γ-linoleic acid (GLA)-rich primrose oil, but not LA-rich safflower oil, showing the role of zinc in the δ-6 desaturase enzyme.[8] The enzyme is also inhibited by high concentrations of saturated fatty acids, monounsaturated acids, and trans fatty acids, all of which compete for the enzyme binding site and yield products that are of less significance to the cell.

The PUFAs impact health due to their conversion to compounds, collectively called eicosanoids, which possess extremely potent biological activities. Their functions of regulating blood vessel leaking, lipid accumulation, inflammation, and immune cell behavior are relevant to the initiation and progress of cardiovascular disease.[9] These compounds, in turn, are used to amplify and balance signals to the organs, the blood clotting system, and the immune system.

Production of eicosanoid hormones is shown in Figure 90-4. The parent compounds are dihomogammalinolenic (DGLA), arachidonic acid (AA), and EPA, and the pathway uses the same cyclooxygenase enzyme for all three series of products. The relative concentrations of the three fatty acids present in the phospholipids of the cell membranes where the hormones are produced determine which product will predominate, due to substrate competition for the active site, as depicted in Figure 90-4. In a similar manner, the lipoxygenase enzyme initiates the sequence of reactions leading to leukotriene formation. The 2-series that is derived from AA is by far the most proinflammatory. The effects of GLA and DGLA on rheumatoid arthritis and many other inflammatory diseases are mediated via this mechanism. Because dietary intake is a primary determinant of the fatty acids that enter this pathway, there is a direct link between the balance of specific fats in the diet and inflammatory responses and other local control processes. Long-term health maintenance is highly dependent on proper balance of dietary fatty acids.

It is no longer adequate simply to recommend the replacement of saturated fats with PUFAs. Balanced intake of n-3 and n-6 fatty acids, not just a high PUFA-to-saturated ratio, is required for

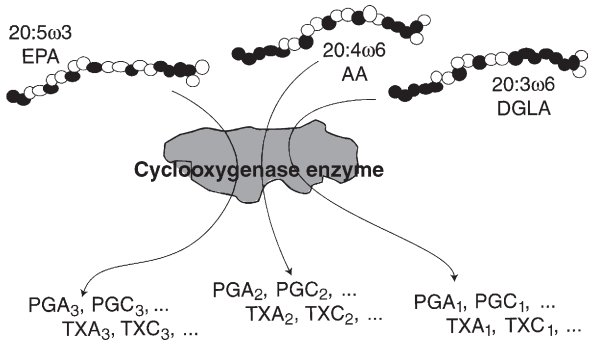


FIGURE 90-4 Fatty acid relationships to eicosanoid formation.

optimal control of every tissue in the body.[10] Chapter 14 discusses the interpretation of fatty acid testing and clinical interventions.

CONTROL OF FATTY ACID SUPPLY AND DISTRIBUTION

Fatty acids are present in the diet in the form of triglycerides in solid fats or liquid oils and as phosphatides in cell membranes of whole foods. They are rarely present in nature as free fatty acids. Table 90-3 lists food sources of the more abundant fatty acids. Foods always contain complex mixtures of fatty acids with enrichment of any single fatty acid rarely exceeding 70%.

Ingested fats are dispersed and digested by the action of bile acids and lipase enzymes. They pass into enterocytes along with cholesterol, where they are associated with proteins, becoming particles called chylomicrons. These are passed into the lymphatic system to flow directly through the heart into systemic circulation. Enzymes in capillary cell walls cause fatty acid transfer from chylomicrons, which become greatly reduced in size and return for uptake by the liver as chylomicron remnants. By this process, the fatty acids in foods become directly incorporated into the membranes of all tissues.

Because of the critical life-supporting functions in forming cell membranes and supplying energy sources and hormone controls, several mechanisms assure that the supply of fatty acids will be continuous, even during short intervals between meals. In the fasting state, fatty acids are either produced from carbohydrates or protein or mobilized from adipose stores. The liver handles the role of supply depot by forming another class of lipid-protein particles called very low-density lipoproteins. These particles deliver fatty acids and cholesterol to the tissues by mechanisms similar to those for chylomicrons, except that the remnant low-density lipoprotein particles are taken up in total by binding to receptor sites on cell surfaces. By ensuring a constant supply of fatty acids, the body controls one of the most critical materials for carrying out the various life-sustaining functions of growth and repair.

Effect of Low-Fat Diets

An individual on a low-fat, high-carbohydrate diet uses the fatty acid synthetic pathway extensively. As shown in Figure 90-5, this pathway requires citrate to leave the mitochondria to generate malonyl CoA. The resultant high concentrations of malonyl CoA inhibit the activity of the enzyme that is the gateway to fatty acid oxidation. For this reason, very low-fat diets do not result in weight loss nearly as quickly as one might expect. The burning of excess fat is actually inhibited by the high carbohydrate intake. In individuals with low body fat and good lean mass, high carbohydrate intake spares the use of fatty acids. In more sedentary individuals with lower rates of fatty acid oxidation, the medium-chain fatty acids that are otherwise so quickly used for energy may accumulate above normal levels in membranes.

Many other factors influence the rate of oxidation of fatty acids. Dramatically increased fatty acid oxidation occurs in starvation and diabetes mellitus with production of large amounts of ketone bodies that accumulate to give the ketoacidotic condition. Carnitine deficiency results in impairment of fatty acid oxidation and failure of gluconeogenesis, leading to hypoglycemia.

TABLE 90-3 **Dietary Sources of Even-numbered Medium-chain and Long-chain Saturated Fatty Acids**

NO. OF CARBONS	COMMON NAME	SOURCE
10	Capric (C10:0)	Most plants and butter
12	Lauric (C12:0)	Palm kernel, coconut, laurels
14	Myristic (C14:0)	Nutmeg, palm kernel, coconut, myrtle
16	Palmitic (C16:0)	Common in all animal and plant fats
18	Stearic (C18:0)	Common in all animal and plant fats
20	Arachidic (C20:0)	Peanut (arachis) oil
22	Behenic (C22:0)	Seeds
24	Lignoceric (C24:0)	Cerebrosides, peanut oil

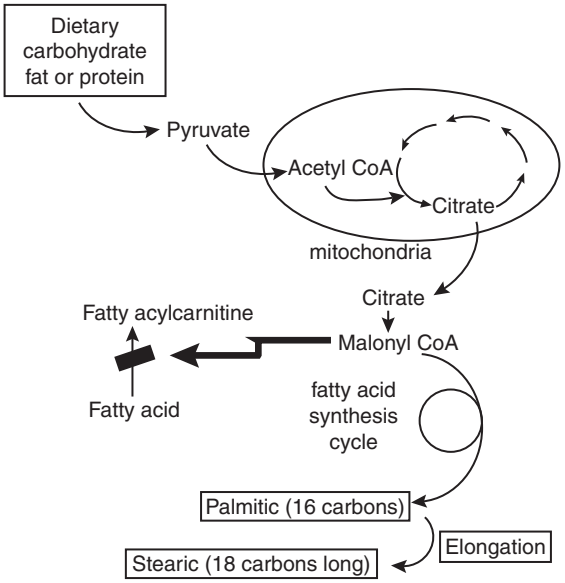


FIGURE 90-5 Carbohydrate conversion to fat; inhibition of fatty acid oxidation.

FATTY ACIDS AND HUMAN DISEASES

Quantification of the approximately 30 fatty acids present in human tissues is now routinely available. Both deficiencies and excesses of individual fatty acids lead to metabolic problems. A brief discussion of a few highly relevant conditions affected by fatty acid intake is presented here (see Chapter 14 for additional discussion of specific fatty acid imbalances). Table 90-4 lists typical signs and symptoms of fatty acid abnormalities, and Table 90-5 lists some well-documented clinical applications of supplemental fatty acids.

TABLE 90-4 **Signs and Symptoms Associated with Fatty Acid Abnormalities**

SIGNS AND SYMPTOMS	FATTY ACID ASSOCIATION	ACTION
Emaciation, weakness, disorientation	Caloric deprivation	Add sources of balanced ω-3 and ω-6 FAs
Reduced growth, renal dysplasia, reproductive deficiency, scaly skin deficiency	Classic essential fatty acid	Add good quality fats and oils
Eczema-like skin eruptions, loss of hair, liver degeneration, behavioral disturbances, kidney degeneration, increased thirst, frequent infections, poor wound healing, sterility (male) or miscarriage (female), arthralgia, cardiovascular disease, growth retardation	Linoleic acid insufficiency	Add corn or safflower oils
Growth retardation, weakness, impairment of vision, or learning disability, poor coordination, tingling in arms/legs, behavioral changes, mental disturbances, low metabolic rate, high blood pressure, immune dysfunction, acid insufficiency	Alpha- or γ-linolenic	Add flax, primrose, borage, black currant oils
Depression, anxiety, learning and behavioral disorders, age-related eye disorders	Long-chain PUFA-dependent	Add fish oils, avoid neuromembrane function hydrogenated oils
Cardiovascular disease risk	Prostanoid balance	Add ω-3 PUFAs
Cancer	Low stearic to oleic ratio	Use ω-6 PUFAs with caution
Rheumatoid arthritis	Low GLA and DGLA	Add primrose oil
Deficiency of vitamin B_{12} or carnitine, or both	Increased odd-numbered FAs	Add vitamin B_{12} or carnitine, or both
Myelinated nerve degeneration	Increased long-chain FAs	Add high-erucate canola or mustard oils
Fatty liver	Saturated and ω-9	Restrict alcohol, add lecithin, accumulation in liver, increase methionine
Accelerated aging	High PUFA intake without increased antioxidants	Add vitamins E and C, Se, Mn, and Zn

DGLA, dihomogammalinolenic acid; FAs, fatty acids; GLA, γ-linolenic acid; Mn, magnesium; PUFA, polyunsaturated fatty acid; Se, selenium; Zn, zinc.

TABLE 90-5 **Clinical Use of γ-linolenic Acid and α-linolenic Acid**

APPLICATION	ALPHA-LINOLENIC ACID	GAMMA-LINOLENIC ACID
Lower blood pressure, lower blood cholesterol, and lower risk of stroke and heart attack	**X**	**XX**
Normalize fat metabolism in diabetes and decrease the amount of insulin required by diabetics	X	X
Prevent liver damage due to alcoholism and decrease withdrawal symptoms after discontinuing the habitual use of alcohol	X	X
Provide adjunctive treatment for schizophrenics	X	XX
Cause weight loss by increasing metabolic rate and fat burn-off	X	XX
Relieve premenstrual breast pain (mastalgia) and premenstrual syndrome of bloating, irritability, depression, and aggressive behavior	XX	X
Prevent drying and atrophy of tear and salivary glands (Sjögren's syndrome)	X	
Prevent arthritis in animals	X	X
Improve the condition of hair, nails, and skin	X	XX
Improve certain kinds of eczema	X	X
Slow down or stop deterioration in multiple sclerosis	X	X
Help treat diabetic neuropathy in type 2 diabetes	X	X
Kill cancer cells in tissue culture without harming normal cells	X	XX

X, moderate response; XX, strong clinical response.

Developmental Disorders

The very-long-chain PUFA docosahexaenoic acid (DHA) has a special role in the formation of the developing nervous system.[11,12] Children with attention deficit hyperactivity disorder have lower concentrations of key fatty acids in plasma and in red blood cells.[13] Preterm infants deprived of EFAs during late pregnancy are likely to have failures of normal development, especially the visual system, unless ω-3 fatty acids are supplemented.[14]

Heart Disease

We are now seeing the emergence of adverse effects from the decades-long encouragement of intake of hydrogenated oils in the form of margarines and many other foods with lower, but hydrogenated fat content. By the late 1960s, processed vegetable fats had displaced animal fats in the diets of most people in industrialized countries due to lower costs and purported health benefits. Increased tissue levels of the trans fatty acids from hydrogenated

oils is clearly a factor in the etiology of heart disease.[15,16] Higher palmitic and lower ω-3 fatty acids in serum are correlated with higher incidence of coronary heart disease in middle-aged men at high risk for cardiovascular disease.[17] Improvements in plasma fatty acids and vitamins E and C were the only factors found to be related to improvements in life expectancy and a 70% lowering of heart disease in a study population.[18]

Cancer

Because of the pivotal role in tumorigenesis of cell–cell recognition factors and the membrane-associated functions controlling that process, changes in the fatty acid composition of cell membranes signal tumor activity. Tumor tissue and virus-transformed cells have a higher content of UFAs, especially oleic acid, which increases relative to the amount of stearic acid. Such shifts increase the metabolic rates of many lipid-dependent enzymes and are associated with a higher capacity for cell division.[19] Changes in dietary fatty acid intake cause alterations in immune response, including antitumor activity.[20]

Neurologic Disorders

Adrenal leukodystrophy and related conditions are associated with the accumulation in nerve sheath membranes of fatty acids more than 20 carbons long.[21] This situation may be made worse by the lack of sufficient long-chain (C16-C20) PUFAs. The indicator for this situation is the sum of the 22-26 carbon length even-numbered fatty acids in erythrocytes or plasma.

The brain has a high content of lipid, and the fatty acid composition is unique in the high content of very-long-chain PUFAs, especially DHA. Strong evidence suggests a relationship between depleted DHA levels in postpartum depression and other forms of depression.[22] These results led to acceleration of studies of the proper clinical application of essential fatty acid therapies in depressed patients.[22-25]

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CHAPTER 91

Fish Oils (Omega-3 Fatty Acids, Docosahexaenoic Acid, Eicosapentaenoic Acid, Dietary Fish, and Fish Oils)

Joseph E. Pizzorno, ND, Cristiana Paul, MS Nutritian, and Alexander G. Schauss, PhD, FACN

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INTRODUCTION

Literally thousands of epidemiologic, observational, experimental, and randomized controlled studies have been published on the effects of the ω-3 fatty acids in fish and fish oil on human health. The benefit of these fatty acids extends to an extraordinary number of chronic diseases and to many physiologic systems and health outcomes, likely because of the cellular and physiologic mechanisms of action. Fish oil is well-established as an antiinflammatory, perhaps one of the most critical, because it supplies the building blocks for the natural resolution phase of inflammation, it favorably affects the genetic expression of nuclear receptors and nuclear transcription factors related to inflammation, and it shifts the production of prostaglandin and leukotrienes to less inflammatory mediators. Fish oil also modulates cellular membrane structures, including their fluidity, which affects protein function, ion permeability, the activity of membrane-associated proteins, and signaling pathways with other cells and intracellular organelles. Rather than treating one specific target, fish oil modulates a variety of cellular pathways to improve function and reduce inflammation, giving it broad-based multisystem benefit. Recent research helped to clarify which individuals are more likely to benefit from fish oil, as well as more optimal dosing.

Initial scientific evidence of fish oil's benefits first appeared in the late 1970s, when it was claimed that fish oil consumption among Greenland Eskimos and other fish-eating populations might convey a lifetime protective effect against coronary heart disease (CHD).[1-3] A large study in the United States, the Diet and Reinfarction Trial (DART),[4,5] and two studies in Europe, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)-Prevenzione Trial and the Lyon Diet Heart Study,[6-8] supported the observational evidence from these indigenous populations, and demonstrated that by increasing dietary ω-3 fatty acid intake, a significant decrease in ischemic heart disease occurred. More recently, the Japan Eicosapentaenoic Acid (EPA) Lipid Intervention Study (JELIS) trial randomized nearly 20,000 individuals to either a statin or a statin plus EPA, and found a 19% reduction in major coronary events in patients using supplemental EPA, as well as a significant reduction in stroke.[9,10] In 2010, the Heart and Soul study documented a significantly lower risk of overall mortality in individuals with higher blood levels of EPA and docosahexaenoic acid (DHA).[11] This latter study is particularly important, because it suggested that we have a biomarker for risk assessment, one that may avoid some of the biases inherent in food frequency questionnaires, variability in fish oil products, etc.

These studies and many others have had a profound effect on public health policymakers' perceptions of the importance of fish and fish oil to human health. For example, on February 8, 2002, the U.S. Food and Drug Administration (FDA) announced that it would permit the claim "consumption of omega-3 fatty acids may reduce the risk of CHD," to appear on labels of ω-3 fatty acid supplements containing a dose level of DHA and EPA of up to 2000 mg/day. The FDA's decision to permit such a claim is significant and timely, in that by 2000, one million Americans were reported to have heart attacks annually. On the basis of these and several other studies, it is now estimated that this one change in diet could save at least 150,000 people annually from fatal heart attacks.[12-17] Of course, increased daily intake of 5 to 7 servings of fruits, vegetables, and nuts rich in antioxidants will also reduce the incidence of heart attacks.

In 2002, the American Heart Association (AHA) released a position paper advocating the consumption of oily fish twice per week among those without heart

TABLE 91-1 **Relative Concentration of Fatty Acids in Fish Oils and Mercury (Hg) in the Respective Fish**

OIL	CHOLESTEROL (MG/100 G)	Unsaturated		n-3 PUFAs			HG (MCG/G)
		MONO- (%)	POLY- (%)	18:3 (%)	20:5 (%)	22:6 (%)	
Cod liver	570	18	51	0.7	9	9.5	0.111
Herring	760	19	60	0.6	7.1	4.3	0.04
Menhaden	600	34	32	1	12.7	8	—
Salmon	485	24	40	1	8	11	0.015
Pilchard	—	25	29	Trace	17	9	—
Mackerel, King	—	21	43	Trace	11	11	0.73
Anchovy	—	28	29	Trace	17	9	0.017
Sardine	—	24	34	Trace	15	10	0.013

Data from Kinsella JE, Lokesh B, Stone RA. Dietary n-3 polyunsaturated fatty acids and amelioration of cardiovascular disease: possible mechanisms. Am J Clin Nutr. 1990 Jul;52(1):1-28. Food Standards Agency. Oily fish advice: your questions answered. www.food.gov.uk/news/newsarchive/2004/jun/oilyfishfaq. Accessed 7/7/2005.
Mercury from FDA. http://www.fda.gov/food/foodsafety/product-specificinformation/seafood/foodbornepathogenscontaminants/methylmercury/ucm115644.htm. Accessed 8/30/11.
PUFAs, Polyunsaturated fatty acids; –, not measured.

disease, and at least 1 g/day of EPA/DHA among those with established coronary artery disease (CAD).[18] This marks the first time the AHA recommended a nutritional supplement for CAD prevention.

Although most clearly established for the prevention and treatment of cardiovascular disease, the benefit of dietary fish oil and fish oil supplements extends much more broadly to other conditions, including autoimmune, inflammatory, neurologic, gastrointestinal, and respiratory conditions. For example, the EPA and DHA found in fish oil were shown in various studies to reduce the pain of rheumatoid arthritis (RA), menstrual cramps by decreasing inflammation, the risk of premature delivery in pregnancy, and low birth weights. Beneficial effects were also reported in the treatment or management of bipolar (manic-depressive) disorder, mild to moderate depression, Raynaud's disease, systemic lupus erythematosus (SLE), immunoglobulin-A (IgA) nephropathy, chronic fatigue syndrome, irritable bowel disease, kidney stones, cystic fibrosis, psoriasis, and cancer. Additionally, DHA was shown to be important for neurogenesis of neuronal synapses and healthy eye development of fetuses and infants. Perhaps most importantly, fish oil has the potential to improve overall physiologic function and well-being, not because it targets one specific abnormality, but because it reduces systemic inflammation and supports optimal cellular function.

DESCRIPTION

Marine life is generally rich in two ω-3 fatty acids (also referred to as n-3 fatty acids), EPA and DHA, which enter the food chain through phytoplankton. These long-chained and highly polyunsaturated fatty acids (PUFAs) contain, respectively, 20 and 22 carbons and 5 and 6 double bonds, also referred to as 20:5n-3 PUFA and 22:6n-3 PUFA. The 20:5n-3 PUFAs and 22:6n-3 PUFAs are abundant in shellfish, sea mammals, and fish, hence, the reason Greenland Eskimos' diet is rich in EPA and DHA. By comparison, EPA and DHA levels are low or absent in domesticated land animals, in part because mammals lack the enzymes needed to insert a double bond in the n-6 or n-3 position. Thus, linoleic acid and α-linolenic acid (ALA), rich in a number of plant oils, are essential fatty acids, and, slowly with significant genetic variation, enzymatically converted to EPA and DHA. Fish oil from herring, cod liver, wild salmon, mackerel, and sardines is particularly rich in ω-3 fatty acids containing EPA and DHA. Table 91-1[19] lists the relative concentration of fatty acids in various common fish species.

The habitat in which fish grow has a major impact on their fatty acid composition.[20] In the wild, fish consume food sources that contain high levels of ALA (18:3n-3). Fish raised in "fish farms" deserve mention. It has been reported that salmon raised in fish farms receive a steady diet of synthetic pigment to give them a rich pink hue; otherwise, they would be unappetizing given their rather morbid, pale gray appearance. In the natural ocean environment, phytoplankton, which is rich in EPA and DHA, form the basis of the food chain for salmon and contribute to its pink color. Commercial fish foods contain less DHA and EPA, and therefore, lower concentrations of ω-3 fatty acids. Studies showed that wild fish have higher concentrations of ω-3 fatty acids than pond-reared and/or cultured fish grown in fish farms and fed commercial feedstuffs that are devoid of EPA and DHA.[21] Additionally, although wild fish are also increasingly contaminated, farmed fish often contain higher levels of toxins, such as organochlorines, brominated flame retardants, and methylmercury, particularly when they are also given fish meal as a food source.[22,23]

For individuals who do not or cannot consume seafood, foods such as tofu, canola oil, black currant oil, flaxseed oil (the best non-fish source), nuts, and soybeans are important sources of ALA (18:3n-3). However, soy-derived oils and foods and most nuts contain large amounts of ω-6 fatty acids that can reduce some of the therapeutic benefits of the ω-3 fatty acids, so finding a prudent balance between ω-3 and ω-6 fatty acids is suggested. Additionally, one analysis indicated that a dramatic 1000-fold increase in the consumption of soybean oil over the last century increased ALA intake, but it was offset by the increase in lineoleic acid, and therefore likely to depress tissue levels of EPA and DHA.[24] A recent review found that the fatty acids found in fish oil, particularly DHA, are substantially lower in tissues of vegetarians and vegans, including plasma levels, breast milk, and blood cells.[25] Fortunately, organically derived supplemental DHA and EPA from algae is now available for those wishing to avoid fish consumption.[26]

Dietary Requirement

The first suspected case of ω-3 fatty acid deficiency in humans was not reported until 1988, and the optimal intake of ω-3 fatty acids, both plant and marine-based, is still not well-established.[27] No

Adequate Intakes (AIs) or Dietary Reference Intakes (DRIs) have been set so far by the Institute of Medicine for EPA and DHA or the long-chain ω-6 arachidonic acid (AA), although it has established AIs for the short-chain ω-3 (ALA of 1.1 g for women and 1.6 g for men). There are several factors that complicate the establishment of clear dietary requirements, and several lines of evidence that offer some guidance. Evolutionary intakes of ω-3 fatty acids ALA and EPA+DHA estimated by Kuipers et al[27a] suggest a probable value of 9g/day (range 8.7 to 9.3g) of ALA and 3.9g/day (range 0.8 to 9.7g) of EPA+DHA per 2000 Kcal/day.

One of the factors involved is the proportional intake of ω-6 fatty acids to ω-3 fatty acids. It appears that the ratio of these two types of fatty acids, as well as their total intake, is important in determining health outcomes, and a change in both variables has occurred in Western diets over the last 150 years. Currently, the ratio of n-6:n-3 fatty acids in a typical Western diet is 15 to 20:1, whereas in wild animals, as well as humans throughout most of evolutionary history, it has been approximately 1:1.[28] This dramatically shifted ratio has skewed the metabolic products (prostaglandins, thromboxanes, leukotrienes, hydroxy fatty acids, and lipoxins) derived from AA (vs n-3 acids) to favor a more inflammatory, prothrombotic, proaggregratory, provasoconstrictive, and proproliferative physiologic state. The n-6:n-3 ratio was found to be important not only to the pathogenesis of cardiovascular diseases, but also in cancer, inflammatory, and autoimmune diseases, as well as in brain function.[29]

One example that highlights the importance of the ratio between oils was demonstrated in a study of over 400 healthy men and 450 healthy women. Researchers found that only at high n-6 intakes were DHA and EPA intakes inversely associated with some markers of inflammation, and a combination of both was associated with the lowest inflammation.[30] Similarly, the intake of n-3 fatty acids in women with a high intake of n-6 fatty acids has an inverse relationship with the risk for breast cancer.[31] This was confirmed in a very large prospective cohort study of Chinese women (Shanghai Women's Health Study), in which the relative intake was more important to the risk of breast cancer than total intake.[32] In other words, the consequence of low n-3 intake is particularly important given a background of high n-6 intake.

Another contributing factor may be variations in the activity of enzymes involved in eicosanoid synthesis. For example, there is some conversion from ALA to EPA and DHA, but this conversion is fairly limited, and has significant interindividual variation.[33] This conversion from ALA is estimated to be approximately 5% for EPA and less than 0.5% for DHA, although the desaturase enzymes involved are influenced by smoking, gender, age, trans fat, and n-6 fatty acid intake. For example, a recent study found that despite large differences in intake of n-3 fatty acids between fish eaters and non-fish eaters, the plasma levels were much closer than expected, likely due to increased conversion.[34] Also of importance is the individual variability of the activity of enzymes involved in mediating the physiologic effects of fish oil. For example, variants in the 5-lipoxygenase (ALOX5) gene appear to modify the effects of fish oil on cardiovascular risk, as do polymorphisms in peroxisome proliferator activated receptor-α (PPAR-α).[35-37]

Despite these limitations, most recommendations suggest a desired DHA and EPA total intake of approximately 0.5 to 1 g/day as preventative therapy, with higher doses indicated for treating specific conditions. A ratio of 2:1 to 1:2 EPA/DHA is often advocated, depending on therapeutic goals. For example, the Technical Committee on Dietary Lipids of the International Life Sciences Institute (North America) suggests an intake between 250 and 500 mg DHA+EPA per day for CAD prevention. Currently, even a 500 mg target would require at least a tripling of current intake in most Western countries.[38]

Because the concentration of EPA and DHA in fish can vary depending on its growth environment, fish oil supplements can offer a viable and reliable source of ω-3 fatty acids standardized around the content of EPA and DHA (see Table 91-1). Most fish oil capsules contain between 300 and 500 mg EPA+DHA fatty acids per gram, while some are concentrated to contain as much as 700 mg EPA+DHA per gram. Patients using fish oil at the therapeutic levels discussed herein may require between 15 and 30 capsules daily to derive the described benefits, depending on their DHA+EPA content. At 9 calories/g of oil, this can represent a significant increase in caloric intake and may necessitate an increase in energy expenditure to avoid weight gain. We recommend using fish oil supplements which are highly concentrated to decrease unnecessary calorie intake.

EPA- and DHA-rich fish oil should be kept in capsules (such as soft gelatin with minimal plasticizer content[39]; see later discussion on "Oxidation") capable of providing an oxygen barrier. Otherwise, toxic lipid peroxides (e.g., malondialdehyde) and anisidine isomers may form. Encapsulated liquid sources generally do not have this protection unless they contain antioxidants. Encapsulated products typically contain fish oil, not fish liver oil. This distinction is important because fish liver oil contains the fat-soluble vitamins which, if taken in excessive amounts, can cause vitamin A toxicity, although some brands are reducing the vitamin A content during processing.

Explaining Inconsistent Results of Fish Oil Supplementation Trials

A number of articles in the fish oil literature have reported equivocal or contradictory results. Many of these differences in outcomes can be explained by the use of olive oil as a placebo or the lack of control for saturated or ω-6 fatty acid intake, as well as an insufficient dose of n-3 fatty acids. For example, in the recent Alpha Omega trial, nearly 5000 patients with a previous myocardial infarction were only given 400 mg DHA/EPA, a dose less than one half used in previous trials.[40] Not surprisingly, this low dose did not improve the rate of major cardiovascular events. It also raised plasma levels to a much lower degree than in previous trials that used a higher dosage.

Olive oil cannot be considered an inert placebo in trials that investigate effects on platelet function or CHD risk. Several studies showed that olive oil supplementation has similar inhibitory effects on various aspects of platelet function, including decreased platelet aggregation and thromboxane A_2 (TXA_2) release, increased platelet membrane oleic acid content, and decreased platelet membrane AA content.[41,42] Further, an excess of oleic acid impairs incorporation of AA into platelet phospholipids.

An additional consideration that is often ignored is the background intake of the enrolled study population. For example, an increase in n-3 intake in Western populations showed a reduction in the risk of sudden death, a benefit not consistently shown in Japanese populations, where the background intake is much higher.[43]

The lack of a relevant biomarker, such as the ω-3 index (discussed in the following section), as well as the lack of consideration of an individual's genetic response, are also variables that certainly contribute to the appearance of ineffectiveness. For example, studies that use food frequency questionnaires often do not accurately gauge n-3 intake. Additionally, they do not take into account differences in fatty acid metabolism that are vital to determining more functional measures. For example, a recent analysis of over 700 individuals found that supplements and the

intake of EPA/DHA rich food explained less than one half of the variability in red blood cell content, which may be due to the individual intake of linoleic and/or arachidonic acid, since they all compete for incorporation in the cell membranes.[44]

Another possible complicating factor is the squalene found in olive oil and some deepwater fishes, but not in other vegetable oils.[45] Other problems include the differing ratios of fatty acids, the position of the fatty acids on the glycerol backbone, and the susceptibility to peroxidation of the various fish oil preparations.[46]

Also, overprocessing of fish oil supplements can result in a loss of its active constituents and, hence, an attendant decrease in its efficacy. This was demonstrated in at least two studies that looked at such variables as how processing affects levels of triglycerides, cholesterol, lipoprotein(a), atherogenic index, and fibrinogen after fish oil supplementation.[47,48]

PHARMACOLOGY

The effects of supplemental and dietary unsaturated fatty acids appear to be mediated through changes in serum lipids, altered ratios of prostaglandins, decreased platelet aggregation, and modification of cell membrane activity.[46] Additionally, n-3 fatty acids have been shown to modify gene expression, and to directly reduce inflammation by binding to n-3 specific receptors. Omega-3 fatty acids (EPA, DHA and docosapentaenoic acid [DPA]) are also the metabolic precursors to the resolvins, lipoxins, and protectins now shown to be essential to the resolution of inflammation.

In 2010, researchers published a breakthrough study in the journal *Cell*, which for the first time identified a new g-protein coupled receptor, GPR120, which "functions as an n-3 FA receptor/sensor in proinflammatory macrophages and mature adipocytes."[49] Through this receptor, DHA and EPA mediated robust antiinflammatory signaling, inhibiting both the toll-like receptor and tumor necrosis factor-α (TNF-α) pathways. This finding was quite important, in part because insulin resistance is modified by these pathways, and also because these same researchers were able to document a direct insulin-sensitizing effect by EPA and DHA mediated via this receptor. This provides a direct and specific mechanism for improving insulin sensitivity.

In recent years, fish oils have also been shown to be the precursors for the modulators of the resolution phase of inflammation.[50] Resolvins, derived from EPA, and protectins, derived from DHA, have been shown to be crucial to both the resolution of inflammation as well as the initiation of tissue repair in multiple body systems. This modulation of inflammation by fish oil has also dramatically changed the way inflammation is viewed. It is now understood to be a carefully orchestrated active process, dependent upon adequate intake of eicosanoid precursors, rather than a passive process.

Fish oils also appear to reduce triglycerides and decrease the production of the prothrombotic substance TXA_2 by occupying TXA_2 receptors and enhancing the production of the platelet antiaggregatory substance prostacyclin. These actions play an important role in inflammation, atherogenesis, thrombosis, and CHD. Fish meals that provide an average of 3.6 g/day of ω-3 fatty acids reduce platelet aggregation and platelet TXB_2 responses.[51] Significant decreases in platelet sensitivity to collagen, serum TXB_2 levels, and urinary TXB_2 metabolites were observed after ω-3 fatty acid treatment.[52] EPA supplementation was shown to decrease synthesis of the ω-6 platelet agonist TXA_2 coincident with formation of the inactive ω-3 form, TXA_3.[53,54] A longitudinal study showed a pronounced action of dietary ω-3 fatty acids to diminish platelet formation and endothelial deposition, which could lead to thrombosis.[55]

Through the vasodilatory effects of prostaglandin I3 (PGI_3), fish oils may improve peripheral circulation, thereby assisting very low-density lipoprotein (VLDL) cholesterol removal. This may be accomplished by altering membrane fluidity in a specific manner, thus affecting the activity of membrane-bound enzymes and resulting in changes in receptor activity, specificity, and signal transduction. The incorporation of fish oil into membranes was shown to have direct clinical consequences. For example, in a case–control study of over 300 patients, a higher red blood cell membrane ω-3 fatty acid content was associated with a 70% risk reduction in cardiac arrest.[56] Evidence also suggested that fish oils decreased hepatic synthesis of fatty acids and triglycerides and reduced secretion of VLDL cholesterol while displacing AA from tissue phospholipids. This results in ω-3 fatty acid levels that inhibit thromboxane synthesis.

Researchers noted that fish oil effects are selective. EPA and DHA not only displace AA from phospholipid pools and inhibit cyclooxygenase, but EPA also becomes a preferred substrate for cyclooxygenase when peroxide tone is high. This results in decreased production of the vasoactive and aggregatory prostacyclin (PGI_2) and increased production of PGI_3, which has more potent antiaggregatory effects. According to some researchers, increased bleeding time is due to either less TXA_2 or higher prostacyclin I_3 levels,[53] although others contend that EPA conversion to PGI_3 is the primary cause.[57] Many researchers believe this change is one of the primary factors that decreases the risk of atherosclerosis and thrombosis.[58-64] These findings may explain some of the epidemiologic evidence of decreased CAD and prolonged bleeding time seen in some Eskimos and in those Japanese found eating a diet rich in fish.[65] Recent analyses also indicated that increases in bleeding time might have been exaggerated, with all current data pointing to minimal, if no affect.

Fish oils rich in EPA and DHA were also found to suppress production of inflammatory mediators found in patients with RA and psoriasis. The antiinflammatory effect of the ω-3 fatty acids is probably due to reduced production of leukotrienes, interleukin-2 (IL-2), and TNF-α, all principal mediators of inflammation. One study found that the ability of fish oil to decrease TNF-α production was influenced by an inherent TNF-α production and by polymorphisms in the TNF-α and lymphotoxin α genes (also known as TNF-β).[66]

In relation to CAD, ingestion of fish oil and its effect on platelets, erythrocytes, neutrophils, monocytes, and liver cells are considered to be important in explaining its benefits. The increased concentrations of EPA and DHA from the ingestion of fish oil were shown to do the following:

- Decrease production of prostaglandin E_2 (PGE_2) metabolites
- Decrease production of TXA_2 (an active vasoconstrictor and platelet aggregator)
- Increase prostacyclin PGI_3 (an active vasodilator and inhibitor of platelet aggregation)
- Increase production of leukotriene B_5 (a weak inducer of inflammation; weak chemotactic agent)
- Decrease production of leukotriene B_4 (a weak inducer of inflammation; inducer of leukocyte adherence and chemotaxis)

Fish oil, particularly DHA, was shown to modify mitochondrial membrane composition, improving mitochondrial function. DHA reduced the vulnerability to opening of the mitochondrial permeability transition pore, a pathologic feature of heart failure.[67,68]

CLINICAL APPLICATIONS

Cardiovascular Disease

No other clinical application for fish oil has been as well-studied as cardiovascular disease, including hyperlipidemia, atherosclerosis, stroke, myocardial infarction, and atrial fibrillation. Perhaps because n-3 fatty acids inhibit the development and progression of atherosclerosis and reduce the systemic inflammation that underlies so much of cardiovascular pathology, fish oil has demonstrated benefit for a wide range of applications.[69] What has emerged in recent years is the use of the ω-3 index, the sum of EPA and DHA expressed as a percentage of the total fatty acid content of red blood cell membranes, as a potential biomarker for heart disease. It was shown to be inversely associated with the risk for both fatal and nonfatal cardiac events, allowing clinicians to assess individual risk for their patients, and might serve as a tool for monitoring therapeutic efficacy.[70,71]

For instance, in a study of nearly 800 patients, the ω-3 index was associated with a 69% risk reduction in those with the highest compared with lowest levels for acute coronary syndrome, with an inverse linear relationship between risk and DHA/EPA levels. This amounts to a three-fold greater risk in those with a low ω-3 index than those with a high one. In this study, "low" levels were defined as less than 4%, whereas "high" levels were more than 8%, suggesting a possible therapeutic target.[72] In the Heart and Soul Study mentioned previously, those with an ω-3 index above median had a 27% decreased risk of death compared with those with a baseline ω-3 index below median, which was unaffected by adjustment for both traditional cardiovascular risk factors or inflammatory markers.[11] This was a prospective cohort study of nearly 1000 patients with stable CHD. Interestingly, in a study published in *Journal of the American Medical Association* in 2010, a subset of patients recruited from the Heart and Soul Study were found to have an inverse relationship between their ω-3 index and the rate of telomere shortening over a 5-year period.[73]

Certainly one population that warrants increased intake of DHA and EPA are those with an uncommon (6% of the population) genetic variant that predisposes them to rapid atherosclerotic progression. Individuals with two variants of the ALOX5 promoter have a greater risk for atherosclerosis, marked by an increase in carotid intima–media thickness. Increased consumption of n-6 fatty acids exacerbated this condition, whereas a higher intake of n-3 fatty acids blunted this atherogenic effect.[36]

Mechanisms of Cardiovascular Benefit

The EPA and DHA in fish oil inhibit the development of atherosclerosis, which can reduce the risk of multiple permutations of cardiovascular disease.[56] As discussed in the "Pharmacology" section, fish oil acts through diverse physiologic mechanisms, related to resolution and inhibition of inflammatory pathways, as well as modulation of cellular membrane fluidity. For example, EPA and DHA were shown to increase cell membrane fluidity, affecting intra- and intercellular signaling, and ultimately improving cell function.[74,75] EPA and DHA were also shown to stimulate endothelial production of nitric acid, decrease production of inflammatory cytokines and IL-1, and inhibit monocyte migration into atherosclerotic plaques. EPA and DHA also affect gene expression, at least partly via activation of PPARs. For example, in a randomized and double-blinded trial that enrolled over 100 participants, supplementation with 1800 mg/day of EPA/DHA was shown to change the expression of over 1040 genes in peripheral blood mononuclear cells, including genes involved in atherogenesis and inflammation, such as nuclear factor-κβ target genes, proinflammatory cytokines, nitric oxide synthase 3, and genes involved in eicosanoid synthesis.[76]

In recent years, a number of biologically active compounds derived from EPA/DHA have been elucidated through newly discovered pathways. These are potent mediators of cellular function, with antiinflammatory actions and actions that promote the resolution of inflammation, and are thus known as "resolution-phase interaction products" or resolvins, as well as maresins.[77,78] The antiinflammatory component of fish oil may at least partly explain its ability to slow the progression of atherosclerosis, as well as to stabilize atherosclerotic plaques against rupture.[79,80] For example, atherosclerotic plaques were shown to incorporate EPA, and a higher EPA content was associated with greater plaque stability, as well as a reduced number of foam and T cells.[81]

Fish oil also demonstrated lipid-lowering effects, likely mediated partly through the inhibition of VLDL and triglyceride synthesis without reducing production of high-density lipoprotein (HDL) cholesterol.[82,83] The triglyceride-lowering effect appears to be dose-dependent, with a greater effect on those with highly elevated triglycerides. This benefit is not seen with plant source oils containing land-based α-linolenic fatty acid–rich polyunsaturated fat sources (e.g., flaxseed oil) or via reduction of saturated animal fatty acids intake.[64] In a review of over 40 studies that examined the use of fish oils for either primary or secondary prevention, fish oils were found to reduce the rates of all-cause mortality, cardiac and sudden death, and perhaps stroke.[84]

As mentioned previously, the AHA for the first time endorsed a nutritional supplement for cardiovascular disease prevention in 2002, advocating consumption of oily fish twice per week among those without heart disease, and at least 1 g/day of EPA/DHA among those with established CAD, and 2 to 4 g EPA/DHA for individuals with hypertriglyceridemia.[18] However, there appears to be substantial variability between dietary intake and the ω-3 index (ω-3 blood levels), the latter of which was inversely associated with total mortality among individuals with CAD.[11] Optimal intake might be more appropriately determined using the ω-3 index as a benchmark, with current evidence suggesting a target of 8% or higher.[85]

Elevated Serum Lipids

The most consistent effect of fish oils on serum lipids is a reduction in total triglycerides and VLDL cholesterol, especially in patients with severe hypertriglyceridemia. In general, dietary fish oils appear to both reduce undesirable serum-circulating fats and decrease production of the prothrombotic thromboxanes. In most studies, fish oil supplementation causes a significant reduction of VLDL cholesterol, plasma triglycerides, plasma cholesterol, and LDL cholesterol. In hypertriglyceridemic patients, fish oil supplementation typically results in a significant decline in VLDL cholesterol levels, because large decreases in triglyceride levels lead to a decrease in VLDLs.[63,86-89]

Recent studies also showed fish oil induced favorable changes in LDL size. It is now well-established that plasma levels of small, dense LDL cholesterol are associated with plasma triglyceride concentrations, are more atherogenic, and are markers for cardiovascular disease risk.[90,91] Data from the Quantification of the Optimal n–6/n–3 ratio in the UK Diet (OPTILIP) study indicated that DHA and EPA reduced the proportion of the small, dense LDL cholesterol, even if no changes were seen in total LDL cholesterol levels.[92] Data from JELIS, a large-scale intervention trial, found that EPA (1800 mg/day) was particularly effective in

patients with the potent risk factor combination of low HDL cholesterol and elevated triglycerides, reducing the risk of CAD in this group by 53%.[93]

Some studies did not find decreases of total cholesterol or LDL cholesterol after fish oil supplementation.[94-97] However, these equivocal studies used olive oil as a placebo, which, as discussed earlier, is a confounder. Additionally, beneficial changes to subfractions and particle size with DHA supplementation (3 g/day) were cited in one randomized trial, despite no significant effect on total LDL cholesterol levels.[98] Furthermore, an inverse relationship was found between serum EPA levels and oxidized LDL. Oxidized LDL is emerging as an important biomarker of cardiovascular risk, and is a very early and critical step in the development of atherosclerosis.[99,100]

For patients with elevated serum cholesterol (>7.75 mmol/L=300mg/dL) or triglycerides (>5.64 mmol/L=500mg/dL), there is sufficient evidence to consider fish oil supplementation of 5 to 10 g/day if lower dosages (2 to 4 g/day) are not effective.[101] In one study of 365 patients, supplementation with 10 mL/day (9.2 g) of MaxEPA resulted in significant reductions in triglyceride levels, which were maintained over 4 years.[102] Continuing reductions were observed in persons remaining in the study more than 4 years. The authors concluded: "For triglycerides to remain depressed it seemed necessary to maintain a daily intake of 9.2 g MaxEPA (1 g MaxEPA contains 180 mg EPA + 180 mg DHA)."

Fish oil (4 g/day) was also shown to improve the non-HDL cholesterol lowering effect when combined with statin medications. Increases in HDL cholesterol as well as decreases in total cholesterol and triglyceride levels were seen when combined with atorvastatin versus atorvastatin alone.[103] Similar results were also documented when used with simvastatin.[104]

Hypertension

A meta-analysis of over 30 trials (22 double-blinded) investigating the effect of fish oils in reducing blood pressure found that higher doses (median dose 3.7 g/day) were associated with a reduction in systolic blood pressure of 2.1 mm Hg and diastolic blood pressure of 1.6 mm Hg, although lower doses (<0.5 g/day) might not have an effect. The blood pressure lowering effect of fish oil was found to be greater among those aged 45+, as well as among hypertensives versus normotensives.[105] A recent review cited a number of mechanisms for a hypotensive effect of fish oil, including changes in eicosanoids, in blood viscosity, in hormonal cellular response, in renin secretion, and decreased response to vasopressors,[106] although they also concluded the effect was likely to be small at a dose of 2 to 4 g fish oil per day.

Epidemiologic evidence indicates a hypotensive effect of dietary fish consumption. The largest study is probably the International Study of Macro- and Micro-nutrients and Blood Pressure (INTERMAP) trial, an international cross-sectional epidemiologic study of nearly 5000 men and women living in China, Japan, United Kingdom, and the United States. Researchers found an inverse relationship of total dietary n-3 fatty acids to systolic and diastolic blood pressure, in both hypertensives and normotensives, although the effect was considered small.[107]

Fish oil seems to have hypotensive effects, ranging from limited (dosages of 5 g/day or less) to substantially larger dosages,[51,64,108-115] although there is some conflicting evidence.[101] It has been proposed that fish oil depresses vascular response to the hormones involved in hypertension.[101] Another suggestion is that fish oil acts by increasing vasodilatory prostaglandins PGI_1 and PGI_3, and that this increase accounts for observed reductions in blood pressure.[101]

To test this hypothesis, one study examined the effect of fish oil on blood pressure in men with mild essential hypertension.[116] One group received 10 mL of fish oil (3 g of ω-3 fatty acids), a second group received 50 mL (9 g of EPA and 6 g of DHA), a third group received 50 mL of safflower oil (39 g of ω-6 fatty acids), and a fourth group received 50 mL of a mixture of coconut, olive, and safflower oils. The latter group represented the approximate amount and ratio of fatty acids consumed in the average American diet (39% saturated fat, 46% monounsaturated fat, and 15% polyunsaturated fat). The group receiving the highest dose of fish oil (50 mL) had an average reduction of 6.5 mm Hg in systolic pressure and 4.4 mm Hg in diastolic pressure. None of the other groups, including the low fish oil-supplemented group, demonstrated blood pressure reductions in the aggregate. The study did not find the expected association between increased production of PGI_1 and PGI_3 and sustained reduction in blood pressure. This suggests that vasodilatory prostaglandins are probably not the primary mediators of blood pressure reduction by fish oil consumption, although they may play a role.

Another proposed mechanism is that fish oils may facilitate excretion of sodium and fluid by the kidneys. This was supported by a reported but unpublished double-blind, crossover study in which researchers placed healthy, nonhypertensive men and women on a diet supplemented with approximately 1 g/day of PUFAs for 28 days.[117] Each participant received capsules with either fish oil or safflower oil. The fish oil dose was similar to the amount consumed in a single daily serving of tuna, lake trout, or salmon. After 2 weeks, the subjects crossed over to the other supplement. The study found an average 2 to 3 mm Hg drop in both diastolic and systolic blood pressure in those who received fish oil supplements. The researchers also found that fish oil increased urine output by approximately 10%, performing much like a low-sodium diet. This resulted in a reduction in fluid volume. Unlike diuretics, the fish oil supplementation did not increase potassium excretion.

Stroke

In the Health Professional Follow-up Study, a prospective cohort with over 12 years of follow-up, a significantly lower multivariate relative risk (RR=0.57) of ischemic stroke was documented for men who ate fish one to three times a month compared with men who consumed fish less than once a month. Interestingly, higher levels of consumption did not further reduce the risk, and no effect was seen on hemorrhagic stroke.[118] A reduction in the risk of ischemic stroke by 30% was also shown in the Cardiovascular Health Study. This trial had nearly 5000 adults aged 65+ years and found a 30% lower risk of ischemic stroke with a fish intake of five or more times a week, and 27% lower risk with a fish intake of one to four times a week, both compared with an intake of less than once a month. In this study, the benefit was limited to tuna or other broiled/baked fish. Consumption of fried fish or fish sandwiches was associated with an increased risk for total and ischemic stroke.[119]

A very recent study with over 30,000 participants in the United States examined the risk of stroke as it relates to fish consumption. This study examined possible explanations for the increased stroke risk in the "Stroke Belt and Buckle" in the southeastern United States, a region known for having at least a 50% higher incidence of stroke. The authors of this study concluded that regional and racial differences in fish consumption might help to explain this anomaly, i.e., those living in the Stroke Belt are less likely to have two or more servings of fish per week.[120]

An earlier published in 1995 found that men who ate fish five or more times a week had a 40% lower risk of experiencing a stroke than men who ate fish less than once a week. A similar study in women by researchers at Harvard Medical School found even more impressive results for women.[121] In this study, 79,839 female nurses between the ages of 34 and 59 years were followed for 14 years, by which time 574 had experienced a stroke; 303 of the strokes were caused by blood clots, whereas another 181 were caused by a ruptured artery, and the remaining 90 were of undetermined origin. It was determined that women who ate fish once a week lowered their risk of a stroke of any kind by 22%. However, women who consumed fish five or more times per week reduced their risk by 52%. The investigators concluded that women whose intake of fish oils was 0.5 g/day or more had a 30% lower risk of a stroke than women whose intake was less than 0.1 g/day. Of particular interest was the finding that in those women who had a high fish or fish oil consumption, there was no evidence of an increased risk of hemorrhagic stroke. The researchers concluded that the protective effect of fish oils was due to their ability to inhibit platelet aggregation, lower blood viscosity, suppress formation of leukotrienes, reduce fibrinogen levels, reduce blood pressure, and reduce insulin resistance. Curiously, the beneficial effects were substantially more likely in women who did not take aspirin on a regular basis, although subsequent studies have not shown a relationship with aspirin intake.

In a subanalysis of the JELIS trial, a 20% reduction in stroke risk was shown for individuals taking EPA and a statin compared with those only taking a statin, although these results were limited to participants who had already experienced a stroke (i.e., secondary vs primary prevention).[10] Currently, more direct intervention trials using fish oil for stroke reduction as the primary outcome are lacking.

Bypass Patients

Some studies demonstrated that fish oil supplementation might help prevent reclosing (restenosis) of the arteries after angioplasty. In one such study, bypass patients were supplemented with 4 g/day of fish oil.[122] One year later, those patients who consumed the fish oil supplements had an occlusion rate of 27%, whereas control patients had a 33% rate of occlusion, or a 23% relative improvement. On the basis of a postoperative evaluation 3 weeks after patients had cardiac transplantation, it was found that patients who consumed fish oil supplements had normal endothelium-dependent coronary vasodilation, which remained abnormal in patients who did not consume fish oil.

A much larger and well-conducted recent study published in the *Annals of Thoracic Surgery* documented a robust protective effect of fish oil after coronary artery bypass grafting (CABG). Of 2100 participants, 44% were given 850 to 882 mg of EPA and DHA as ethyl esters, in the average ratio of EPA/DHA of 1:2. In addition to a lower risk for late mortality (hazard ratio = 0.51 to 0.55), those consuming fish oil had roughly one-half the need for repeat revascularization. Furthermore, they had lower adjusted risk for the composite of death, Q-wave myocardial infarction, or cerebrovascular events. Those with poor left ventricular function had a quite large 64% reduction in mortality when taking fish oil.[123] The authors of this study supported the use of fish oil supplementation for all patients as part of standard medical therapy after CABG.

Atrial Fibrillation

A link has long been suspected between fish oil consumption and atrial fibrillation based upon epidemiologic and experimental evidence, although the benefit is not clearly established. In the prospective cohort study (described previously in the "Stroke" section) that found a reduction in the risk of stroke with broiled or baked fish, a roughly 30% lower risk of atrial fibrillation was also found for those consuming fish regularly, although not fried fish.[124] The association between fish oil intake and reduced fatal CHD and sudden cardiac death also lent strong support for its use in preventing ventricular arrhythmias.[125]

Additionally, fish oil targets several of the underlying abnormalities found in atrial fibrillation, including the

(1) modulation of electrophysiologic and metabolic heterogeneities secondary to atherosclerotic disease,
(2) modulation of cardiac myocyte metabolic activity and cardiovascular oxidant stress,
(3) direct modulation of ion channel and transporter activity,
(4) indirect modulation of ion channel and transporter activity, via modulation of autonomic nervous system activity, and
(5) modulation of inflammatory pathways that promote ectopic electric activity and abnormal conduction.[126]

Also, atrial fibrillation is known to occur more frequently in damaged hearts, which may contribute to mitochondrial pathology and insufficient adenosine triphosphate production, an effect possibly modulated by fish oil.[127]

However, not all epidemiologic studies found a protective effect, including the Rotterdam study, and the Danish Diet, Cancer, and Health Study, two very large prospective cohort studies.[128,129] Most recently, the Women's Health Initiative, a large cohort of healthy women, also reported no apparent benefit of increased fish consumption.[130]

A recent meta-analysis of randomized clinical trials published in the journal *Heart* also did not find benefit for the prevention of atrial fibrillation. However, this study had important limitations, including significant heterogeneity and methodologic flaws in the included trials, and fairly limited statistical power to detect a benefit. Its authors also acknowledged that most of the studies used a dose that might have been too low (3 to 4 g/day fish oil) to have a clinical benefit.[131] A randomized and placebo-controlled study published recently in *Journal of the American Medical Association* also found no benefit when giving 8 g of prescription ω-3 fatty acids (1 g prescription ω-3 fatty acids contains 375 mg of DHA and 465 mg of EPA), during the first 7 days and 4 g/day for 24 weeks.[132]

The optimal dosage as well as composition of fish oil for prevention of atrial fibrillation is not well established. One prospective study of over 2000 men found that blood levels of n-3 fatty acids appeared to be inversely associated with the risk of atrial fibrillation. However, they found that this protective effect was limited to DHA.

It is thus difficult to determine the role fish oil has on incidence as well as the recurrence of atrial fibrillation, given the conflicting evidence published so far. It may be that optimal administration, dosage, etc., play a role, but given the complexity underlying atrial fibrillation, it may also depend on the specific etiology and the timing. For example, some data suggested that fish oil was more likely to be of benefit if CAD was also present for ventricular arrhythmias, whereas those without heart disease were unlikely to benefit.[133]

Not all atrial fibrillations have the same pathology, with different pathophysiologic mechanisms characterizing distinct clinical presentations. Some authors suggested that n-3 fatty acids might be more likely to be of benefit for preventing the structural remodeling that leads to resistant and/or permanent atrial fibrillation, which is more likely with underlying heart conditions or after myocardial infarction.[134]

In summary, doses used clinically so far may not be sufficient for benefit, and not all presentations of atrial fibrillation may

respond to treatment. Earlier treatment with fish oil is more likely to have an effect, before significant structural remodeling has taken place. Furthermore, given the mechanisms involved with fish oil, a longer time until benefit is seen might be expected, an effect not considered in many trials. For example, in the randomized trial cited previously by Kowey et al[132] almost half of recurrences occurred within the first 2 weeks of follow-up (of 24 total), suggesting insufficient time for the build up of tissue levels.

Myocardial Infarction and Acute Coronary Syndrome

One of the largest trials to document a protective benefit for individuals following a myocardial infarction was the GISSI study.[135] In this large secondary prevention trial, 1 g of n-3 fatty acids (containing 850 to 882 mg EPA/DHA ethyl esters) greatly reduced sudden cardiac death within 4 months of starting therapy, as well as an all-cause and cardiovascular reduction in mortality. The reduction in the incidence of sudden cardiac death accounted for about 57% of the total improvement in mortality rates. At the end of the study, 2.7% of the placebo group participants died from sudden cardiac death compared with 2% in the fish oil group. Overall, cardiovascular death (including stroke) at the end of the study was 6.5% in the placebo group versus 5.5% in the fish oil group. There was no statistically significant difference in the incidence of nonfatal heart attacks between the fish oil and placebo groups. The researchers concluded that fish oils exerted their protective effect by preventing fatal ventricular arrhythmias rather than through an improvement in cholesterol profile. They did note a small drop in triglyceride levels of 4.6% in the fish oil group but found no significant differences in LDL and HDL cholesterol between the two groups. They also pointed out that the number of lives per 1000 patients that could be saved every year by giving heart attack survivors fish oil exceeded the number of lives per 1000 patients estimated to be saved by treating heart disease patients with high cholesterol levels with pravastatin. This puts fish oil supplements squarely in the category of a highly effective unpatentable heart drug, although now, Lovaza, a prescription-only form of fish oil is available.

Furthermore, a second trial with over 9000 participants from the GISSI study found that treatment significantly reduced sudden death, with greater benefit in those with left ventricular systolic dysfunction (four-fold greater risk reduction), which increases the risk for mortality.[136]

The JELIS trial, a prospective trial that combined 1800 mg EPA with a statin for hypercholesterolemic patients, found a 51% reduction in risk for myocardial infarction or cardiac death over 5 years. A reduced risk for myocardial infarction was found for those with and without a previous myocardial infarction, although the effect was greater in those with the former. This study was particularly important because they were able to examine adherence to therapy, and found a greater effect in those with complete adherence.[137,138]

These studies indicate that fish oil reduces the risk for myocardial infarction and cardiac death, and that some populations receive quite significant benefit.

However, more recent studies did not find benefit for survivors of myocardial infarction in terms of reducing the rate of major cardiovascular effects. For example, a double-blinded, randomized trial with nearly 5000 participants reported no benefit with 400 mg/day of EPA+DHA. Participants in this study were also treated aggressively with other antihypertensive, antithrombotic, and lipid-modifying therapies, which greatly reduced their risk for subsequent cardiovascular events, which might have reduced any potential benefit of fish oil therapy. Additionally, this study was criticized for using too low of a dose of fish oil for a clinically meaningful effect.[40] Similarly, the German OMEGA trial (a randomized, placebo-controlled trial to test the effect of highly purified ω-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction), which also used aggressive therapies and a fairly low dose of fish oil (460 mg EPA, 380 mg DHA) did not report a therapeutic effect.[139] The authors of this study reported limitations, including its low power to detect benefit, given the risk reduction associated with other therapies. Also, they reported that both groups (those receiving fish oil and those not) significantly increased their dietary fish consumption during the study period. Given the low dose used, it was not clear that those receiving supplements had a significantly higher intake of EPA/DHA than those who did not.

Considerable animal based and experimental evidence showed that dietary fats modulate the electrical stability of the myocardium, and that the appropriate fatty acids can reduce the vulnerability to arrhythmia during myocardial ischemia.[140-142] Raising the ω-3 fatty acids to higher levels in the myocardium may also prevent postinfarction ventricular fibrillation.[143-145] Recent data in humans with acute myocardial infarction found that 465 mg/day EPA and 375 mg/day DHA improved ultrasound indexes of endothelial function without affecting serum asymmetric dimethylarginine levels, suggesting preclinical benefit.[146]

One early study (DART) evaluated the effect of dietary intervention in 2033 men recovering from myocardial infarction.[4] Patients were randomly allocated to receive one of four types of dietary advice:

1. Lowered intake of dietary fat
2. Consumption of at least two portions of fatty fish (200 to 400 g) a day
3. Supplementation with three capsules (1.5 g) of MaxEPA (1 g Max EPA contains 180 mg EPA + 180 mg DHA) a day
4. Increased dietary fiber intake

At the end of 2 years, those in the group consuming fish were found to have increased their EPA intake to four times that of other subjects. This group also experienced significantly lower mortality. The fat and fiber advice groups showed no differences in mortality. Although the rate of recurrence of heart attack was similar in all groups, the fish and fish oil group had a 29% reduction in risk of death compared with the other groups. These findings are in direct conflict with an earlier study showing no such benefits.[147] However, it may be significant that the earlier study was conducted over a short period of 6 weeks.

Even in patients with no apparent clinical evidence of arterial disease, fish consumption was shown to improve arterial wall function. One study found that in both healthy and non–insulin-dependent diabetes mellitus patients, those who ate fish showed significantly better compliance of their left subclavian artery and femoral arteries.[148]

Fish and fish oil intake were also associated with the risk for angina and acute coronary syndrome. In one case–control study, individuals with acute coronary syndrome were found to have a 20% lower EPA/DHA content in their red blood cell membranes than controls. Those with the highest levels had a nearly 70% lower risk for acute coronary syndrome than those with the lowest levels.[72] Another recent epidemiologic study suggested that the benefit of dietary fish consumption might be limited to fatty fish (i.e., not lean fish), with a more apparent benefit in men.[149] Long-term fish consumption might be particularly protective, providing another rationale for fish oil use in those with increased cardiovascular risk.[150]

Interestingly, one study of men with acute coronary syndrome found that symptoms of depression increased as blood levels of EPA/DHA decreased, supporting a possible link between depression and cardiovascular outcomes.[151] Given the underlying pathophysiology, this seems quite plausible from a systems biology perspective.

A meta-analysis published in the *Annals of Medicine* in 2009 found an overall 29% and 23% reduction in risk for cardiac death and all-cause mortality, respectively, when using fish or fish oil. In patients with a previous myocardial infarction, the reduction in risk was even greater (57%). Surprisingly, they found an increased risk for sudden cardiac death in patients with angina with higher fish/fish oil intake.[152] This increased risk for participants with angina was unexpected, because previous studies showed that fish oil supplementation reduced the number of angina attacks and reduced mortality in men recovering from myocardial infarction.[4,153] Significant rheologic improvements in patients with stable angina pectoris might occur after daily fish oil supplementation with 2.8 g of EPA and 1.8 g of DHA.[154] In a double-blind, placebo-controlled study, fish oil supplementation resulted in increased red blood cell deformability, reduced whole blood viscosity, and prolonged bleeding time compared with olive oil supplementation. The frequency of angina attacks decreased in both groups. However, neither type of oil affected exercise capacity or hemodynamic response to exercise.

Finally, as mentioned previously, a comprehensive review of use of fish oils for either primary or secondary prevention concluded that they reduced the rates of all-cause mortality, cardiac and sudden death, and perhaps stroke.[84] Additionally, an analysis of over 15,000 patients from the JELIS trial published in 2011 in the *Journal of Atherosclerosis and Thrombosis* found a significant reduction in major coronary events, defined as sudden cardiac death, fatal or nonfatal myocardial infarction, unstable angina pectoris, and angioplasty/stenting or coronary artery bypass grafting. Those with higher plasma levels of EPA (participants were supplemented with EPA only, not DHA) had the greatest reduction in risk.[155]

Immune Function

Several of the mechanisms by which fish oil modulates immune function have now been clarified, although much remains to be determined, including optimal dosing and proportions of DHA/EPA necessary for a clinical effect. Additionally, how in vitro or ex vivo changes translate into clinical significance has not been well established. In healthy subjects, the effect of EPA and DHA on ex vivo lymphocyte proliferation was reported in at least 14 articles, at 27 different dose levels, ranging from 0.2 to 7 g EPA+DHA per day, whereas the influence on cytokine production by monocytes was evaluated in 24 studies in 46 treatment cohorts.[156] It was shown that increasing the EPA/DHA content of immune cells affected a number of immune functions, and that DHA and EPA had varying effects. For example, in one double-blinded study of healthy volunteers, a marker of T-lymphocyte activation was inhibited by approximately 5 g/day of DHA, whereas EPA and olive oil had no effect.[157] Most studies, however, did not show any effect on lymphocyte activation, although differences were cited between different age groups and genders. Similarly, although some reports suggested an inhibitory effect on natural killer cell function and/or modulation of cytokine production by lymphocytes, there was considerable inconsistency among the studies, and no clear relationship exists.[156]

Per an excellent review published in 2007, the greatest modulation of immune function by fish oil was mediated via alterations in inflammatory cytokine production by monocytes, including IL-1β, TNF-α, and IL-6.[156] This ties in with an increased awareness of the links between inflammatory and immune function. Even here, however, there are inconsistencies. Not all studies documented an inhibitory effect (although none showed an increase in inflammatory cytokine production), and the expected dose-dependent relationship was not always observed. One very plausible hypothesis for these inconsistencies is that highly relevant genetic polymorphisms are often not taken into account, such as those that affect TNF-α production.[158]

Decreased production of the proinflammatory mediator PGE_2, as well as the incorporation of EPA and DHA into human inflammatory cells does appear to follow a dose-dependent relationship, along with an inverse relationship between EPA and TNF-α and IL-1β in most studies. One study suggested that at supplementation levels of 1.65 g EPA+DHA per day, no effect was seen, and a threshold existed between 1.65 and 3.3 g EPA+DHA per day.[159] Data also suggested that older individuals, as well as those with specific inflammatory conditions, might experience a greater therapeutic effect of fish oil than young healthy individuals.

Some research also suggested that a higher n-6:n-3 ratio has an inhibitory effect on phagocytic function, suggesting higher intake of n-3 fatty acids might improve this activity.[160] This was confirmed in one trial of healthy volunteers given 3 g/day fish oil (26% EPA and 54% DHA), which found an increase in phagocytic activity of 62% and 145% in neutrophils and monocytes, respectively.[161] Very recent data described resolvin D1 (derived from DHA) recognition sites on phagocytes (G-protein coupled receptors), which mediate its actions, leading to enhanced phagocyte and clearance functions, as well as resolution of acute inflammation.[162] Research published in 2009 in *Nature* also pointed to critical immune roles for other resolvins related to microbial sepsis and immune vigilance.[163]

Autoimmune and Inflammatory Diseases

Fish oils may play a role in the treatment of autoimmune disease (e.g., SLE, dermatomyositis, autoimmune nephritis, multiple sclerosis, celiac disease)[164-167] and inflammatory disorders (e.g., RA,[168] psoriasis,[169] atopic dermatitis[1]). This may be in part due to the chronic inflammation that often plays a role in the development and perpetuation of these conditions. For example, DHA may directly inhibit the release of AA in intestinal epithelial cells when stimulated by gliadin.[170] Furthermore, fish oils may help to improve the comorbidities that often accompany autoimmune disease, such as the premature incidence and acceleration of atherosclerosis associated with SLE. Clinical trials in humans demonstrated a benefit not only for disease activity, but also for improving markers of cardiovascular function. In one trial, patients with SLE taking 3 g MaxEPA (1g Max EPA contains 180 mg EPA + 180 mg DHA) had a significant reduction in disease activity (measured by Systemic Lupus Activity Measure [SLAM-R][171]). In a second randomized and double-blinded, placebo-controlled trial, participants given Omacor (1.8 g EPA and 1.2 g DHA per day) showed significant improvement in two markers of disease activity (British Isles Lupus Assessment Group and SLAM-R). Additionally, markers of endothelial function and oxidative stress improved after therapy.[172] Importantly, this study used olive oil as a placebo, which also showed benefit for several cardiovascular risk factors, yet fish oil provided a statistically significant benefit in comparison.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is in many ways a representative chronic inflammatory autoimmune disorder, and may serve as a model for other conditions. The enzyme COX-2 is overexpressed

in the synovium of patients, as are products of the enzyme 5-LOX. Interestingly, a study from Spain found decreased levels of ω-3 fatty acids in the blood and synovial fluids of male and female RA patients compared with healthy controls.[173] Epidemiologic evidence suggested that RA might be linked to n-3 fatty acid intake. For example, it is rare among Eskimos, yet by comparison, 2% of the world's population is affected. Studies of the Japanese population confirmed an inverse relationship between high dietary fish consumption and a low incidence of RA.[174] Further support comes from a population-based, case–controlled study in women that found a decreased risk of RA in those who consumed the most fish.[168]

A number of reviews concluded that fish oil supplementation was associated with a number of benefits; it reduced pain, the number of tender joints, the duration of morning stiffness, as well as the use of non-steroidal antiinflammatory drugs (NSAIDs) in patients with RA, and was associated with improved physical performance.[175] A meta-analysis of 17 randomized controlled trials published in 2007 in the journal *Pain* supported these conclusions, although the authors concluded that it might take several months of therapy for an effect.[176] This slow building effect might also explain results of an earlier study that found the anti-inflammatory effect of the fish oils continued for up to 4 weeks after cessation of supplementation.

The reduction in the use of NSAIDs is no small benefit. Growing concern about the adverse effects and safety of long-term NSAID use makes any therapy that reduces their necessity quite attractive. For example, in an extremely large meta-analysis published in 2011, every single NSAID evaluated, including ibuprofen and celecoxib, was associated with an increased risk for cardiovascular death.[177] In one small but well-controlled study, cod liver oil was able to reduce NSAID use more than 30% in 39% of patients versus only 10% of controls.[178] Fish oil was also shown to enhance the COX inhibiting effect of other medications, specifically of paracetamol, offering additive clinical benefit.[179] Similar benefit for reducing disease activity was also cited for indomethacin.[180]

Interestingly, in a recent review of the efficacy of fish oil for RA, researchers looked at the combination of benefits, including a reduction in symptoms, decreased use of medications, and improvement in comorbidities, and concluded that an argument for the use of fish oil in RA is strong.[181] However, they also concluded that:

> *It is probable that the main barrier to clinician acceptance is the promotion of pharmaceutical use as the dominant treatment modality by the pharmaceutical industry sales force that attends to the "detailing" of doctors. In the absence of an equivalent marketing effort for fish oil, rheumatologists are not inclined to consider, or even be aware of fish oil as a potential component of routine therapy for RA patients, despite the efficacy for symptom relief, the NSAID sparing and the benefits for cardiovascular health, which is compromised in RA patients due to their disease.*

As discussed earlier, the intake of n-3 fatty acids should probably not be considered in isolation, as the ratio to n-6 fatty acid intake is quite significant. This is particularly true for RA. A low AA diet, often vegan and gluten-free, has been used with considerable success for individuals with RA, possibly by supplying reduced amounts of inflammatory precursors. The beneficial effect of fish oil appears to be amplified by a low AA diet.[182] The authors also cited a time-dependent effect (2 months before improvement), and the EPA/AA ratio as being decisive for clinical effectiveness.

Psoriasis

Despite its underlying inflammatory process, very little recent research has been conducted for the use of fish oil to benefit individuals with psoriasis. Psoriasis is accompanied by high concentrations of AA in the plaques and profound changes in the metabolism of eicosanoids, leading to an increase in proinflammatory agents. Fish oils presumably improve the condition by decreasing the levels of inflammatory leukotriene compounds, especially leukotriene B_4, a lipoxygenation product of AA. The EPA in fish oil replaces the AA in phospholipids, leading to the formation of leukotriene B_5 rather than B_4, resulting in a much weaker inflammatory response.[183] This effect was demonstrated in neutrophils isolated from the peripheral blood of patients given fish oil to treat their psoriasis.[184] Patients who showed evidence of clinical response to fish oil therapy for their psoriasis were shown to have higher levels of leukotriene B_5 than those failing to improve.

In a recent controlled observational study, participants were given 2 capsules of Oravex per day (280 mg of EPA, 40 mg of DHA, 50 mg of thyme extract, 50 mg of olive leaf extract, 20 mg of green tea extract, 7.5 mg of zinc, 27.5 mcg of selenium per capsule), for a total of 560 mg EPA and 80 mg DHA. Compared with those treated topically with tacalcitol, those given Oravex and tacalcitol had a significantly greater improvement in several markers of disease severity and quality of life.[185]

Patients with psoriasis (vulgaris) were successfully treated with a low-fat diet supplemented with fish oil.[184] An impressive 77% (23% were nonresponders) of the patients reported either excellent, moderate, or mild improvement. It was interesting to note that a number of patients did not show improvement until at least 4 months after initiation of supplementation. Again, this may indicate the importance of allowing adequate time for clinical improvement after initiating fish oil therapy.

Etretinate is a powerful drug used to treat skin disorders such as psoriasis. It can cause serious adverse effects, however, when used in the regularly prescribed dose of about 1 mg/kg per day. One study showed that a combination of EPA and etretinate at a lower dose (0.3 to 0.5 mg/kg per day) worked as well as the pure, high dose, and had significantly fewer side effects.[186] Forty-five percent of the patients in the combination group showed excellent improvement (more than 75%) compared with 15% in the pure etretinate group. The time to achieve a 50% improvement in symptoms was also considerably shorter in the combination group (5.1 weeks) than in the monotherapy group (7.6 weeks). Adverse reactions such as inflammation of the lips, dry mouth and eyes, and scaling were observed in both groups but were mild and tolerable. The researchers concluded that the combination regimen was effective in the treatment of psoriasis without marked adverse reactions.

Another study investigated whether topical application of fish oil to skin areas affected by psoriasis would alleviate symptoms. The clinical trial involved 25 patients with psoriasis who were randomly assigned to apply either fish oil or liquid paraffin to their psoriatic plaques and leave them covered for 6 hours overnight under an occlusive dressing.[187] The treatment was repeated daily for a 4-week period. Fish oil proved highly effective in reducing scaling (severity of scaling went from an average rating of 2.91 to 0.32 on a scale from 0 to 4), plaque thickness (from a rating of 2.21 to 0.52), and erythema (from a rating of 2.71 to 0.90). Itching was not relieved by the fish oil treatment. The 4-week liquid paraffin treatment was also effective in reducing erythema, but was significantly inferior to the fish oil treatment in reducing scaling and had no significant effect on itching or plaque thickness. Both

treatments were well accepted by the patients, and the researchers concluded that they were both clinically effective, with the fish oil treatment being superior to the paraffin treatment.

Asthma

Elevated intakes of n-6 fatty acids combined with low intakes of n-3 fatty acids may play a causative role in increasing asthma incidence. A recent review cited five epidemiologic studies that all found a protective effect of maternal n-3 fatty acid consumption for asthma and atopic diseases. Intake during infancy and childhood was not as consistently shown to be beneficial, but the majority found a protective benefit.[188] The authors suggested that early life programming might help regulate immune system function. For example, children of mothers receiving fish oil during pregnancy had a nearly 40% lower risk of asthma in the 16 years after their birth compared with mothers receiving olive oil.[189] However, a recent long-term study found that dietary fatty acid modification, as implemented in a study from birth to age 5 years, reduced the prevalence of asthma, atopy, or other atopic disorders at age 8 years. However, the dose used in this study contained less than 200 mg n-3 fatty acids, along with nearly identical amount of saturated fatty acids per capsule. Compliance was also poorly monitored.[190]

The effectiveness of fish oil for treating established asthma is controversial. In one recent study, a small number of participants with exercise-induced asthma were given 3.2 g EPA and 2.0 g DHA per day, and shown to have equal benefit when given the 5-LOX inhibitor, montelukast.[191] However, not all trials documented benefit, although parameters of some studies seem designed to better evaluate drug-type interventions than nutritional ones. For example, a recent controlled trial reported no benefit on lung function or asthma control comparing placebo with n-3 supplementation.[192] This study was only a 2-week study, however, considering that the delay before benefit in other inflammatory conditions, such as RA, may be 2 to 3 months, it is worth bearing in mind the slower onset of action expected of fish oil therapy. Many of the clinical trials that did not find benefit were less than 2 months' duration.[193]

Lastly, a recent study documented increased asthma severity with a polymorphism of the ALOX5 promoter. Given that individuals with genetic variants in this promoter have been found to have an increase in cardiovascular disease risk that is mitigated by a high n-3 diet, future studies seem warranted to assess potential benefit in asthmatic patients with or without this genetic predisposition.[194]

A note of caution: aspirin-intolerant asthmatics may have a worsening of symptoms, associated with the inhibition of COX by EPA.

Cancer

Fish and fish oil demonstrated multiple beneficial roles related to cancer, specifically both its prevention and as an adjunct to cancer treatment. They were associated with a reduced risk of several cancers, and both might improve the efficacy of other interventions, as well as reduce adverse effects associated with cancer therapy. In some studies, fish oil was also shown to increase survival times. Although specific mechanisms vary from various cancer sites, the ratio of n-6 to n-3 fatty acids might also be an important feature for cancer development. For example, AA was shown to be elevated in a variety of cancer cell types, whereas DHA and EPA were both depressed.[195-197] The role of resolvins and other eicosanoid mediators might play a role in regulating inflammatory precursors to some cancers, such as colorectal cancer.[198]

Prevention

Most epidemiologic studies showed some benefit of n-3 consumption on either cancer incidence or cancer-related mortality. A recent meta-analysis of fish consumption and prostate cancer risk found that although there was no association between risk of developing prostate cancer and fish consumption, there was a 63% reduction in prostate cancer specific mortality.[199,200] A very important case–control study of 466 men found that not only did those with the highest n-3 consumption have a 63% lower risk for aggressive prostate cancer compared with those with the lowest n-3 consumption, but a genetic polymorphism in the COX gene (SNP rs4648310) strongly modified this risk. Those with the polymorphism and a low n-3 intake had 5.5-fold increased risk for aggressive prostate cancer, a risk that was reversed with a high n-3 intake.[201]

A large epidemiologic study of 23 dietary factors in countries with high and low risks of cancer found a strong association between the percentage of calories from fat and the risk of breast cancer.[202] Fish consumption was found to have the next most significant association, a negative correlation. As mentioned previously, for breast cancer, the ratio of n-3:n-6 fatty acids might be particularly important, as demonstrated by two large trials, one of which enrolled over 70,000 women. This trial found that those with high intake of n-6 combined with a low intake of n-3 fatty acid had over two times the risk of developing breast cancer.[31,32]

A previous study of 4052 postmenopausal women found that not only was the type of dietary fat associated with breast cancer, but this risk might be modified by the activity of the enzyme δ-9-desaturase. These women were followed for an average of 5.5 years, and those with DHA concentrations in the highest tertile had less than half the risk of breast cancer than did women in the lowest tertile. PUFAs overall were also protective, with ω-3 acids being somewhat more protective than ω-6 acids. Saturated fatty acid concentrations were not significantly related to breast cancer risk. A higher concentration of monounsaturated fats, especially oleic acid, was associated with a significantly increased risk. The researchers pointed out that most oleic acid in mammalian tissue is derived from saturated stearic acid through a process involving the enzyme δ-9-desaturase. Saturated fatty acids, cholesterol, carbohydrates, insulin, testosterone, and estrogen all activate this enzyme, whereas dietary PUFAs and fasting deactivate it. The researchers concluded that the δ-9-desaturase enzyme might be an important link between breast cancer risk and dietary fat consumption.[203]

A recent meta-analysis that examined 19 prospective cohort studies found a 12% decrease in the relative risk of colorectal cancer comparing high fish consumption with low fish consumption.[204] The largest study (nearly 500,000 men and women) contributing to this meta-analysis was the European Prospective Investigation into Cancer (EPIC) study, which found a 31% lower risk of colorectal cancer comparing highest with lowest fish intake.[205] An intervention trial using 2 g/day of EPA compared with placebo was shown to reduce the number and size of polyps in familial adenomatous polyposis, further strengthening the evidence for its effectiveness.[206]

This also builds upon a previous study in which 34 men and 26 women who had just undergone surgery to remove benign polyps from their colon were followed.[207] Patients were divided into four groups. Group 1 was supplemented with 1.4 g/day of EPA and 1.1 g/day of DHA, group 2 with 2.7 g of EPA and 2.4 g of DHA, and group 3 with 4.1 g of EPA and 3.6 g of DHA. Group 4 received

placebo capsules containing olive oil. Biopsy samples from the lower part of the colon and blood samples were taken and analyzed at the start of the trial and at 30 days. Overall, patients in the fish oil groups experienced a significant decline in the number of abnormal cells in their colon lining compared with the placebo group. Further analysis showed that the reduction in the number of abnormal cells was limited to patients who had a large number of abnormal cells at the beginning of the trial. The researchers also noted a significant increase in EPA and DHA levels and a significant drop in AA levels in the biopsy samples from the fish oil–supplemented patients. A separate 6-month trial involving 15 patients taking 1.4 g/day of EPA and 1.1 g/day of DHA also showed a significant drop in the number of abnormal colon-lining cells. The researchers concluded that low-dose supplementation with fish oils inhibited the proliferation of those abnormal cells associated as precursors to polyps in patients at risk for colon cancer, and that this effect could be maintained with long-term treatment. Similar to several other studies concerned with oxidation of fish oil in vivo, the authors cautioned that it might be advisable to increase vitamin E intake during fish oil administration.

A British investigation of the association between a high dietary fat intake and the risk of developing breast and colon cancer revealed interesting findings concerning the incidence of cancer. The study compared cancer mortality rates in 24 European countries, Canada, and the United States with fish consumption and the intake of animal fats.[208] In countries where the animal fat intake was high, the researchers found a clear inverse correlation between the ratio of fish fat to animal fat and the risk of developing breast cancer in women and colon cancer in both men and women. A similar correlation was found between cancer risk and the ratio of fish fat to total fat intake. This led the investigators to conclude that fish and fish oils not only protect against colon cancer in men but also against colon and breast cancer in women. This protective effect, however, is only apparent in countries where the intake of animal fats is high. In other words, a high intake of fish or fish oils counteracts the detrimental effects of a high animal fat consumption. The researchers further concluded that a 15% decrease in animal fat intake combined with a three-fold increase in fish oil intake could possibly reduce male colon cancer risk by as much as 30% in countries with a high animal fat intake. A threefold increase in fish oil intake could be achieved by eating fish three times a week or by taking two standard fish oil daily supplements containing EPA and DHA.

A prospective cohort study published in *Journal of the American Medical Association* in 2006 also found a protective effect of fish consumption on renal cancer. For women consistently reporting high consumption of fatty fish (once per week or more), a risk reduction of as high as 74% was observed compared with women reporting no fish consumption. Lean fish consumption did not reduce the risk of over 60,000 women in this 15 year study.[209]

Cachexia and Treatment Efficacy

Some, but not all studies showed that fish oil supplementation, especially at higher doses, might help with weight stabilization in participants with cancer. For example, one early study found that supplementation with approximately 2.2 g of EPA and 1.4 g of DHA assisted stabilization of weight in patients with inoperable pancreatic cancer. Researchers documented not only a weight gain and improved appetite, but these patients also survived an average of 8 months, compared with the expected survival time of 4.1 months typically reported for patients given chemotherapy.[210] In another study, 18 patients with inoperable pancreatic cancer, including 9 patients with Stage 4 tumors, were started on a dose of 2 g of fish oils (containing 360 mg/day of EPA and 240 mg/day of DHA).[211] The dose was subsequently increased by 2 g/day every week until the patients' body tolerance was reached, with an average final intake of 12 g/day. Before entering the trial, the mean weight loss among the patients was 2.9 kilos per month. After 3 months of fish oil supplementation, an average weight gain of 0.3 kilos a month was observed. Overall, 11 patients (61%) gained weight, 3 became weight stable, and 4 continued to lose weight, but at a significantly reduced rate. The concentration of EPA in plasma phospholipids increased from 0% to 5.3% of total fatty acids after 1 month of supplementation, whereas the concentration of DHA increased to 6.6% from a base level of 3.5%. The researchers concluded that fish oil supplementation arrested weight loss in cancer patients with cachexia.

A more recent study published in the journal *Cancer* found a very significant benefit when supplementing patients with non-small cell lung cancer (NSCLC) at a dose of 2.2 g/day of EPA. These patients also received chemotherapy and were compared with a group receiving standard of care only (i.e., chemotherapy without fish oil). Despite having a mean weight loss of 6.3% over the previous 6 months before chemotherapy, patients receiving EPA maintained weight, muscle mass, and adipose tissue throughout approximately 10 weeks of chemotherapy. Those who received standard of care only lost on average 2.3 kg over the same period. This study also might have been the first to monitor not just body weight, but body composition directly, using computed tomographic imaging. They found that gains were made in muscle and adipose tissue, an important distinction from the accelerated weight gains sometimes observed in lean tissues (liver and spleen) in terminal stages. Additionally, those with the greatest increases in plasma levels of EPA had the greatest gains in muscle mass, suggesting again that a biomarker may be worth incorporating into fish oil therapy. Although this was a very small study, these gains were potentially quite significant, especially given the fairly low dose of fish oil used.[212]

These same researchers also published a trial that enrolled patients with advanced NSCLC, and although the study was also small, it suggested significant benefit of fish oil therapy. Patients received 2.2 g/day of EPA and 240 to 500 mg/day of DHA, along with standard of care chemotherapy, and were compared with those receiving chemotherapy alone. In this trial, fish oil supplementation appeared to increase the efficacy of chemotherapy, without increasing its toxicity. The authors reported an approximately two-fold increase in response rates and clinical benefit compared with standard of care alone. Additionally, a greater portion of patients who received fish oil were still alive at the time of reporting than the control group, suggesting a likely increase in survival.[213] Other studies also reported benefits for treating patients with NSCLC with fish oil.[214]

Similar improvements in survival time were also seen in earlier studies of patients with other end-stage cancers with generalized malignancies. In one study, 60 patients with generalized solid tumors were divided into two groups: one group received 18 g of fish oil containing 170 mg of EPA and 115 mg of DHA per capsule, whereas the other received a placebo.[215] The fish oil group also received 200 mg of vitamin E daily to reduce oxidation in vivo from the effect of so much fish oil. Each group included 15 well-nourished and 15 malnourished patients. None of the well-nourished patients had cancer cachexia (abnormally low weight and general weakness). The researchers measured the levels of T cells, natural killer cells, and the synthesis of IL-1, IL-6, and TNF before the start of the supplementation and on day 40 of the trial. The study followed all patients until they died. Malnourished

patients were found to have a considerably impaired immune function and a decreased production of TNF; both parameters were restored through fish oil supplementation. Malnourished patients overall had a much shorter survival time than well-nourished ones (mean of 213 vs 481 days). Both malnourished and well-nourished patients who received fish oil and vitamin E survived significantly longer than did patients on placebo. The researchers speculated that fish oils exerted their beneficial effect by decreasing the body's production of PGE_2, which is believed to play an important role in the initiation and progression of cancer. They concluded that supplementation with dietary ω-3 polyunsaturated fatty acids, specifically fish oils with an antioxidant such as vitamin E, might offer significant palliative support to cancer patients with end-stage metastatic disease.

Potential mechanisms for benefit were outlined in several recent reviews, including one published in the journal *Nutrition and Cancer* that called for major clinical trials to be conducted using fish oil as adjunctive therapy. The authors reviewed previous research, and concluded that long-chain PUFAs not only had cytotoxic anticancer effects by themselves, but they modulated the effectiveness of particular chemotherapeutic agents.[216] For example, DHA was shown in vitro to have synergistic toxicity with taxanes toward cancer cells, and downregulated Her-2/neu oncogene expression, an effect confirmed in a animal model of breast cancer.[217,218] Other mechanisms included modulation of eicosanoid production, modulation of gene expression and of transcription factor activity (e.g., nuclear factor-κB), and alteration of membrane-associated signal transduction, to name just a few.[219] Interestingly, one recent study even suggested that fish oil might offer benefit for both breast cancer as well as cardiac arrhythmias through a similar mechanism, the regulation of a sodium channel, NaV1.5, although this has certainly not been proven yet.[220] Lastly, one review cited both a cytotoxic effect of cancer cells and a protective effect toward healthy cells by the downstream products of DHA (protectins), allowing them to work "as both a sword and a shield."[221]

Despite considerable evidence for a beneficial effect of fish oil in the prevention and treatment of various cancers, not all research showed a positive effect. Although some studies might have been too short-term or used too low of a dose for a clinical effect,[222] others found benefit for only a subset of patients, even at higher doses.[223] Many older studies used fish oil with a very low concentration of DHA/EPA, requiring an intolerable amount of pills, a limitation recent advances in available products might remedy. Also, the use of biomarkers, such as the ω-3 index, as well as genetic polymorphisms might help identify those most likely to benefit, as well as those who need higher dose supplementation. For example, a Phase II trial of DHA (1.8 g/day) given to patients with metastatic breast cancer receiving chemotherapy found that those who incorporated it the most (into plasma and/or red blood cells) delayed time to tumor progression and had longer overall survival, compared with those who incorporated it the least.[224]

Migraine Headache

A role for inflammation in migraine was established for at least some migraineurs, yet surprisingly few studies have been conducted with fish oil for its prevention (benefit for an acute migraine seems unlikely). Two placebo-controlled studies were performed, both finding no benefit compared with placebo, yet methodologic flaws might be found in both. In both studies, olive oil was used as a placebo, and a high placebo effect was observed.[225,226] Well-designed clinical trials have not been conducted.

Anecdotal reports indicated that patients with migraine headaches who were given 1 g/day of MaxEPA (1 g MaxEPA contains 180 mg EPA + 180 mg DHA), particularly males, had significantly less frequent or less intense, or both, episodes. These results might be due to changes in prostaglandin synthesis or reduction, or both, in platelet serotonin release, with resultant reduction in cerebral vasospasm.

Diabetes

The relationship between fish consumption and diabetes incidence and treatment is not as simple as previously believed. As mentioned previously, a G-protein coupled receptor was identified that modulates many of the physiologic effects of DHA/EPA, including an increase in insulin sensitivity, and most epidemiologic evidence suggested either no effect or a reduced incidence of diabetes among populations with higher fish intake.[227] For example, the incidence of diabetes is low in Greenland Eskimos.[228]

However, recent studies suggested that greater intake of fish might pose a risk for diabetes. One of the largest was a prospective study of over 35,000 women (Women's Health Study), which found a fairly linear increase in risk for type 2 diabetes (T2D) with fish intake, and particularly high risk for those consuming the highest portions (two or more servings of fish per day). This increase in risk with increasing n-3 fatty acid intake from fish was not observed with n-3 fatty acids from plant sources, which provides ALA.[229] This increase in risk with fish intake was also observed in three other prospective cohorts of both men and women in the United States (152,700 women and 42,504 men), with a 22% increase in risk in those consuming fish more than five times per week compared with those consuming it less than once per month.[230] In a large prospective trial in China (the Singapore Chinese Health Study), no association between n-3 fatty acid intake from fish was seen, although ALA from plant sources reduced the risk of diabetes.[231]

One very recent study may shed some light on these disturbing findings. In this large prospective study of older adults, researchers measured the plasma phospholipid levels of EPA/DHA as well as ALA, and examined the risk for diabetes. They speculated that many of the previous trials that found an increased risk for diabetes were prone to error, such as the error associated with food frequency questionnaires. Using a more objective biomarker, they found that phospholipid levels of EPA+DHA along with ALA were not associated with an increased risk of diabetes, and instead, those individuals with the highest concentrations of EPA+DHA or ALA had a lower risk of diabetes.[232] Earlier studies that used biomarkers in younger populations also found no increase in risk.[233,234]

Although further studies may help to clarify the relationship, it is worth noting two additional points. One is that fish are becoming contaminated with compounds such as persistent organic pollutants (POPs), which have been associated with a surprisingly large increase in risk for diabetes. Some studies showed fish consumption to be an important predictor for POPs serum levels.[235-237]

The second consideration is the favorable effect of fish oil on cardiovascular parameters, an important cause of morbidity and mortality among diabetics. In individuals with T2D, fish oil ingestion was demonstrated to favorably alter arterial wall compliance without adversely affecting cholesterol levels, blood pressure, or fasting blood sugar levels, thereby contributing to a reduced risk of vascular complications seen in insulin-dependent diabetes mellitus and non–insulin-dependent diabetes mellitus patients.[238,239]

One study even showed a desirable significant decrease in VLDL triglyceride and cholesterol concentrations in T2D patients consuming three fish oil capsules a day containing 320 mg EPA and 530 mg DHA.[240] In one recent study, 2 g of fish oil per day given to the offspring of individuals with diabetes for 12 weeks was associated with reduced inflammation and markers of endothelial function. Thus, in those at an increased risk for diabetes, fish oil might have an important cardiovascular and metabolic benefit.[241] Interestingly, increased fish oil consumption might also reduce the risk of type 1 diabetes in those with an increased susceptibility.[242]

Although fish oil has not always been shown to improve markers of diabetes and glucose control among those with T2D, its cardiovascular benefit warrants consideration for use in all diabetic patients.[84,243]

Neurodegenerative Disease

Several lines of evidence point to a protective role for EPA and DHA for neurodegenerative diseases. DHA specifically is the predominant n-3 fatty acid in the brain, and appears to play a key role in structures involved in the formation of new memories. Additionally, DHA is the precursor for neuroprotectin 1, an important neuronal modulator of function, with anti-inflammatory as well as antiapoptic functions. N-3 fatty acids, particularly DHA and its downstream metabolites, have been shown to act via several pathways associated with neurologic function, including[244]:

- Facilitation of the interaction of α-secretase with amyloid precursor protein to produce nontoxic fragments and prevent the formation of Aβ
- Shield the essential recognition sequence and intramembrane cleavage site for γ-secretase
- Serve as a local sink for free radicals that reduce the enzymatic augmentation of γ-secretase activity, which can be induced by free radical damage to the protein complex, which is important for the regulation of normal γ-secretase function
- Directly inhibit fibrillation and formation of toxic oligomeric species of Aβ

Observational data also implied an important protective role of n-3 fatty acids. For example, participants in the Rancho Bernardo study had plasma levels of DHA, as well as dietary fish and dietary DHA levels evaluated. Each of these variables was associated with the subsequent risk for developing either dementia or Alzheimer's disease. Having the highest levels of plasma DHA reduced the odds of all-cause dementia by 65% and Alzheimer's disease by 60%. Dietary DHA had similar benefits, and although fish consumption followed this trend, it was not a statistically significant association.[245] A study published in 2007 that enrolled over 8000 participants found a quite important association. Overall, fruits and vegetables, as well as weekly consumption of fish, was associated with a reduced risk for dementia. However, although the protective effects of fruit and vegetable intake applied to all participants, fish consumption was only associated with those who did not carry the apolipoprotein-E ε-4 allele (*APOE*-ε4 allele). Similarly, excess n-6 consumption increased the risk for dementia over two-fold, but it was modified by two factors. It increased risk only if not compensated by high n-3 intake, and only among *APOE*-ε4 non-carriers. Thus, the relationship between n-3 consumption was not only modified by other dietary factors, such as n-6 consumption, but also by genetic variables.[246] A similar association was found in the Cardiovascular Health Cognition Study, which found that fatty fish, but not lean fish, was associated with reduced risk for dementia, but again, only in noncarriers of the *APOE*-ε4 allele.[247]

Regarding the treatment of neurodegenerative disease, efficacy also appears to be modulated by genetic predisposition. In an analysis of n-3 fatty acid erythrocyte membrane content and cognitive variation in a birth cohort study of cognitively normal volunteers, cognitive benefits were associated with higher erythrocyte n-3 content, but again, this was only significant in *ApoE*-ε4 non-carriers.[248]

Not all studies have shown benefit, perhaps because the optimal dose and composition have not yet been clearly established. For example, as evidenced in trials for major depression, although DHA is the predominant n-3 fatty acid in the brain, EPA appears to have greater clinical effect. Perhaps this is why a controlled trial published in *Journal of the American Medical Association* in 2010 that supplemented participants with 2 g/day of DHA (no EPA) did not find any evidence of benefit. This study also did not report *APOE* status.[249]

The first large-scale, well-designed trial was published in 2006, and used 1.7 g DHA and 0.6 g EPA per day or placebo among participants with mild to moderate Alzheimer's disease, all of whom were also taking a cholinesterase inhibitor. Although no difference in primary outcome was observed, a subgroup with mild disease demonstrated a significant reduction in decline compared with placebo. Although *APOE* status was reported, the treatment effects per *APOE* status were not. Importantly, only 31% of those in the treatment group were non–*APOE*-ε4 carriers. This study suggests those most likely to benefit are at earlier stages of disease.[250]

Overall, the bulk of the data suggested that those with earlier disease are more likely to benefit, but this benefit is mediated by *APOE* status (and perhaps other genetic polymorphisms), and perhaps by n-6 fatty acid intake. The optimal dosage and DHA/EPA composition is not known, but DHA by itself may not be effective. N-3 fatty acids from fish also appear to have a protective effect on other neurodegenerative diseases, including Parkinson's disease, likely through similar mechanisms.[251,252]

Depression

A number of epidemiologic studies showed a reduced risk for major depression, perinatal depression, and bipolar disorder with diets high in n-3 fatty acids.[253,254] Also, a recent meta-analysis of 14 trials found that lower levels of EPA, DHA, and total n-3 fatty acids levels in plasma and erythrocytes (data was combined) were associated with depression. When these studies restricted their analysis to studies that used *Diagnostic and Statistical Manual of Mental Disorders* criteria for major depressive disorder diagnosis, the magnitude of differences in EPA/DHA and total n-3 became larger.[255]

Regarding trials for the treatment of depression, results have been quite varied, often due to differences in methodology and the type and dose of fish oil used. However, most have shown a beneficial effect. A recent review of published randomized controlled trials indicated that studies that found positive effects generally included a high ratio of EPA to DHA, and 1 to 2 g/day might be necessary for effect, but higher levels were not associated with greater benefit.[256] Also, the earlier the supplementation of DHA/EPA began during pregnancy, the greater the chance for benefit.[257] Despite DHA being a much more prevalent structural component of phospholipids in neuronal cell membranes compared with EPA, it is EPA that has more apparent effectiveness in clinical trials.[258] A second meta-analysis of randomized trials over a 40-year period also found a positive effect of n-3 fatty acids on both major depression and bipolar disorder.[259]

A small but important study also compared a fairly low dose of EPA (1 g/day) to fluoxetine for major depression, and found that both were equally effective. Furthermore, when used together, they were more effective than either agent used alone. Given the likely differences in mechanisms of action, this is not surprising, and combination therapy should be considered in those not responding to monotherapy.[260]

A case–control study published in 2010 examined some of the links between cardiovascular disease and depression, which are known to have a high comorbidity rate. Among individuals with major depressive disorder, a number of cardiovascular risk factors indicated heightened risk, including a low ω-3 index.[261] This biomarker might provide a useful tool for determining efficacy of n-3 fatty acid therapy for depression as well as cardiovascular disease.

Lastly, little attempt has been made to examine the role of genetic polymorphisms in regard to the interaction between n-3 fatty acids and depression. However, this may be a promising area of investigation. A recently published study found that patients with chronic hepatitis C were more likely to experience depression when given interferon-α if they had polymorphisms in the COX-2 gene or the phospholipase-A2 gene. Both of these genes are involved in eicosanoid metabolism, and may modulate the influence of n-3 fatty acid therapy.[262]

Raynaud's Disease

Preliminary evidence indicated that symptoms of Raynaud's disease improved in primary but not secondary Raynaud phenomenon, on the basis of a double-blind, placebo-controlled clinical trial involving 32 patients.[263] Patients were given either twelve 1-g fish oil capsules daily for 12 weeks containing 4 g of EPA and 2.6 g of DHA, or a placebo. The group receiving the fish oil supplements reported significant alleviation of symptoms associated with Raynaud's disease at the end of the study, including 5 patients, who developed symptoms before the experiment began but could not induce symptoms at all after either 6 or 12 weeks of supplementation.

Surprisingly, a follow-up study has not been conducted, and in a review of complementary and alternative medicine treatments for Raynaud's disease, the authors did not include the previous study in their analysis because they reported that it did not specifically cite changes in the "frequency, severity, pain or duration of symptoms."[264] Thus, despite a promising initial trial, this therapy has largely been ignored.

Malaria

Malaria afflicts more than 500 million people worldwide, with about 5% of victims dying each year. Unpublished studies at the U.S. Department of Agricultural Research Service Center in Beltsville, Maryland, found evidence that the ω-3 fatty acids in fish oil may be beneficial in the treatment of malaria.[265] In their research, mice were fed dietary fish oils for 4 weeks and then inoculated with parasites, either *Plasmodium yoelii* or *P. berghei*. As the mice continued to eat the high fish oil diet, the parasites multiplied as usual. However, after 3 to 4 weeks, the mice were free of the parasites. The researchers suspected that the cause of the parasite's death was rupture of the parasites' cell membranes or red blood cell hosts. The researchers theorized that infected cells were more susceptible to rupture because the parasites fostered a number of destructive oxidative reactions to which a diet high in fish oils makes them more vulnerable. Subsequent studies are lacking, although one animal-based study found that fish oil without vitamin E may improve survival and reduce re-infection.[266] Human trials are lacking.

Renal Disease/Immunoglobulin-A Nephropathy

Fish oil supplementation was shown to be effective for several renal diseases, including IgA nephropathy, the nephrotic syndrome, and a deficit of n-3 fatty acids, which was demonstrated in several studies for those with end-stage renal disease. In a small study of continuous ambulatory peritoneal dialysis patients, a depletion of reduced n-3 fatty acids as well as a high ratio of n-6:n-3 fatty acids was observed.[267] Lower EPA and DHA in plasma/serum phospholipids of those with chronic kidney disease was also documented, and intravenous n-3 therapy was used to restore normal levels.[268,269]

Both hypertriglyceridemia and hypercholesterolemia are common in patients with nephrotic syndrome. This association results in an increased risk of cardiovascular disease. Fish oils were found to lower serum triglycerides in patients with nephrotic syndrome and might therefore be of clinical benefit.[270] Unfortunately, no recent trials have examined this benefit.

IgA nephropathy is a kidney disease that can follow a viral infection of the gastrointestinal or upper respiratory tract. About 20% to 40% of all IgA nephropathy patients develop renal failure 5 to 25 years after diagnosis. One study at the Mayo Clinic found that fish oil supplementation could be effective in slowing down the progression of the disease.[263] The progression of the disease was judged by regularly measuring the level of creatinine in blood serum during the 2 years of the trial. A clear difference was observed. The patients in the fish oil group who received 12 fish oil capsules a day, containing 1.9 g of EPA and 1.4 g of DHA, had an average median increase in serum creatinine of only 0.03 mg/dL, whereas the patients in the placebo group experienced an increase of 0.14 mg/dL annually, indicating that their disease was progressing significantly faster. After 4 years, 40% of the patients in the placebo group died or developed end-stage renal disease compared with only 10% in the fish oil group. No adverse effects of fish oil supplementation were observed. A recent re-analysis of this data did not find that body size was helpful in predicting optimal dosage.[271]

A more recent study using 1.8 g/day of EPA for 1 year found small but significant benefits, including an improvement in the estimated creatinine clearance.[272]

Muscle and Bone

In recent years, n-3 fatty acids have emerged as being of potential clinical importance for the health of both muscle and bone tissue. In a study of over 1500 men and women from the Rancho Bernardo Study, a cohort of community dwelling individuals, a higher n-6:n-3 fatty acid ratio (based on food frequency questionnaires) was associated with a lower bone mineral density of the hip in both men and women.[273] A second smaller study published in 2007 found that among young men (women were not studied) serum phospholipid levels of n-3 fatty acids, particularly DHA, were associated with peak bone mineral density in the total body and spine, and with bone accrual in the spine.[274]

Intervention data are still lacking, however. In one small trial that enrolled adults with depression, no change in C-terminal cross-linking telopeptide of type 1 collagen, a bone resorption marker, was seen following 1.45 g EPA/DHA for 12 weeks. However, not only could this study be criticized for using a low dose over a short period of time and evaluating only 1 marker of bone

resorption, more importantly, the patient population did not necessarily have increased bone resorption to begin with. This was a sample of patients of a wide range of ages with depression, not osteoporosis or other risk factors for bone loss. The authors' conclusion that n-3 supplementation might not be useful for preventing bone loss may only be appropriate to the population they studied, not more generally, and perhaps not using different doses or markers of bone health.[275] A study published in 2007 found just the opposite. Although researchers used plant-based n-3 fatty acids, which might not be equivalent to DHA/EPA, they did find that supplementation with ALA did have a protective effect, and inhibited bone resorption. This indicates that in principle, n-3 fatty acids play an important role.[276] The impact of fish oil supplementation as an intervention to prevent and/or treat osteoporosis awaits well-designed clinical trials.

In a study published in 2008, a retrospective analysis was done of a cohort of nearly 3000 men and women aged 59 to 73 years. When examining multiple dietary influences on grip strength, a potential marker for muscle strength and function, fatty fish consumption emerged as having the greatest effect.[277] Although very small, a second interventional study compared the effects of either corn oil or n-3 fatty acid supplementation on muscle synthesis in older adults; 1.86 g EPA and 1.50 g DHA were shown to increase muscle protein synthesis. Particularly, supplementation augmented the hyperaminoacidemia-hyperinsulinemia induced synthesis of muscle, suggesting it may be beneficial for the treatment and/or prevention of sarcopenia.[278]

Pregnancy and Lactation

Many studies have now been published on the effects of DHA and/or fish oil during pregnancy and lactation, with many indicating that maternal intake of n-3 fatty acids reduces the chance of premature birth, improves children's neurologic development, and also reduces the risk of maternal depression.[253,279,280] No significant adverse effects were cited with intakes of up to 1 g/day DHA or 2.7 g/day long-chain n-3 fatty acids in randomized trials. As mentioned earlier, the sooner supplementation begins during (or before) pregnancy, the greater the chance for benefit, at least in regard to maternal depression.[257]

A study recently published in *Journal of the American Medical Association,* however, did not find a reduction in maternal depression or improved cognition and/or language in the children of mothers given 800 mg DHA and 100 mg EPA during pregnancy and challenged existing thought regarding supplementation.[281] One possible limitation of this study was their failure to assess the n-3 intake of participants in the study, aside from the provided supplement, although cord blood determinations suggested a low intake in the control group. The median gestational age was 19 weeks in this study. Perhaps supplementation earlier or before conception would have had a greater effect. In contrast, a review of interventional and epidemiologic studies supported the use of DHA and EPA supplementation for childhood cognition and development, as well as preventing childhood psychiatric disorders.[282]

Mercury toxicity is also of concern, and may accompany increased fish consumption. A study published in 2008 found that although maternal fish consumption was associated with a benefit on children's cognition at age 3, mercury levels were associated with poorer test scores. This certainly suggests that obtaining fish oil from purified supplements or low-mercury fish is preferable, and may provide greater benefit than is often cited due to fish consumption (which may be contaminated with mercury).[283] Recommendations to avoid fish (perhaps due to mercury) may be associated with worse outcomes, as suggested by an observational study published in the *Lancet* in 2007.[284]

Finally, an article published in 2011 suggested that genetic variation might significantly modulate n-3 fatty acid levels in pregnancy, children, and in breast milk composition.[285] Here too, the use of a biomarker such as the ω-3 index might be of clinical value.

TOXICITY AND TOXIN CONTAMINATION

Despite widespread use, toxicity with fish oil is quite rare, with the most frequent side effects being mild dyspepsia, nausea, and belching ("fish burps"). Of growing concern, however, is the increasing contamination by environmental toxins such as mercury and POPs (e.g., organochlorine pesticides). An excellent risk and/or benefit analysis of fish consumption was published, and offered a species specific analysis of ω-3 content as well as mercury contamination of each species.[286] The authors of this study suggested that in theory, fish oil supplementation from a high quality source avoids the contamination of consuming fish. Previous studies found commercial fish oil to be free of mercury, polychlorinated biphenyls, and organochlorines, but quality control is essential.[287] Additionally, supplements that use fish oil derived from small, cold-water fatty fish are much less likely to be contaminated.[288]

Care must also be taken to use fish oil, not fish liver oil, because the latter can be excessively high in vitamins A and D and possibly result in toxicity.

Finally, large dosages of fish oil supplements may result in a significant increase in total caloric intake, which can be ameliorated by an increase in energy expenditure.

Bleeding Time

Concerns have been expressed about prolonged bleeding time in populations having a relatively high intake of fish. Several studies showed that this effect appears to be dose dependent, although collagen-induced platelet aggregation was not shown to be inhibited.[289] Many studies showed that fish oil supplements prolong bleeding time, inhibit platelet aggregation, and decrease TXA_2 production.[58,108,290-300]

However, many of these studies are several decades old. In a recent editorial published in March 2007 in the *American Journal of Cardiology*, the author concluded that current research was nearly unanimous: "omega-3 fatty acid supplements do not increase the risk for clinically significant bleeding, even in patients also being treated with antiplatelet or antithrombotic medications. Anecdotal reports of an increased bruising tendency have not been tested in a controlled setting." He also considered this to be at the "A" level of evidence, i.e., based upon well-designed, randomized controlled clinical trials. One caution was that interactions with newer antiplatelet drugs such as clopidogrel have not been evaluated.[301] A second review in the same issue also concluded that clinical trials showed high-dose fish oil consumption to be safe, even when concurrently administered with other agents that may increase bleeding, including aspirin and warfarin. This review also suggested that the reported antiatherothrombotic effects of fish oils might outweigh the unproven bleeding risks, particularly for those patients at high risk for thrombosis.[302]

Some early research suggested that the effect of fish oil supplementation on bleeding time was largely determined by the dosage, duration, and composition of the supplement, and the typical treatment regimens are safe. In one double-blind, placebo-controlled

trial, daily supplementation with 30 mL of a Scandinavian fish oil formulation (ESKIMO-3: 35% n-3 fatty acids, 18% EPA, and 12% DHA) given for both short (4 weeks) and long (6 months) durations resulted in no changes in bleeding time.[61] Another controlled study used 1.5, 3, or 6 g of fish oils (SuperEPA) as a supplement for 3 months and found no effect on bleeding time in 45 healthy male volunteers with normal triglycerides.[303] In the large Enoxaparin MaxEPA Prevention of Angioplasty Restenosis (EMPAR) trial (of over 800 patients receiving fish oil and low-molecular-weight heparin), a decrease in bleeding frequency was seen in the fish oil group compared with placebo.[304]

Evidence as to the degree to which fish oil may affect fibrinolysis is conflicting. Plasma plasminogen activator inhibitor (PAI-1) is an inhibitor of fibrinolysis. Increased PAI-1 activity was linked to the development of myocardial infarction and thrombosis by several investigators. In at least one double-blind, randomized study conducted on an untreated essential hypertensive population, a modest increase in fibrinogen levels was observed after fish oil and corn oil intake by 4 g of ω-3 PUFAs.[305] However, no change in PAI-1 activity or tissue plasminogen activator activity was found. A recent crossover study found fish oil to have the same effect on PAI-1 activity as olive oil.[306]

Oxidation

It was reported in an animal-based study that a diet rich in fish oil taken for many months can induce a deficiency of vitamin E, leading to cardiac necrosis.[307,308] For this reason, periodic vitamin E (mixed tocopherol or γ-tocopherol) supplementation may be warranted. However, there is no evidence that the incidence of cardiac necrosis is higher in Eskimos.

The ω-3 fatty acids found in fish oil are susceptible to oxidative breakdown. For this reason they must be protected from oxidation by proper extraction and storage, encapsulation, or stabilization with an antioxidant such as vitamin E. Inappropriately stored fish oils (i.e., exposure to oxygen) may result in the formation of toxic lipid peroxides over time.



MEASUREMENT OF LIPID OXIDATION PRODUCTS IS ESSENTIAL IN FATTY ACID SUPPLEMENTS

The consumption of essential fatty acid supplements and vegetable oils is increasing, with fish oil now one of the most frequently consumed nutritional supplements. However, the high concentration of unsaturated fatty acids in these products make them more susceptible to spoilage and oxidative damage. A number of factors accelerate spoilage of these oils, including the presence of reactive metals, high water content, or high temperatures during processing and storage.

Consumers perceive oxidative damage as rancidity or off-flavors and off-odors. Health implications for this damage are important. Oxidative damage diminishes the nutritional value of these oils by destroying vitamins and other nutrients. Oxidative products may also interact with protein and carbohydrates. In addition, the byproducts of lipid oxidation may pose a health risk to consumers.

Some edible oils are more resistant to oxidative damage. For example, vegetable oils may naturally contain antioxidants such as tocopherols or vitamin E. Antioxidants prevent the oxidative reactives that can lead to rancidity. Many pathways of oxidation of lipids are not completely understood. Two pathways that received attention are oxidative and hydrolytic rancidity.

Oxidative reactions tend to be more complex, and their byproducts are difficult to measure. Initially, oxygen combines with free fatty acids to form hydroperoxides and free radicals. These reactions are influenced by many factors: the percentage of unsaturated fatty acids present in the oil; processing and storage temperatures; oxygen concentration; light exposure; presence of antioxidants in the oil; moisture content of the oil; and the presence of reactive transition metals, such as iron, nickel, or copper.

The primary oxidative products are unstable. Hydroperoxides are rapidly degraded to aldehydes, ketones, alcohols, and hydrocarbons. These secondary products are relatively stable and are responsible for the characteristic flavor and odor associated with rancid oils.

Historically, manufacturers of edible oils relied on two analytic tests to determine the level of oxidation in oil: the free fatty acid percentage and peroxide value. More recently, two additional measures, the anisidine value and the total oxidation value, were the focus of attention.

The percentage of free fatty acids in oil is an indication of freshness. As oil ages, triglycerides cleave to glycerol and free fatty acids through hydrolysis. Free fatty acids are more prone to oxidation than triglycerides, so their presence in oils increases the possibility of rancidity. A fresh, carefully processed oil has a free fatty acid percentage of less than 0.05%.

The peroxide value measures the level of hydroperoxides in oil. Hydroperoxides are the primary byproduct of oxidation. For example, 4-hydroxy-hexenal is a byproduct of DHA peroxidation known to be elevated in disease states.[309] Peroxide value alone is not indicative of the actual oxidative state of the oil because hydroperoxides decompose rapidly to secondary byproducts such as aldehydes. Therefore, an oil might also have a low peroxide value as a result of extensive oxidation rather than due to low levels of oxidation. In theory, a fresh oil would have a peroxide value of zero. In practice, most vegetable oils have peroxide values ranging from 0.1 to 1. Besides the peroxide value, the anisidine value must also be calculated.

The anisidine value is a measure of the amount of α- and β-unsaturated aldehydes. Anisidine is an aromatic amine. Synonyms for anisidine include aminoanisole, methoxyaniline, methoxyphenylamine, and methoxybenzenamine. Anisidine has two isomeric forms. Both were reported to enhance mutagenicity in bacterial strains.[310] The ortho-anisidine isomer was associated with bladder tumors. Data on carcinogenicity are almost exclusively on the ortho-isomer, not the para-isomer, which most companies focus on when they measure anisidine values in fish oils.

The total oxidative value used to express the extent of oxidation of an oil is the sum of the peroxide value and the anisidine value. Tests for peroxide value should comply with the *American Oil Chemists, Society* (AOCS) *Official Method* Cd 8-53 and not exceed a maximum of 5 mEq/kg, whereas the para-anisidine value should comply with *AOCS Official Method* 18-90 and not exceed a maximum of 20.

Many commercially available oils contain high levels of hydroperoxides and secondary byproducts of oxidation. In the 1990s, Shukla and Perkins[311] analyzed various oils for oxidative stability. Their results showed that fish oils were more prone to oxidation than vegetable oils. The total oxidation values of fish oils ranged from 20 to 60 compared with 5 to 20 for vegetable oils (Tables 91-2 and 91-3).[19]

Shukla and Perkins made the following recommendations to prevent oxidation during the manufacturing process[39]:

- Always use top-quality, freshly produced raw materials stored in temperature- and humidity-controlled facilities.
- Prevent exposure to oxygen by using closed, impermeable containers.

TABLE 91-2 **Analytic Constants of Various Encapsulated Essential Fatty Acid Oils (1985 to 1988)**

PRODUCT	PEROXIDE VALUE (Px)	ANISIDINE VALUE (Av)	TOTAL OXIDATION (2 Px + Av)	IODINE VALUE	PERCENTAGE OF FREE FATTY ACIDS
Vegetable oils					
A	5.4	6	16.8	151.5	1.02
B	1.5	4.4	7.4	146.2	4.1
C	6.9	4.8	18.6	178.6	0.14
D	3.4	0	6.8	152	0.80
Fish oils					
E	3.7	30.2	37.6	189	0.10
F	2.7	14.3	19.7	196.5	0.09
G	20.8	17.9	59.5	241.7	0.25
H	2.2	29.2	33.6	199.4	0.31

Data from: Kinsella JE, Lokesh B, Stone RA. Dietary n-3 polyunsaturated fatty acids and amelioration of cardiovascular disease: possible mechanisms. Am J Clin Nutr. 1990 Jul;52(1):1-28.

TABLE 91-3 **Analytic Constants of the Same Brand of Fish Oil Capsules Bought in Four Different Countries**

COUNTRY	PEROXIDE VALUE (Px)	ANISIDINE VALUE (Av)	TOTAL OXIDATION VALUE (2 Px + Av)
England	3.8	16.6	24.2
The Netherlands	1.8	34	37.6
Denmark	3.7	30.2	37.6
United States	2.2	20.6	25

Data from Kinsella JE, Lokesh B, Stone RA. Dietary n-3 polyunsaturated fatty acids and amelioration of cardiovascular disease: possible mechanisms. Am J Clin Nutr. 1990 Jul;52(1):1-28.

- Avoid exposure of raw materials to sunlight.
- Use stringent quality control.
- Use stainless steel equipment.
- Minimize heating of oil during processing.
- Use antioxidants to prolong shelf life.
- When using soft gelatin capsules, choose a shell with the lowest concentration of plasticizer possible.

By the early twenty-first century, many manufacturers of fatty acid supplements and vegetable oils took the lead to protect consumers by producing oils with the lowest levels of oxidative byproducts possible. Consumer education and accurate measurement of peroxide and anisidine values are vital to this effort.

DOSAGE

A daily dose of 1000 mg EPA+DHA may be sufficient as a general health adjunct. However, for more therapeutic indications the dosage range based upon most clinical studies is between 3 and 4 g/day of EPA+DHA. Research also suggests that biomarker assessment may be of value for determining optimal dosage for a variety of conditions, especially protection against cardiovascular disease. In a small study, supplementation with 1296 mg EPA + 864 mg DHA per day increased the erythrocyte ω-3 index, a potential biomarker for at least cardiovascular disease risk, to near 8%.[312] Interindividual differences in eicosanoid metabolism as well as digestive and/or absorptive function, along with genetic polymorphisms, may call for more individualized dosing. As clearly evidenced by clinical trials such as those on RA, benefit may not be seen for 2 to 3 months.

The optimal ratio of EPA/DHA is not well-established, and may vary for individuals as well as conditions. Research in depression suggests that although DHA is the more prevalent fatty acid in brain tissue, EPA may be more clinically effective. This should be kept in mind when considering other conditions, such as fish oil supplementation for neurodegenerative disease.

Also, the form of fish and fish oil supplements is an important consideration. In one small trial comparing cod liver oil supplementation to actual fish consumption, cooked salmon increased serum levels to a greater extent than cod liver oil, despite providing less total DHA/EPA.[313] This may be because in fish, the fatty acids are triacylglycerols and phospholipids, whereas in almost all refined fish oils used in studies, EPA and DHA were in the ethyl ester form. Currently, EPA/DHA supplements are widely available in the triglyceride, phospholipid, and ethyl ester forms. While several studies have shown similar absorption for ethyl esters, phospholipids, or triglycerides, other studies have shown that EPA/DHA consumed as triacylglycerides increased the ω-3 index more rapidly and to a greater degree than the ethyl esters of DHA/EPA.[314-316] However, the clinical significance of this advantage has not yet been demonstrated, especially with chronic administration.

DRUG INTERACTIONS

Individuals known or suspected to have a bleeding disorder, as well as those prescribed therapeutic levels of aspirin or warfarin, should have their bleeding time parameters measured, although as previously described (see "Bleeding Time"), this risk is not likely to exist in actuality. Patients may benefit from fish oil when taking cyclosporine.[317] Fish oil may also have synergistic or additive effects with the cholesterol- and triglyceride-lowering drugs pravastatin and simvastatin and have broader therapeutic value.[318] Fish oil is likely to modulate the cytotoxicity of many chemotherapeutic agents, as previously described, to increase therapeutic efficacy without increasing toxicity. It may also reduce adverse effects of many chemotherapeutic regimens, including the unintentional loss of weight. It may increase the efficacy of some antidepressants without an increase in toxicity.[260] A thorough review by Stargrove et al[319] found nearly every drug interaction to be a beneficial one.

CONCLUSION

A substantial body of evidence continues to grow, documenting the safety and efficacy of n-3 fatty acids from fish and fish oil for a broad range of diseases, as well as for improving optimal cellular and physiologic function. The mechanisms by which EPA and

DHA from fish oil modulate cellular function and membrane structure continue to be elucidated in greater detail, and the potential of biomarkers, such as the ω-3 index, as well as genetic variants related to fish oil metabolism, highlight the need for individualized and targeted fish oil supplementation.

The list of conditions for which fish oil is of benefit extends well beyond this chapter, since its use has been researched for most medical conditions. Here we have highlighted many of the common and most well-established uses for fish oil, such as for cardiovascular disease and modulation of inflammatory activity. The growing contamination of fish as well as the potential decline in world-wide fish stocks are of considerable concern, especially given the broad-ranging benefit of this under-consumed nutrient. Also, a growing awareness of the importance of not just n-3 intake, but also of the ratio of n-6 fatty acids may help to increase the efficacy of its nutritional modulation. A recent article cited that despite a 0.005% change in our genes over the last 10,000 years, an extraordinarily significant shift in the ratio of n-6:n-3 occurred only recently, and might help to explain so many of today's modern illnesses.[28]

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CHAPTER 92

Flavonoids—Quercetin, Citrus Flavonoids, and Hydroxyethylrutosides

Michael T. Murray, ND

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INTRODUCTION

Flavonoids, a group of plant pigments, are largely responsible for the colors of many fruits and flowers. Recent research suggests that flavonoids may be useful in the treatment and prevention of many health conditions. Many of the medicinal actions of foods, juices, herbs, and bee pollen are now known to be directly related to their flavonoid content. More than 4000 flavonoid compounds have been characterized and classified according to their chemical structure. Flavonoids are a bit of an enigma to scientists, because they are quite reactive compounds. They can enter into almost any type of reaction known to organic chemistry, such as oxidation-reduction reactions, carbonyl reaction, acid-base reactions, free-radical reaction, hydrophobic interactions, tautomery, and isomerizations.[1] As such, characterization of the many diverse physiologic properties of flavonoids is a considerable challenge to biochemists and researchers alike. This chapter discusses a few representatives of this class of useful clinical agents (quercetin, citrus bioflavonoids, and hydroxyethylrutosides).

Another beneficial group of plant flavonoids are the proanthocyanidins (also referred to as procyanidins). Collectively, mixtures of proanthocyanidin dimers, trimers, tetramers, and larger molecules are referred to as procyanidolic oligomers (PCOs). Chapter 117 discusses PCOs.

HISTORICAL PERSPECTIVE

Flavonoids, as well as vitamin C, were discovered by Albert Szent-Györgyi (1893 to 1986), one of the most respected and honored biochemists of the twentieth century. Szent-Györgyi received the Nobel Prize in 1937 for his discovery of some of the properties of these molecules.

Szent-Györgyi discovered the flavonoids while isolating vitamin C. A friend with bleeding gums had stopped the bleeding by taking a crude vitamin C preparation isolated from lemon. When the problem reappeared, Szent-Györgyi gave his friend a purer form of vitamin C. He expected to observe an even more impressive result, but the purer form of vitamin C did not work. Szent-Györgyi then isolated the flavonoid fraction from the original crude vitamin C preparation, gave it to his friend, and observed complete healing.

Szent-Györgyi termed his discovery "vitamin P" due to its ability reduce vascular permeability, one of the hallmark features of scurvy. He went on to show that the clinical symptoms of scurvy are the result of a combined deficiency of vitamin C and flavonoids. However, because flavonoids could not fulfill all the requirements of a vitamin, the designation as vitamin P was abandoned. Although flavonoids are often referred to as "semiessential" nutrients, their importance in human nutrition appears to be as important to good health as the essential vitamins and minerals.

Good dietary sources of flavonoids include citrus fruits, berries, onions, parsley, legumes, green tea, and red wine. The average daily intake in the United States for flavonoids is estimated to be between 150 and 200 mg.

CHEMICAL DESCRIPTIONS

Quercetin

Quercetin (Figure 92-1) is a flavonoid that serves as the aglycone for many other flavonoids, including the citrus flavonoids rutin, quercitrin, and hesperidin.

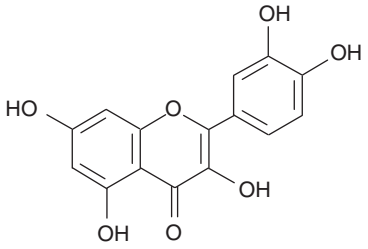


FIGURE 92-1 Quercetin.

These derivatives differ from quercetin in that they have sugar molecules attached to the quercetin backbone. Quercetin is consistently the most active of the flavonoids in experimental studies, and many medicinal plants owe much of their activity to their high quercetin content.

Citrus Bioflavonoids

Citrus bioflavonoid preparations can include rutin, hesperidin, quercitrin, and naringin. Most of the clinical research on rutin and crude bioflavonoid complexes occurred before 1970. Since then, most of the clinical research has used a standardized mixture of rutinosides known as hydroxyethylrutosides (HERs). Impressive clinical results have been obtained in the treatment of capillary permeability, excessive bruisability, hemorrhoids, and varicose veins with HERs (discussed in "Collagen Matrix Support"). Citrus bioflavonoids can be viewed as providing similar effects to, but probably not as potent as, HERs or quercetin.

PHARMACOLOGY

As a class of compounds, flavonoids have been referred to as "nature's biological response modifiers" because of their ability to modify the body's reaction to other compounds, such as allergens, viruses, and carcinogens, as evidenced by their anti-inflammatory, antiallergic, antiviral, and anticarcinogenic properties.[2] In addition, flavonoids act as powerful antioxidants, providing remarkable protection against oxidative and free radical damage;[3] they also have the ability to traverse the blood–brain barrier, thus exerting a neuroprotective effect.[4] Flavonoids are known to form strong ligand complexes with heavy metal ions and may prove to be a good agent of heavy metal detoxification.[1]

The practical aspect of this antioxidant activity was highlighted by the results of a study in 805 men designed to determine the effect of dietary flavonoids on protecting against heart disease. The study demonstrated an inverse correlation between flavonoid intake and death from a heart attack.[5] This effect was probably a result of the potent antioxidant effects of the flavonoids preventing, similar to vitamins C and E, the formation of oxidized cholesterol. However, the antioxidant activity of flavonoids is generally more potent and effective against a broader range of oxidants than traditional antioxidant nutrients like vitamins C and E, selenium, and zinc.[6,7]

Because different flavonoids tend to provide different benefits, additional and more specific beneficial effects are discussed under the key selected flavonoid categories. There is significant overlap among these flavonoids, however.

Quercetin

Quercetin consistently demonstrates the greatest activity among the flavonoids studied in experimental models, particularly in vitro studies. The primary actions that are briefly reviewed here are its anti-inflammatory effects, inhibition of aldose reductase, antiviral activity, and anticancer properties.

Antiinflammatory Effects

Quercetin has demonstrated significant anti-inflammatory activity due to direct inhibition of several of the initial processes of inflammation via interaction with calcium channels or calmodulin (the intracellular calcium-binding protein), or both. It works through other mechanisms as well, such as inhibiting mast cell and basophil degranulation, neutrophil and monocyte lysosomal secretion, prostaglandin (most notably, leukotriene) formation, lipid peroxidation, and the resultant cascade of effects that are often a result of these processes. For example, it inhibits both the manufacture and release of histamine and other allergic/inflammatory mediators. In addition, it exerts potent antioxidant activity and vitamin C–sparing action.[6-9]

Effect on Histamine Release

The release of histamine and other inflammatory mediators from mast cells and basophils is involved in the pathogenesis of acute allergic and inflammatory responses. Mast cells are widely distributed throughout the human body but are found in higher concentrations in the blood vessels of the subepithelial connective tissue of the respiratory tract, conjunctiva, gastrointestinal tract, and skin. Mast cell and basophil degranulation is an active process that requires calcium influx. Quercetin and many other flavonoids have been shown to be potent inhibitors of mast cell, neutrophil, and basophil degranulation. A generally accepted hypothesis for this action is that quercetin inhibits receptor-mediated calcium influx, thereby inhibiting the primary signal for degranulation. However, quercetin is also active under conditions in which the calcium channel mechanism is not operative, indicating that other mechanisms are responsible as well.[6-9]

Membrane Stabilization, Antioxidant Activity, and Hyaluronidase Inhibition

Quercetin inhibits many of the inflammatory processes attributed to activated neutrophils. This effect is probably due to its membrane-stabilizing action, potent antioxidant effect (which prevents the production of free radicals and inflammatory leukotrienes), inhibition of the enzyme hyaluronidase (thus preventing the breakdown of the collagen matrix of connective tissue and ground substance), and finally inhibition of the proinflammatory cytokines. Quercetin's membrane-stabilizing effect could also account for its action in preventing mast cell and basophil degranulation. This effect also inhibits inflammation by decreasing neutrophil lysosomal enzyme secretion.[10] Neutrophils and monocytes contain lysosomes that, on secretion of their contents, contribute greatly to the inflammatory process.

Effects on Eicosanoid Metabolism

Excessive leukotriene formation has been linked to asthma, psoriasis, atopic dermatitis, gout, ulcerative colitis, and possibly cancer. Quercetin has been shown to inhibit many steps in eicosanoid metabolism. Its inhibition of phospholipase A2 and lipoxygenase enzymes is probably its most significant action (see Chapter 149 for diagram). The net result is a significant reduction in the formation of leukotrienes. The leukotrienes C4, D4, and E4 (composing the slow-reacting substances of anaphylaxis) are derived from arachidonic acid and are 1000 times as potent as histamine in promoting inflammation. Leukotrienes promote inflammation by causing vasoconstriction (thereby increasing vascular permeability) and bronchoconstriction

(thus inducing asthma) and by promoting white blood cell chemotaxis and aggregation. The reduction of leukotriene formation by quercetin has significant anti-inflammatory effects.

Inhibition of Aldose Reductase

Quercetin is a strong inhibitor of aldose reductase, the enzyme responsible for the conversion of blood glucose to sorbitol. This compound is strongly implicated in the development of diabetic complications such as diabetic cataracts, neuropathy, and retinopathy.[11] The mechanism by which sorbitol is involved in the development of diabetic complications is best understood by considering its involvement in cataract formation. Although the lens does not have any blood vessels, it is an actively metabolizing tissue that continuously grows throughout life. Elevated blood sugar levels result in shunting of glucose to the sorbitol pathway.

Because the lens membranes are virtually impermeable to sorbitol and lack the enzyme required to break down sorbitol (polyol dehydrogenase), sorbitol accumulates to high concentrations. These high concentrations persist even if glucose levels return to normal. This accumulation creates an osmotic gradient that results in water being drawn into the cells to maintain osmotic balance. As the water is pulled in, the cell must release small molecules like amino acids, inositol, glutathione, niacin, vitamin C, magnesium, and potassium to maintain osmotic balance. Because these latter compounds function to protect the lens from damage, their loss results in an increased susceptibility to damage. As a result, the delicate protein fibers within the lens become opaque, and a cataract forms.

Quercitrin, which is hydrolyzed by gut bacteria to yield quercetin and a sugar moiety, was shown to significantly decrease the accumulation of sorbitol in the lens of diabetic animals, effectively delaying the onset of cataracts.[12] In addition to its effect on aldose reductase, quercetin is also of value in diabetes for its ability to enhance insulin secretion and protect the pancreatic β cells from the damaging effects of free radicals, and for its inhibition of platelet aggregation.[6,7]

Antiviral Activity

Flavonoids as a group possess significant antiviral activity, with quercetin having the greatest antiviral activity against herpes virus type I, parainfluenzae 3, polio virus type I, and respiratory syncytial virus.[13] Quercetin was shown, in vitro, to inhibit both viral replication and infectivity. In vivo studies in animals also showed quercetin to inhibit viral infection.[14] This would suggest that quercetin might be of some benefit in viral infections, including the common cold.

Anticancer Properties

Many flavonoids have also been shown to inhibit tumor formation, but again quercetin has consistently been the most effective. In experimental models, quercetin demonstrated significant antitumor activity against a wide range of cancers, including squamous cell carcinoma, leukemia, and cancers of the breast, ovaries, colon, rectum, and brain. The cancer preventive effects of quercetin have been attributed to various mechanisms, including antioxidative activity, inhibition of enzymes that activate carcinogens, modification of signal transduction pathways, and interactions with receptors and other proteins, such as the androgen receptor involved in the development and progression of prostate cancer.[15-17]

Clinically, quercetin holds great promise in reversing multidrug resistance (MDR) in cancer cells. Transporter-mediated active efflux of cytotoxic agents is one of the best characterized mechanisms by which cancer cells develop MDR. Quercetin demonstrated multitargeted effects in reversing MDR.[17]

Citrus Flavonoids

Collagen Matrix Support

In addition to possessing antioxidant activity and an ability to increase intracellular levels of vitamin C, rutin, hesperidin, and HER exert many beneficial effects on capillary permeability and blood flow, primarily via strengthening endothelial cells and supporting collagen structures. Collagen, the most abundant protein of the body, is responsible for maintaining the integrity of "ground substance," as well as the integrity of tendons, ligaments, and cartilage. Collagen is also the support structure of the skin and blood vessels. Citrus flavonoids affect collagen metabolism in several ways.

They reinforce the natural cross-linking of collagen that forms the so-called collagen matrix of connective tissue and protect against free radical damage with their potent antioxidant and free radical scavenging action. They also inhibit enzymatic cleavage of collagen by enzymes secreted by leukocytes during inflammation and microbes during infection. Like quercetin, citrus flavonoids also prevent the release and synthesis of compounds that promote inflammation and allergies, such as histamine, serine proteases, prostaglandins, and leukotrienes.[8,9] It is believed that the citrus bioflavonoid hesperidin possesses antihistaminic activity through its metabolite heparitin, a weak inhibitor of cyclooxygenase-2 enzymes. This metabolite is produced as a product of intestinal bacteria, which underscores the need for a balanced intestinal flora to gain the antihistamine benefits of citrus bioflavonoids.[18]

Bone Metabolism Effects

Histomorphometric research on ovariectomized mice showed that marked decreases in trabecular bone volume and trabecular thickness of the femoral distal metaphysis were significantly prevented by hesperidin. Additionally, calcium, phosphorus, and zinc concentrations in the femur were significantly higher in the hesperidin-fed group, whereas serum and hepatic lipids were lower in mice that consumed hesperidin-containing diets.[19]

Pharmacokinetics

Before discussing clinical applications of quercetin, it is important to address absorption and metabolism. Previous pharmacokinetic studies in animals and humans indicated that little quercetin is absorbed intact, with the majority of the oral dose (53%) being excreted in the feces.[20,21] One of the main problems in studying the absorption of quercetin and other flavonoids is their degradation by microorganisms in the colon. To sidestep this issue, one study examined the absorption of quercetin in healthy ileostomy patients with complete small intestines.[22] The study examined the absorption of quercetin from fried onions (a rich source of quercetin glycosides), rutin, or 100 mg of pure quercetin. Absorption was defined as oral intake minus ileostomy excretion and corrected for degradation within the ileostomy bag. Absorption results were as follows: 52% from onions, 17% from quercetin rutinoside, and 24% for pure quercetin. These results indicate that humans do absorb appreciable amounts of quercetin and that absorption (but not necessarily pharmacologic activity) may be enhanced when quercetin is bound to glucose. In other words, citrus bioflavonoid preparations or HERs, or both, may prove to be more effective clinically.

Subsequent studies shed additional light on the absorption and metabolism of quercetin. In a study of 35 healthy volunteers, the volunteers were randomly assigned to take 50, 100, or 150 mg/day (groups Q50, Q100, and Q150, respectively) quercetin for 2 weeks. Fasting blood samples were collected at the beginning and end of

the supplementation period. Compared with baseline, quercetin supplementation significantly increased plasma concentrations of quercetin by 178% (Q50), 359% (Q100), and 570% (Q150). Pharmacokinetics of quercetin were investigated in a subgroup of 15 volunteers. The areas under the plasma concentration–time curves ranged from 76.1 to 305.8 μmol/min/L(–1) (50- and 150-mg doses, respectively). Median maximum plasma concentrations of quercetin (431 nmol/L) were observed 360 minutes after intake of 150 mg quercetin.[23]

In a much larger study, 1002 subjects were randomized to one of three groups: Q-500 (500 mg/day), Q-1000 (1000 mg/day), or placebo. Quercetin supplementation over 12 weeks caused a significant increase in overnight-fasted plasma quercetin, with a net increase of 332 and 516 mcg/L for Q-500 and Q-1000 compared with 53.6 mcg/L for placebo. However, the increase in plasma quercetin was highly variable within each quercetin supplementation group.[24]

Once absorbed, much of absorbed quercetin is conjugated to glucuronic acid in the liver by phase II enzymes. It is thought that β-glucuronidase released from neutrophils at inflammatory sites may be able to deconjugate and thus activate quercetin glucuronides. This effect was demonstrated in vitro.[25]

Given the relatively poor bioavailability and high variability of absorption among subjects, improved clinical results may be achieved with newer forms of quercetin, such as enzymatically modified isoquercitrin (EMIQ) to overcome these shortcomings (discussed in "Commercial Forms").

CLINICAL APPLICATIONS

Allergic and Inflammatory Conditions

Largely on the basis of in vitro studies, quercetin appears to be indicated in virtually all inflammatory and allergic conditions, including asthma, hay fever, rheumatoid arthritis, and lupus, as well as in diabetes and cancer. Clinical documentation in these areas, however, is lacking. In a study using a highly biovailable EMIQ, very good results were achieved. In a parallel-group, double-blind placebo-controlled study design, 20 subjects with hay fever due to Japanese cedar pollinosis took two capsules daily of 100 mg EMIQ or a placebo for 8 weeks during the pollen season. During the entire study, total ocular score and ocular itching score for the EMIQ group were significantly lower than those of the placebo group. When limited to the individual periods, total symptom score for the EMIQ group was significantly lower than that for the placebo group. The levels of serum cytokines, such as interleukin (IL)-4, IL-5, IL-12, IL-13, interferon-γ, and eotaxin and immunoglobulin-E, were not significantly downregulated by the intake of EMIQ, but the serum concentrations of oxidized low-density lipoprotein and thymus and activation-regulated chemokines were reduced.[26]

In another study of EMIQ in subjects with hay fever due to Japanese cedar pollinosis, 24 subjects took 100 mg EMIQ or a placebo for 8 weeks, starting 4 weeks before the onset of pollen release. During the entire study period, ocular symptom plus medication score for the EMIQ group was significantly lower than that of the placebo group. When limited to the pollen release period, ocular symptom scores and ocular congestion scores for the EMIQ group were significantly lower than that for the placebo group, whereas other scores for the EMIQ group, such as ocular itching scores, lacrimation scores, and ocular congestion scores, all tended to be lower. However, no significant differences were found in nasal symptoms between the two groups. These results indicate that EMIQ is useful in reducing ocular symptoms of hay fever, especially ocular congestion.[27]

Topical application of quercetin showed anti-inflammatory effects. In a study of 40 patients with aphthous stomatitis randomly divided into two groups (group 1 patients used a benzydamine hydrochloride mouthwash three times daily; group 2 patients placed two to three dabs of quercetin three times daily directly on their ulcers), the topical application of quercetin cream to minor mouth ulcers relieved pain and produced complete healing in seven of the group 2 patients (35%) in 2 to 4 days, in 18 patients (90%) in 4 to 7 days, and in 20 patients (100%) in 7 to 10 days. Although aphthous ulcers typically resolve on their own in 1 to 2 weeks, the daily topical application of quercetin might be useful in accelerating the healing process of minor aphthous ulcers.[28]

Performance, Ergogenic, and Mitochondrial Effects

By far the most popular application, quercetin is in beverages designed for athletic performance. The commercial success of this application led to significant scientific investigation of quercetin's ability to improve physical performance. In a number of clinical trials, quercetin was shown to improve mental/physical performance and reduce infection risk after intense exercise.[29] In one small trial, 12 volunteers were randomly assigned to one of two treatments: (1) 500 mg of quercetin twice daily dissolved in vitamin-enriched Tang or (2) a nondistinguishable placebo (Tang). Baseline maximal oxygen consumption (VO_2max) and bike-ride times to fatigue were established. Treatments were administered for 7 days using a randomized, double-blind, placebo-controlled, crossover study design. After treatment, both VO_2max and ride time to fatigue were determined. Seven days of quercetin feedings were associated with a modest increase in VO_2max (3.9% vs placebo) along with a substantial (13.2%) increase in ride time to fatigue. These data suggest that as little as 7 days of quercetin supplementation can increase endurance without exercise training in untrained participants. However, a similar study using treadmill testing failed to show the same sort of effect.[30]

In a more detailed study, 26 young adult males were given quercetin (1 g/day) or placebo for 2 weeks and then crossed over.[31] Subjects provided blood and muscle biopsy samples before and after supplementation periods and underwent 12-minute time trials on 15% graded treadmills after 60 minutes of moderate exercise preloads at 60% VO_2max. Plasma quercetin levels rose significantly during the 2-week quercetin supplementation period. Quercetin produced a 2.9% increased net distance in the 12-minute trial; skeletal muscle messenger RNA expression tended to increase (range, 16% to 25%) during quercetin use for sirtuin 1, peroxisome proliferator-activated receptor γ coactivator-1α, cytochrome c oxidase, and citrate synthase. Muscle mitochondrial DNA (relative copy number per diploid nuclear genome) increased by 4.1% with quercetin compared with a 6.0% decrease with the placebo. This result seems to indicate that quercetin does provide some benefit in improving physical performance in untrained volunteers.

In regards to moderately trained men and women, the data are not clear on indicators of performance, but quercetin showed other benefits in this group. In one study, 58 subjects were randomly assigned to quercetin (1 g/day) or placebo groups. Six weeks of dietary quercetin supplementation did not improve VO_2max or other indicators of performance.[32] In double-blind studies, however, quercetin (1 g/day) was shown to reduce upper respiratory infections in moderately trained individuals.[33,34] Of 20 trained male cyclists who received quercetin or placebo before,

during, and for 2 weeks, after a 3-day period in which subjects cycled for 3 hours/day at approximately 57% maximal workload, only 1 of 20 developed upper respiratory infection symptoms in the quercetin group compared with 9 of 20 in the placebo group.[33] In another study, reduction in upper respiratory tract infection total sick days and severity was noted in middle aged and older subjects ingesting 1000 mg/day quercetin for 12 weeks who rated themselves as physically fit.[34]

Cardiovascular Effects

Various studies indicated quercetin and citrus bioflavonoids beneficially affected cardiovascular risk factors. In animal studies, increases in high-density lipoprotein and decreases in low-density lipoprotein cholesterol, total lipid, and triglyceride plasma levels in normolipidemic rats and in rats with diet and induced hyperlipidemia were observed.[35] Animal studies also showed antihypertensive effects in spontaneously hypertensive rats and normotensive rats.[36] EMIQ was even more effective based upon animal studies that evaluated the antihypertensive effects and antiatherogenic effects in spontaneous hypertensive rats.[37,38]

A variety of human studies substantiated some of these effects and many more. Hesperidin and quercetin both improved endothelial function.[39,40] In particular, quercetin at a dosage of 200 mg/day augmented nitric oxide status and reduced endothelin-1 concentrations to improve endothelial function.[40] In a pilot study with quercetin-4′-O-β-D-glucoside, which like EMIQ is a prodrug for quercetin, subjects given either 50 or 300 mg had significant inhibition of platelet aggregation at 30 and 120 minutes after ingestion.[41]

In the most detailed study on the cardiovascular benefits of quercetin to date, the effect of quercetin supplementation on blood pressure, lipid metabolism, markers of oxidative stress, inflammation, and body composition was studied in an at-risk population of 93 overweight-obese volunteers (aged 25 to 65 years of age) with metabolic syndrome traits in relation to apolipoprotein-E (Apo-E) genotype.[42,43] Participants were randomized to receive 150 mg/day quercetin in a double-blinded, placebo-controlled, crossover trial with 6-week treatment periods separated by a 5-week washout period. Participants were classified into the following 3 Apo-E phenotypes: Apo-E2 (n = 3), Apo-E3 (n = 60), and Apo-E4 (n = 26). Data were analyzed for Apo-E3 and Apo-E4 subgroups. Quercetin decreased systolic blood pressure by 3.4 mm Hg in the Apo-E3 group, whereas no significant effect was observed in the Apo-E4 group. Quercetin decreased serum high-density lipoprotein cholesterol (i.e., from 52 to 47 mg/dL), resulting in a slightly increased low-density lipoprotein/high-density lipoprotein cholesterol ratio in the Apo-E4 subgroup, whereas the Apo-E3 subgroup had no significant changes in these variables. Quercetin significantly decreased plasma oxidized low-density lipoprotein and tumor necrosis factor-α in the Apo-E3 and Apo-E4 groups, whereas no significant intergroup differences were found. Serum C-reactive protein and nutritional status (body weight, waist circumference, fat mass, fat-free mass) were unaffected compared with placebo. In conclusion, quercetin exhibited blood pressure-lowering effects in overweight-obese carriers of the Apo ε3/ε3 genotype but not in carriers of the ε4 allele. Although the degree of blood pressure reduction was not clinically meaningful in this study, in another randomized, double-blind, placebo-controlled, crossover study, 730 mg/day of quercetin for 28 days was shown to lead to meaningful reductions in systolic (–7 mm Hg), diastolic (–5 mm Hg), and mean arterial pressures (–5 mm Hg) in stage 1 hypertensive patients.[44]

Chronic Venous Insufficiency, Capillary Fragility, Excessive Bruisability, and Hemorrhoids

A deficiency of hesperidin in the diet was linked with abnormal capillary leakiness, as well as pain in the extremities, causing aches, weakness, and night leg cramps.[45] Early studies demonstrated rutin to be effective in reducing capillary fragility, easy bruising, swelling and bruising after sports injuries, and nosebleeds.[46-48] More recent and much more extensive studies were performed with HERs. Positive double-blind clinical studies exist in the treatment of venous insufficiency, including varicose veins, hemorrhoids, diabetic vascular disease, and diabetic retinopathy.[49-60]

In double-blind studies of patients with chronic venous insufficiency, HER improved microvascular blood flow and clinical symptoms (pain, tired legs, night cramps, and restless legs) in 73% to 100% of patients.[49-60] Several studies were conducted on pregnant women, in whom HER was shown to be of great benefit in improving venous function, as well as in helping to relieve hemorrhoidal signs and symptoms. In one study, 90% of the women given HER (1000 mg/day for 4 weeks) had improved symptoms compared with only 12% in the placebo group.[60] Similar results in hemorrhoids not associated with pregnancy were also reported.[59]

In a very practical study, the effects of HER at a dose of 1 g/day on the prevention and control of flight microangiopathy and edema were studied in subjects with varicose veins and moderate chronic venous insufficiency who flew for more than 11 hours.[58] Measurements of skin laser Doppler resting flux venoarteriolar response, ankle swelling, and edema were made within 12 hours before and within 3 hours after the flights. The resulting edema after the flights was evaluated with a composite edema score (analogue scale line). A group of 20 subjects was treated with HER (1 g/day, starting 2 days before the flight and 1 g for every 12 hours on day of travel). Another group of 18 subjects formed the control group. The length of the flights was between 11 and 13 hours; all seats were in coach class. Fifty patients were enrolled, and 38 patients were evaluable at the end of the trial. The results showed clearly that HER was useful for reducing the level of microangiopathy and the increased capillary filtration, and in controlling edema in patients with venous disease during long flights. The higher level of flux and venoarteriolar response and the reduction in edema indicated a positive effect of HER on microcirculation.

There are a number of natural therapeutic agents to choose from in chronic venous insufficiency. In a double-blind study, the effects of HER were compared with micronized diosmin plus hesperidin (D+H). A first group of 90 patients with severe venous hypertension was randomized to treatment with HER or D+H. The HER group received oral HER (2 g/day); the D+H group received 3 (500 mg) tablets daily every 8 hours for 8 weeks. A second group of 122 comparable patients was included in a registry following the same study format. Results showed HER was more effective in relieving signs and symptoms of chronic venous insufficiency as well as improving the quality of life scale in this study.[57]

Diabetes

Flavonoids appear to be important in the long-term care of diabetes for many reasons. One of the hallmark features of diabetes is a significant disturbance of blood flow through small blood vessels. HERs appear to improve blood flow in diabetics significantly and can be useful in the treatment of diabetic microvascular disease and retinopathy. Flavonoids can also stimulate an otherwise weak insulin effect in several ways. For example, they can influence the protein phosphokinases, which modulate second messenger

pathways known to upregulate the gene encoding the glucose transporters.[1] PCOs or bilberry extracts may be better than quercetin, citrus flavonoids, and HER in diabetics.[49,61,62]

Thalassemias

Although it may be difficult to treat the long-term outcomes of thalassemia conditions, it is possible that quercetin may serve to protect abnormally sensitive lymphocytes from common dietary substances. An in vitro study evaluated the effect of food mutagens on the lymphocytes from three different types of thalassemia patients: β-thalassemia major, β-thalassemia/Hb E, and a β-thalassemia trait with a 3.7-kb deletion. When the mutagen exposure was combined with quercetin, reduced sensitivities among the various thalassemic genotypes were observed in a dose-dependent manner.[62a] Although human studies are necessary to confirm this beneficial effect, quercetin might be worth a try to attenuate the toxic mutagenic effects commonly found in these susceptible patients.

COMMERCIALLY AVAILABLE FORMS

Quercetin

Quercetin is available alone in powder and capsule form. However, if quercetin is being used for its anti-inflammatory properties, products that combine it with the pineapple enzyme bromelain may provide additional benefit. Bromelain (see Chapter 71) exerts anti-allergy and anti-inflammatory activity on its own and may also enhance the absorption of quercetin. Combination preparations of protein-digesting enzymes, like bromelain, and flavonoids have been shown to potentiate each other's anti-inflammatory activity.[54]

EMIQ is a new form of quercetin that showed greater absorption in both human and animal studies. It is prepared by enzymatic deglycosylation and the subsequent α-oligoglucosylation of quercetin-3-O-rutinoside (rutin). The plasma level of quercetin conjugates is instantly increased by oral intake of EMIQ.[63,64] In a rat study, the absorption of EMIQ was compared with quercetin, quercetin-3-O-rutinoside (rutin), quercetin-3-O-glucoside (isoquercitrin [IQC]), quercetin-3-O-maltoside (Q3M), quercetin-3-O-gentiobioside (Q3G), α-monoglucosyl rutin (α-MR), and α-oligoglucosyl rutin (α-OR). Bioavailability (F value) was calculated from the concentrations of total quercetin in plasma from 0 to 12 hours after administration. F value of quercetin was 2.0%, and those of IQC, Q3M, and EMIQ were 12%, 30%, and 35%, respectively. Although Q3G, α-MR, and α-OR have high water solubility, their F values were low (3.0%, 4.1%, 1.8%, respectively). In an in vitro study, the homogenate of rat intestinal epithelium rapidly hydrolyzed EMIQ, IQC, and Q3M to quercetin, and α-MR and α-OR to rutin. However, it could not hydrolyze Q3G or rutin to quercetin. These results indicated intestinal epithelial enzymes such as lactase-phrolizin hydrolase or mucosal maltase-glucoamylase might play important roles in the hydrolysis and absorption of flavonol glycosides like EMIQ.

Citrus Bioflavonoids

Mixed preparations of citrus bioflavonoids are the most widely used and least expensive flavonoid sources. However, mixed citrus flavonoids are the least active and generally the least quantified source of flavonoids, as most commercially available sources of mixed citrus flavonoids only contain 50% flavonoids. Preparations containing pure rutin and hesperidin or those that clearly state the levels of rutin and hesperidin are better than products that do not quantify the amount of the individual flavonoid components. HERs are probably the better choice when opting for the benefits in this class of flavonoids.

DOSAGES

The recommended dosage range for quercetin is 200 to 400 mg 20 minutes before meals (three times per day). If quercetin is being used for its anti-inflammatory properties and bromelain supplementation is also indicated, administration with bromelain may enhance absorption. Combination preparations of proteolytic enzymes and flavonoids have been shown to have significant anti-inflammatory activity in experimental studies.[54] If used with bromelain, the amount of bromelain (1800 milk clotting units [mcu]) should be equal to the amount of quercetin.

Dosages used for HERs in double-blind clinical studies for the treatment of venous insufficiency and hemorrhoids ranged from 1000 to 3000 mg/day. This translates to a dosage of citrus bioflavonoids, rutin, and hesperidin of 3000 to 6000 mg/day.

TOXICITY

Quercetin appears to be well tolerated in humans. Carcinogenic and teratogenic studies in rats and rabbits showed that quercetin does not have apparent side effects, even when consumed in large quantities (2000 mg/kg body weight and 5% to 10% of total diet) for long periods of time (up to 2 years).[65-71] In addition, quercetin administration (up to 2000 mg/kg body weight) to pregnant rats had no teratogenic effects.[70] The weight of the available evidence supports the safety of quercetin.[72] As is true of any other compound, allergic reactions may occur. Although uncommon, if they occur, discontinue use. EMIQ has a generally recognized as safe status in the United States.

Citrus bioflavonoids, rutin, hesperidin, and HER appear to be extremely safe and without side effects even during pregnancy.

DRUG INTERACTIONS

Rutin, hesperidin, and HER do not appear to interact with any drug. Quercetin was shown to elevate the plasma concentrations of fexofenadine in healthy subjects, probably via the phosphoglycoprotein (Pgp)-mediated efflux in humans.[72] The Pgp enhances the uptake from the intestine of many drugs, including vinblastine, cyclosporine, digoxin, fexofenadine, and losartan and can also increase the oral bioavailability of drugs like nifedipine, felodipine, verapamil, and terfenadine, as well as inhibit the breakdown of various drugs, particularly caffeine, coumarin, and estrogens. Unlike naringin from grapefruit, quercetin does not appear to impact CYP2C8 activity, and has little possibility of interacting with drugs that are metabolized by this enzyme.[73]

Citrus bioflavonoid preparations generally are not an issue. However, if derived from grapefruit, they may contain naringin and interact with many drugs. Naringin activates Pgp and suppresses the expression of the cytochrome P450 3A4 gene that can enhance oxidative decomposition of some drugs, including drugs used frequently in the therapy of cancer, human immunodeficiency virus, immune disorders, hypertension, and other serious conditions.[74] Avoidance of grapefruit juice and flavonoid preparations containing naringin is recommended where drug interactions are likely.

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CHAPTER 93

Ginkgo biloba (Ginkgo Tree)

Michael T. Murray, ND

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Ginkgo biloba (family: Ginkgoaceae)
Common names: ginkgo tree, maidenhair tree

GENERAL DESCRIPTION

Ginkgo biloba is a deciduous tree that lives up to 1000 years old and grows to a height of 100 to 122 ft and a diameter of 3 to 4 ft. The ginkgo has short horizontal branches with short shoots bearing fan-shaped leaves that measure 2 to 4 inches across. Because the leaf resembles a maidenhair fern, the ginkgo has been called "maidenhair tree." Ginkgo bears an inedible foul-smelling fruit and an edible ivory-colored inner seed that is sold in marketplaces in the Orient. Extracts from the leaves of the ginkgo tree are used medicinally.

CHEMICAL COMPOSITION

The active components of ginkgo leaves are the ginkgo-flavone glycosides or ginkgo heterosides (flavonoid molecules with sugars attached, which are unique to the ginkgo), several terpene molecules unique to ginkgo (ginkgolides and bilobalide), and organic acids.[1]

Ginkgo biloboa extract (GBE) is often standardized to contain 24% flavone glycosides, as these molecules represent a convenient analytic reference group. Although they play a major role in the pharmacologic activity of GBE, other components are also important. The three major backbone flavonoids of the *G. biloba* flavonols are quercetin, kaempferol, and isorhamnetine (Figure 93-1). The glucoside components are glucose and rhamnose, which are present as single sugars or disaccharides.

Other significant flavonoid components of the extract include proanthocyanidins, largely composed of dimers and oligomers of delphinoidine and cyanidine. The major terpene molecules of GBE, which account for 6% of the extract, are the ginkgolides and bilobalide (Figure 93-2). These substances are unique to ginkgo and are not found in any other plants. Other constituents of GBE include a number of organic acids. These compounds contribute valuable properties to the extract by making the usually water-insoluble flavonoid and terpene molecules of ginkgo water soluble.

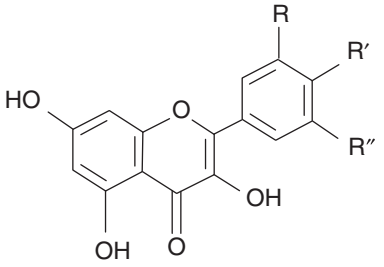
HISTORY AND FOLK USE

G. biloba is the world's oldest living tree species. The sole surviving species of the family Ginkgoaceae, the ginkgo tree can be traced back more than 200 million years to the fossils of the Permian period, and for this reason, it is often referred to as "the living fossil."

Once common in North America and Europe, the ginkgo was almost destroyed during the Ice Age in all regions of the world except China, where it has long been cultivated as a sacred tree.

In the late seventeenth century, Engelbert Kaempfer, a German physician and botanist, became the first European to discover and catalog the ginkgo tree. The flavonoid kaempferol is named after Kaempfer. In 1771, Linnaeus named the tree *G. biloba.*

The ginkgo tree was brought to America in 1784 to the garden of William Hamilton near Philadelphia. The ginkgo is now planted throughout much of the



Compound	R	R′	R″
Kaempferol	H	OH	H
Quercetin	OH	OH	H
Isorhamnetine	OCH_3	OH	H

FIGURE 93-1 The major backbone flavonoids of *ginkgo biloba* extract.

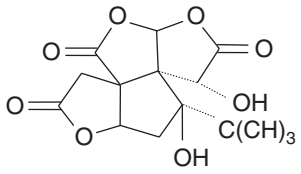


FIGURE 93-2 Bilobalide.

United States as an ornamental tree. The ginkgo, which is the tree most resistant to insects, disease, and pollution, is frequently planted along streets in cities.[1] The first green growth to reappear at the center of Hiroshima in 1946 was the sprout of a ginkgo tree that grew to be a normal, full-size tree.[2]

G. biloba's medicinal use can be traced back to the oldest Chinese materia medica (2800 BC). Ginkgo leaves have been used in traditional Chinese medicine for their ability to "benefit the brain," relieve the symptoms of asthma and coughs, and help the body eliminate filaria.

Ginkgo leaf extracts are now among the leading prescription medicines in both Germany and France, where they account for 1% and 1.5%, respectively, of total prescription sales. In America, it was the top-selling botanical medicine in 1999 with $148 million in sales.[3]

PHARMACOLOGY

The GBE extract standardized to contain 24% ginkgo flavone glycosides has demonstrated remarkable diverse pharmacologic effects. Interestingly, the total extract is more active than single isolated components.[1,4] This suggests synergism between the various components of GBE, an explanation that is well supported in more than 400 clinical and experimental studies using the extract.[1,4-6]

General Effects

GBE exerts profound, widespread tissue effects, including membrane-stabilizing, antioxidant, and free radical-scavenging effects. GBE also enhances the use of oxygen and glucose.[1,4,5]

Red blood cells provide excellent models for evaluating the effects of substances on membrane functions. Red blood cell studies using GBE demonstrated that, in addition to directly stabilizing membrane structures and scavenging free radicals, GBE also enhanced membrane transport of potassium into the cell and sodium out by activating the sodium pump. In essence, GBE leads to better membrane polarization. This effect is particularly important in excitable tissues such as nerve cells.[1,4] GBE prevents metabolic and neuronal disturbances in experimental models of cerebral ischemia.[1,4,7-10] It accomplishes this by enhancing oxygen utilization and increasing cellular uptake of glucose, thus restoring energy production.

GBE also helps to reestablish effective tissue perfusion during hypoxia. Particularly interesting is GBE's ability to normalize the circulation in areas most affected by microembolization, namely, the hippocampus and striatum.[1,4] Discussion of additional nervous tissue actions of GBE is incorporated later in the section on "Clinical Applications". Briefly, GBE promotes an increased nerve transmission rate, improves synthesis and turnover of brain neurotransmitters, normalizes acetylcholine receptors in the hippocampus (the area of the brain most affected by Alzheimer's disease),[1,4] and inhibits β-amyloid deposition.[11]

Vascular Effects

The mechanisms of GBE's vascular effects were investigated using a number of in vivo and in vitro techniques (Table 93-1).[1,4] Isolated vessel techniques allowed for separation of GBE's effects on different parts of the vascular system (e.g., arterial, arteriolar, microcirculatory, venular, and venous components), whereas in vivo studies provided information on the total circulatory phenomena (i.e., GBE's ability to increase the perfusion rate to various regions).

In general, GBE exerts its vascular effects primarily through its effects on the lining of the blood vessels (vascular endothelium) and the system that regulates blood vessel tone. Its vasodilating action is explained by direct stimulation of the release of endothelium-derived relaxing factor and prostacyclin (a beneficial prostaglandin). In addition, GBE inhibits 3′,5′-cyclic guanosine monophosphate phosphodiesterase, an enzyme that results in relaxation of blood vessels.[1,4]

On the venous system, GBE stimulates greater tone, thus aiding the dynamic clearing of toxic metabolites that accumulate during ischemia (Figure 93-3).[1,4]

GBE normalizes circulation by producing tonic effects. These effects are much more apparent in an ischemic vascular area than on a normally perfused area.[12] However, despite intense investigation, many of GBE's tonic effects on vascular components are still largely unexplained. GBE can simultaneously combat the phenomena resulting from vascular spasm and, with the same efficiency, restore circulation to areas subject to vasomotor paralysis.

The importance of this dual action is becoming more apparent in cerebral insufficiency, because single-direction drugs (i.e., vasodilators) can often aggravate the condition by preferentially dilating the healthy areas, thereby deflecting blood and oxygen away from the ischemic area.

Another prime clinical application of GBE's effects on vascular endothelium is early stage diabetic nephropathy. In one 8-week clinical trial, in the GBE group, the brachial arterial endothelium-dependent dilation increased from 4.91% before treatment to 6.78% after treatment, whereas the level of von Willebrand factor decreased from 182% to 128.5%, and nitrous oxide increased from 50.16 to 70.65 μmol/L.[13]

GBE also protects against endothelial damage caused by oxidized low-density lipoprotein cholesterol, thereby preserving endothelial adhesive properties and disruption of ionic homeostasis.[14]

Platelet Effects

GBE and isolated ginkgolides have profound effects on platelet function, including inhibition of platelet aggregation, adhesion, and

TABLE 93-1 **Cellular and Membrane Mechanisms of the Vasoregulatory Effects of *Ginkgo biloba* Extract**

SITE OF ACTION	UPSTREAM FLOW (ARTERIOLE)			EXCHANGE AREA (CAPILLARY)			DOWNSTREAM FLOW (VENOUS)	
Tissue pathologic condition	Arterial spasm	Arterial thrombosis	Vascular atony	Hypoxic vasoparalysis	Capillary hyperpermeability and plasma	Debilitated capillary walls	Venous relaxation and vasoparalysis extravasation	Venular spasms
Effects found with *ginkgo biloba* extract	Vasorelaxation	Diminished platelet hyperaggregability	Restitution of arterial tone	Diminished accumulation of toxic wastes: K^+, CO_2, and lactate	Amelioration of capillary hyperpermeability	Increased capillary resistance	Venous tonic effect	Antagonism of experimental venous spasms
Cellular and membrane mechanisms explaining *ginkgo biloba*'s effects	Release of EDRF from endothelium	Release of PGI_2	Direct effect	Consequence of venous tonic effect	Direct membrane effect	Direct membrane effect	Direct effect	Inhibition of PDE (?)
	Inhibition of PDE	Direct membrane effect	Potentiation of α-adrenergic effects*	Mitochondrial metabolic restart			Indirect effect via α-adrenergic effects	Release of dilating prostaglandins
	Potentiation of α-adrenergic effects*							

CO_2, carbon dioxide; EDRF, endothelium-derived relaxing factor; K, potassium; PDE, phosphodiesterase; PGI_2, prostaglandin I_2.
*Partly through catechol-o-methyl transferase inhibition.

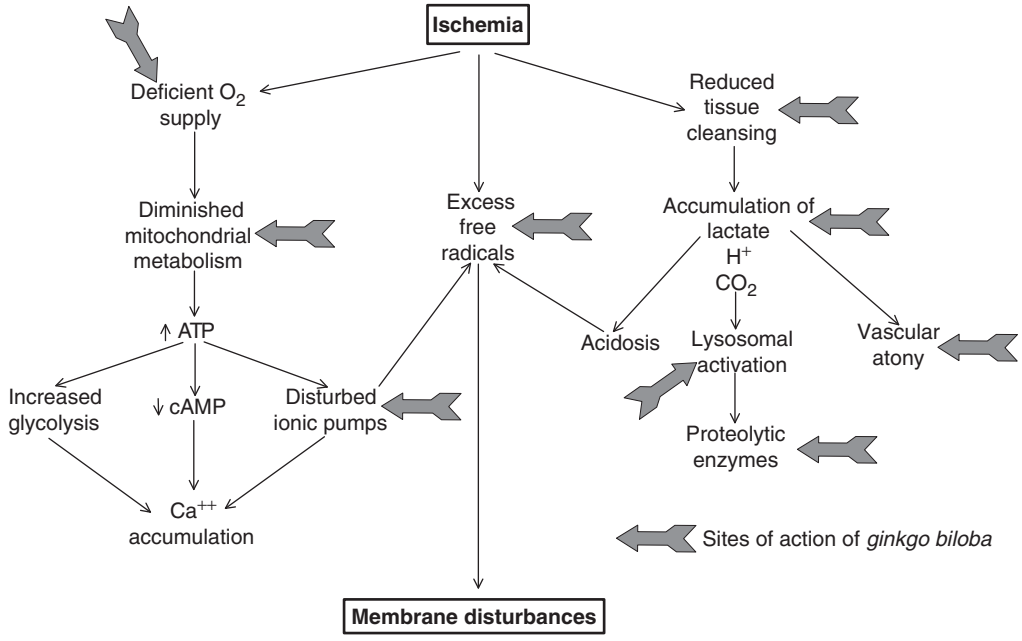


FIGURE 93-3 *Ginkgo biloba* extract's impact on ischemia.

degranulation.[5] These effects appear to be due to direct membrane and antioxidant effects, increased synthesis of prostacyclin, and an antagonism of a substance known as platelet-activating factor (PAF).

GBE and the ginkgolides were shown to be potent inhibitors of PAF.[5,15-17] PAF is a potent stimulator of platelet degranulation and is involved in many inflammatory and allergic processes, including neutrophil activation, increased vascular permeability, smooth muscle contraction including bronchoconstriction and reduction in coronary blood flow. GBE and ginkgolides compete with PAF for binding sites and inhibit the various events induced

by PAF.[1,4,18,19] These actions may be responsible for many of GBE's clinical effects. Interestingly, despite these effects on PAF, GBE exerts no inhibition of platelet aggregation in humans.

Absorption and Distribution of *Ginkgo biloba* Extract

The pharmacokinetics (absorption, distribution, and elimination) of GBE were studied in rats using radiolabeled extracts.[1,4,5] After oral administration, at least 60% of the radiolabeled extract was absorbed. Because blood levels peaked after 1.5 hours, upper gastrointestinal tract absorption was suspected.

The flavonoids appear to have an affinity for organs rich in connective tissues, such as the aorta, eyes, skin, and lungs. Levels of radioactivity in these tissues are two to three times higher than those in blood and decrease little over time. Retained specific activity in the heart is twice that found in the skeletal muscles. Of the glands, the adrenals retain the greatest level of radioactivity.

At 72 hours, the hippocampus and striated bodies show radioactivity five times greater than that of the blood. This deposition pattern, which parallels the circulation improvement observed after ischemia due to blood clotting in rats, is alleviated by GBE extracts. Other areas of the brain such as the cerebral cortex, brain stem, and cerebellum do not show such high levels of radioactivity.

Complexing GBE with phospholipids showed that the bioavailability of quercetin, kaempferol and isorhamnetin were increased significantly, indicating these preparations might offer the best clinical response.[20] For central nervous system effect, complexing GBE with phosphatidylserine may prove superior to phosphatidylcholine (discussed in "Cerebral Vascular Insufficiency and Impaired Mental Performance").[21]

CLINICAL APPLICATIONS

GBE's primary clinical application has been in the treatment of vascular insufficiency. In more than 50 double-blind clinical trials, both patients with chronic cerebral arterial insufficiency and peripheral arterial insufficiency responded favorably to GBE. As described earlier, GBE exerts an extraordinary array of pharmacologic activities that imply a broad spectrum of possible clinical applications, an implication borne out by the new applications of GBE, which are constantly being discovered.

Cerebral Vascular Insufficiency and Impaired Mental Performance

Cerebral vascular insufficiency is an extremely common condition in the elderly of developed countries due to the high prevalence of atherosclerosis (hardening of the arteries). In well-designed studies, GBE displayed a statistically significant regression of the major symptoms of cerebral vascular insufficiency and impaired mental performance. The following symptoms were reported*:

- Short-term memory loss
- Vertigo
- Headache
- Ringing in the ears
- Lack of vigilance
- Depression

The significant regression of these symptoms by GBE suggests that vascular insufficiency may be the major causative factor accounting for these so-called age-related cerebral disorders versus a true degenerative process.

In a comprehensive review, the quality of research on more than 40 clinical studies with GBE in the treatment of cerebral insufficiency was analyzed. The results indicated that GBE was effective in reducing all symptoms of cerebral insufficiency, including impaired mental function (senility). The quality of research was comparable to Hydergine (dihydroergotamine), a Food and Drug Administration-approved drug used in the treatment of cerebral vascular insufficiency and Alzheimer's disease. Eight studies stood out as being extremely well designed and are summarized in Table 93-2.[16-19,23-25]

It appears that by increasing cerebral blood flow, and therefore, oxygen and glucose utilization, GBE offers relief from these presumed "side effects" of aging and may offer significant protection against their development. Furthermore, *G. biloba*'s antiaggregatory effect on platelets offers additional protection against a stroke. This was supported in a clinical study of poststroke patients, which demonstrated that GBE improved blood flow and blood viscosity.[26] In another study using dynamic susceptibility contrast-enhanced magnetic resonance imaging, elderly human subjects taking a modest dosage of 60 mg of GBE for 4 weeks experienced a significant increase of global cerebral blood flow, 15% in white matter and 13% in gray matter.[27]

In addition to improving blood supply to the brain, experimental and clinical studies showed that GBE increased the rate at which information was transmitted at the nerve cell level.[28-30] One study investigated the effects of acute doses of standardized GBE on memory and psychomotor performance in 31 healthy volunteers who were 30 to 59 years old. The study was randomized, double-blind, and placebo-controlled with a five-way crossover design. Ginkgo improved working memory in all volunteers, especially those who were 50 to 59 years old.[31] However, GBE's memory-enhancing effects are not limited to the elderly. In another double-blind study, the reaction time in healthy young women performing a memory test was improved significantly after administration of GBE.[30] GBE complexed with phosphatidylserine might show even better results in these sorts of applications. In one study, 28 healthy young participants received 120 mg GBE, 120 mg GBE complexed with phosphatidylserine (Virtiva), 120 mg GBE complexed with phosphatidylcholine, and a matching placebo, on separate days 7 days apart. Cognitive performance was assessed using the Cognitive Drug Research computerized test battery and Serial Subtraction tasks immediately before dosing and at 1, 2.5, 4, and 6 hours thereafter. In keeping with previous research utilizing the same methodology, 120 mg of GBE was not associated with markedly improved performance on the primary outcomes. However, administration of Virtiva resulted both in improved secondary memory performance and significantly increased speed of memory task performance across all of the postdose testing sessions. Enhancement following GBE complexed with phosphatidylcholine was restricted to a modest improvement in secondary memory performance, which was restricted to one postdose time point.[21]

Alzheimer's Disease

GBE was extensively investigated in cases of dementia, including Alzheimer's disease (AD).* In addition to GBE's ability to increase functional brain capacity via the mechanisms described earlier, it was shown to normalize the acetylcholine receptor in the hippocampus of aged animals, increase cholinergic transmission, inhibit β-amyloid deposition,[11] and address many of the other major

*References 1, 4-6, 16-19, 24, 25.

*References 1, 4-6, 28, 32, 33-35.

TABLE 93-2 **Studies Demonstrating the Significant Regression of the Major Symptoms of Cerebral Vascular Insufficiency Through the Use of *Ginkgo biloba* Extract**

PRINCIPAL AUTHOR	YEAR	DIAGNOSIS	NO. OF PATIENTS	AGE (yr)	DURATION (wks)	DOSAGE (mg)	TYPE	COMPARED WITH:	EFFICACY
Agnoli	1984	CCI	30	60	4	120	DB, CS	Placebo (n = 30)	76%
Arrigo	1984	CCI	80	40-80	7	120	DB, CS	Placebo (n =40)	65%
Augustin	1976	Misc	99	77	24	120	DB	Placebo (n = 90)	44%
Bono	1975	CCI	14	65	5	120	DB	Placebo (n = 14)	65%
		CCI	40	67	5	120	Open	ED (n = 19)	90%
Boudouresques	1975	CCI, CVA	47	35-80	3	120	Open		80%
Choussat	1977	CCI	48	69-95	8	360	Open		60%
Dieli	1981	CCI	20	62	5	160	DB	Placebo (n = 20)	80%
Eckmann	1982	CVA	25	60	4	120	DB	Placebo (n = 20)	92%
Gessner	1983	Senescence	19	57-88	12	120	DB	(Placebo n = 19) Nicergoline (n = 19)	69%
Hofferberth[29]	1989	COS	36	53-69	8	120	DB	Placebo (n = 18)	83%
Israel	1977	D	48	72	8	240	Open		NS
Leroy	1978	CVA	27	78	8	120	Open	Raubasine + ED (n = 24)	74%
Moreau	1975	CCI	30	84	12	120	DB	Placebo (n = 30) ED (*n* = 30)	79%
Pidoux	1983	CCI	12	87	12	160	DB	Placebo	85%
Safi	1977	CCI	20	47-86	2	35 (IV)	Open		76%
Tea	1979	CVA	19	67	8	160	Open		
Terasse	1976	Misc	20	59-84	1-3	17.5 (IV)	Open		55%
Vorberg	1985	CCI	112	55-94	52	120	Open, M		68%
Wackenheim	1977	CCI	50	50	27	160	Open		76%
		CCT	50	50	27	160	Open		72%

CCI, chronic cerebral insufficiency; CCT, cerebral circulation time; COS, cerebral organic syndrome; CS, crossover; CVA, cerebral vascular accident; D, dementia; DB, double-blind; ED, ergot derivatives; M, multicenter; NS, not specified.

elements of AD.[1,4,34] However, although preliminary studies in established AD patients were quite promising, at this time it appears that at best GBE only helps to reverse or merely delay mental deterioration in the early stages of AD. However, even this application was fraught with conflicting results in double-blind studies, that is, in several studies no benefit over placebo was observed in halting cognitive decline.[33,36,37] In more advanced cases of AD, it did not appear that GBE offered any significant advantage over placebo.[33]

The benefits of GBE in early stage AD were quite evident in several double-blind studies and a meta-analysis of studies of more than 6 months' duration.[38] In one study, 216 patients with AD or multi-infarct dementia were given either 240 mg/day of GBE or placebo for 24 weeks.[39] Improvements were noted in several clinical parameters, including the Clinical Global Impressions scale, as shown in Table 93-3. Similar results were seen in another double-blind study, in which the 240-mg dose was administered once daily.[36]

One study that deserves special mention was the first U.S. clinical study on GBE published in the *Journal of the American Medical Association*.[40] The study was conducted at six research centers. Harvard Medical School and the New York Institute for Medical Research approved the design of the study, in which 202 patients with AD were given either a modest dose of GBE (120 mg/day) or a placebo for 1 year. GBE not only stabilized AD but also led to significant improvements in mental function in 64% of the patients. There were no side effects with GBE.

TABLE 93-3 **Effect of *Ginkgo biloba* Extract on Cardiovascular Performance Measures**

	Time of Measurement	
PARAMETER	WEEK 0	WEEK 104
Pain-free walking distance, m	62.9	172.4
Total walking distance, m	113.8	384
Rest flow, mL/100 mL/min	1.6	2.7
Peak flow, mL/100 mL/min	3.7	6.9
Doppler measurement after strain, mm Hg	46.5	72.6

The results from these positive studies indicate that GBE in early stage AD or other causes of dementia may lead to some mild cognitive improvement as well as help enable patients to maintain a normal life and avoid being institutionalized.

It is important to point out that direct comparison studies on ginkgo versus standard pharmaceutic regimens indicated similar efficacy in AD. A comparative analysis of studies of at least 6 months in duration demonstrated that GBE and second-generation cholinesterase inhibitors (tacrine, donepezil, rivastigmine, metrifonate) were equally effective in treating mild to moderate AD.[41] In a meta-analysis of 50 articles that examined the effect of ginkgo on objective measures of cognitive function in

patients with AD, using standardized measures of cognition including the Alzheimer's Disease Assessment Scale–cognitive subscale, it was concluded that GBE produced comparable benefits with standard cholinesterase inhibitors.[42]

In addition to possibly being beneficial in early stage AD, if the mental deficit is due to vascular insufficiency or depression and not AD, GBE is usually effective in reversing the deficit.[1,4-6] Importantly, GBE should be taken consistently for at least 12 weeks to determine its effectiveness. Although some people with AD report benefits within a 2- to 3-week period, most will need to take GBE for a longer period of time.

Tinnitus

Permanent, severe tinnitus is an extremely difficult condition to treat. Previous studies showed contradictory results of GBE in the treatment of tinnitus. For example, in Meyer's study,[43] GBE improved the condition in all patients regardless of prognostic factor. However, in Coles's study,[44] 21 patients with tinnitus took GBE for 12 weeks: 11 reported no change, 4 reported slight to very slight improvement, and 5 reported that their tinnitus was worse. The explanation for these different results is that in Meyer's study the patients had recent-onset tinnitus, whereas in Coles's study, 18 patients had tinnitus for at least 3 years.

A 1994 study of GBE in tinnitus used a two-part design: the first part was an open part, without a placebo control; the second part was a double-blind, placebo-controlled, crossover study.[45] The 80 patients in the open study were referred to the Department of Audiology, Sahlgren's Hospital, Goteborg, Sweden, due to permanent severe tinnitus. Twenty patients reporting a positive effect with GBE (14.6 mg twice daily) after 2 weeks were recruited for the double-blind study. Patients were given either GBE or placebo for 2 weeks and then crossed over into the other group. Evaluation indicated that six patients preferred GBE, seven preferred placebo, and seven had no preference.

On the surface, this study seemingly indicated that GBE was ineffective for permanent, severe tinnitus. However, the study was really designed for the GBE to fail. First, the dosage used (14.6 mg twice daily or 29.2 mg/day) was far less than the standard dosage of 40 mg three times daily (or roughly four times the daily dosage used in the study). Secondly, in studies on patients with cerebral vascular insufficiency, it is well established that GBE often takes at least 2 weeks before benefits become apparent. The longer that GBE is used, the more obvious the benefit. In a condition like permanent, severe tinnitus, 2 to 4 weeks is simply not enough time. However, given the small, insufficient dosage, it probably would not have mattered if the subjects had been studied for a longer period of time.

A more recent study of 1121 healthy people between 18 and 70 years old with tinnitus that was comparatively stable showed no benefit over placebo when given 50 mg of standardized ginkgo three times a day. Although these data were discouraging, it should be noted that outcome measures were obtained through questionnaires and phoned-in patient reports, without objective audiometric metering.[46]

The degree to which GBE is of benefit in permanent, severe tinnitus remains to be determined, but given GBE's excellent safety profile, it is certainly worth a try.

Cochlear Deafness/Ototoxicity

Ischemia is usually the underlying factor in acute cochlear deafness. GBE improved recovery in cases of acute cochlear deafness due to unknown factors or due to sound trauma or pressure (barotrauma).[47] GBE was also shown to be a protective agent against ototoxicity from treatment with the chemotherapeutic agent cisplatin, without decreasing antineoplastic efficacy.[48]

Senile Macular Degeneration and Diabetic Retinopathy

GBE appears to quite effectively address the multifactorial pathophysiology of senile macular degeneration, the most common cause of blindness in adults. In double-blind studies, GBE demonstrated a statistically significant improvement in long-distance visual acuity in both macular degeneration and diabetic retinopathy.[1,4,49]

GBE demonstrated impressive protective effects against free radical damage to the retina in experimental studies. Furthermore, GBE was shown to prevent diabetic retinopathy in diabetic rats, suggesting it might have a protective effect in human diabetics as well.[1,4]

Peripheral Arterial Insufficiency

Peripheral arterial disease's primary lesion is the same cholesterol-containing plaque that is responsible for other conditions associated with atherosclerosis (e.g., coronary artery disease, cerebral vascular insufficiency).

The arterial obstruction or narrowing causes a reduction in blood flow during exercise or at rest. Clinical symptoms are caused by the consequent ischemia. The most common symptom of peripheral arterial disease is pain during exertion as a result of intermittent claudication. The pain usually occurs in the calf and is described as cramping, tightness, or severe fatigue. The pain is usually bilateral. The cause of the pain is not only reduced oxygen delivery but also an increase in the production of toxic metabolites and cellular free radicals. These free radicals accumulate and react with the lipid constituents of the cell membrane.

Pain at rest indicates serious reduction in resting blood flow. It is obviously a sign of severe disease. The pain may be localized to one or more toes, or it may have a stocking-type distribution. The character of the pain is usually described as burning or gnawing and is generally worse at night. Cyanosis or pallor of the extremity is usually apparent. In moderate to severe narrowing of the artery, there are trophic changes, including a dry, scaly, and shiny epidermis. Hair may disappear, and the toenails may become brittle, ridged, and deformed.

The standard medical approach to peripheral vascular disease and intermittent claudication includes avoidance of tobacco (which causes vasoconstriction), a regular exercise program consisting of walking, and the prescription drugs pentoxifylline (Trental) or cilostazol (Pletal). Surgery is also an option, although most patients with intermittent claudication need not take this risk.[50]

Trental has emerged as the "drug of choice" in the standard medical treatment of intermittent claudication.[51] A total of 17 placebo-controlled trials showed that Trental prolongs the total and pain-free walking distance in patients with intermittent claudication. However, the level of improvement (approximately 65% for pain-free walking distance) is less than that achieved with exercise or with GBE.

In nine double-blind, randomized clinical trials of GBE versus placebo in two matched groups of patients with peripheral arterial insufficiency of the leg, GBE was shown to be quite active and superior to placebo (eight studies) and equal to pentoxifylline (one study).[1,4,5,52-57] Not only did measurements of pain-free

walking distance (75% to 110%) and maximum walking distance (52.6% to 119%) dramatically increase, but plethysmographic and Doppler ultrasound measurements also demonstrated increased blood flow through the affected limb. Blood lactate levels also dropped.[8-10,12,15-19,22]

The demonstration that GBE improves limb blood flow, as well as improved walking tolerance (in studies following strict methodology and with sufficient patients for reliable evaluation), indicates that GBE is far superior to pentoxifylline, cilostazol, and standard medical therapy in peripheral arterial insufficiency. This includes other peripheral vascular disorders such as diabetic peripheral vascular disease, Raynaud's disease, acrocyanosis, and postphlebitis syndrome. In the treatment of intermittent claudication, the effects are somewhat modest, especially compared with exercise programs.[58-60]

The longer the period over which GBE is used, the greater the benefit. Table 93-3 summarizes a 2-year trial of GBE (160 mg/day) in the treatment of peripheral arterial disease (Fontaine stage IIb). Pain-free walking distance increased by more than 270%.[1]

The usual daily dosage of GBE is 120 mg (40 mg three times a day); however, some of the studies employed a dosage of 160 mg/day, including the study summarized in Table 93-3. Given the excellent safety profile of GBE, dosages similar to those used in cerebral vascular insufficiency, e.g., 240 mg/day, may prove to be more effective.

Sexual Dysfunction

Most cases of impotence (erectile dysfunction) are due to impaired blood flow to erectile tissue. Evidence indicated that GBE might be extremely beneficial in the treatment of erectile dysfunction due to lack of blood flow.[61] Sixty patients with proven erectile dysfunction who had not reacted to papaverine injections up to 50 mg were treated with 60 mg/day GBE for 12 to 18 months. The penile blood flow was reevaluated by duplex sonography every 4 weeks.

The first signs of improved blood supply were seen after 6 to 8 weeks. After 6 months' therapy, 50% of the patients regained potency, and in 20% a new trial of papaverine injection was then successful; 25% of the patients showed an improved blood flow, but papaverine was still not successful. The remaining 5% were unchanged.

According to preliminary study results, GBE appears to be effective in the treatment of erectile dysfunction due to lack of blood flow. The improvement of the arterial inflow to erectile tissue is assumed to be due to the known effect of GBE on enhancing blood flow through both arteries and veins without any change in systemic blood pressure.

Ginkgo's effects are more apparent with long-term therapy, and better results may have been obtained with a 120 mg/day dose to take full advantage of its effect on improving blood flow.

With the current epidemic use of antidepressant medications, including selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, and tricyclics for various conditions, antidepressant-induced sexual dysfunction is becoming a prevalent side effect. A study of 33 women and 30 men showed an overall 84% effectiveness rate at curbing symptoms, with GBE exhibiting a positive effect on all four phases of the sexual response cycle: desire, excitement (erection and lubrication), orgasm, and resolution (afterglow).[62] This research group also demonstrated the efficacy of ginkgo for these side effects after other management trials of cyproheptadine, yohimbine, amantadine, and buspirone hydrochloride failed.[63]

In a study in women with sexual arousal disorder, a single dose of 300 mg GBE had a small but significant facilitatory effect on physiologic, but not subjective, sexual arousal compared with placebo in 99 sexually dysfunctional women. Long-term GBE administration at this dosage did not significantly enhance arousal responses beyond placebo. The authors concluded that (1) neither short- or long-term administration of GBE alone substantially impacted sexual function in women, (2) a substantial placebo effect on sexual function existed in women with sexual concerns, and (3) teaching women to focus on genital sensations during sex enhanced certain aspects of women's sexual functioning.[64]

Premenstrual Syndrome and Idiopathic Cyclic Edema

Premenstrual syndrome (PMS) is often characterized by fluid retention, vascular congestion, increased capillary permeability, and breast tenderness. A recent double-blind, placebo-controlled study sought to determine the effectiveness of GBE on these symptoms.[65] The population studied was a group of 165 women between the ages of 18 and 45 years who had congestive symptoms for at least three cycles. The patients were then assigned to receive either GBE (80 mg twice daily) or placebo from the sixteenth day of the period to day 5 of the next. On the basis of extensive symptom evaluation by patients and physicians, it was concluded that GBE was effective against congestive symptoms of PMS, particularly breast pain or tenderness. Patients taking the GBE also noted improvements in neuropsychologic assessments. These results indicated that GBE might hold some promise in the treatment of PMS.

Antidepressant Effects

The ability of GBE to improve general mood in patients with cerebral vascular insufficiency in double-blind studies led researchers to begin investigating GBE's antidepressive effects. In a recent double-blind study, 40 elderly patients (ranging from 51 to 78 years old) with depression who had not benefited fully from standard antidepressant drugs were given either 80 mg of GBE three times daily or a placebo.[66] By the end of the eighth week, the total score of the Hamilton Rating Scale for Depression in the GBE group dropped from 14 to 4.5. In comparison, the placebo group dropped from 14 to only 13. This study indicated two things:

1. GBE can be used with standard antidepressants.
2. GBE enhanced the effectiveness of standard antidepressants, particularly in patients older than 50 years of age.

Importantly, the dosage used in the study (80 mg three times daily) was higher than the standard dosage of 40 mg three times daily.

See the previous section on "Sexual Dysfunction" regarding ginkgo's ability to decrease unwanted side effects of standard antidepressant medications.

Allergies/Asthma

Mixtures of ginkgolides, as well as GBE standardized to contain 24% ginkgoflavonglycosides, showed clinical effects in allergic conditions due to their inhibition of PAF, a key chemical mediator in asthma, inflammation, and allergies.[18,19]

In one double-blind placebo study, the ability of a mixture of ginkgolides to block the effects of PAF when PAF was injected into the skin was investigated.[18] Normally, when PAF is injected it causes an immediate formation of a hive (classic wheal and flare reaction). However, if the ginkgolide mixture (120 mg) was given

before PAF injection, it effectively counteracted the wheal and flare reaction. Specifically, the ginkgolide reduced the flare (reddened) area by a mean of 62.4% and the wheal (hive) volume by a mean of 60%.

A study from the Qingdao Hospital of Integrated Traditional and Western Medicine in Shandong, China, assessed the efficacy of an oral ginkgo liquor to alleviate airway hyperreactivity. It was found that the treatment significantly reduced airway inflammation and improved pulmonary function and clinical symptoms of asthmatic patients.[67]

Mixtures of ginkgolides, as well as purified ginkgolides, are under investigation in several European countries. The hope is that they will be proven clinically effective in eczema, allergies, and many other conditions in which PAF plays a central role.[18,19]

Raynaud's Disease

Most common in young women (60% to 90% of reported cases), Raynaud's disease is a condition of vasospastic response that causes areas of the body, including the fingers, toes, and tips of the nose and ears to feel numb and cool in response to cold temperatures or stress. During a Raynaud attack, these blood vessels that supply the skin narrow, limiting blood circulation to affected areas. Ginkgo's vasodilating activity is most likely responsible for its effectiveness in treating this problem.

Given the side-effect profile of pharmaceutic treatments for Raynaud's disease, a recent double-blinded, placebo-controlled study evaluated the use of GBE to treat this difficult condition. A 10-week trial revealed a 56% reduction in the number of weekly attacks, whereas placebo reduced the number by 27%.[68] The World Health Organization recommended the use of ginkgo in Raynaud's disease, acrocyanosis, and postphlebitic syndrome.[69]

High Altitude Sickness

A recent study demonstrated the usefulness of ginkgo to prevent symptoms of acute mountain sickness. For a Himalayan expedition of moderate altitude with gradual exposure, 44 volunteers were divided into a placebo group and a group that received 80 mg of ginkgo twice a day. No subject in the ginkgo group developed acute mountain sickness, unlike 40.9% of subjects in the placebo group. Vasomotor disorders of the extremities were also prevented in the ginkgo group.[70]

FUTURE APPLICATIONS OF *Ginkgo biloba* EXTRACT

Experimental studies, as well as some preliminary clinical evidence, indicate that GBE may be of benefit in cases of angina, congestive heart failure, and acute respiratory distress syndrome. Its action on PAF may also make it useful for a great number of other applications in addition to allergies, including various types of shock, thrombosis, graft protection during organ transplantation, multiple sclerosis, and burns.[1,4]

DOSAGE

Most of the clinical research on *G. biloba* used a standardized extract, containing 24% ginkgo flavone glycosides, at a dose of 40 mg three times a day. However, some studies used the higher dosage of 80 mg two to three times daily.

Devising a dosage schedule using other forms of ginkgo is difficult due to extreme variation in the content of active compounds in dried leaf and crude extracts. Whatever form of ginkgo is used, it appears to be essential that it is standardized for content and activity. For example, a standard 1:5 tincture obtained from the highest possible flavonoid content crude ginkgo leaf would require 1 oz/day to provide the equivalent dosage level of the standardized extract.

Clinical research clearly shows that GBE should be taken consistently for at least 12 weeks to determine effectiveness. Although most people report benefits within 2 to 3 weeks, some may take longer to respond.

TOXICITY

GBE is extremely safe, and side effects are uncommon. In 44 double-blind studies involving 9772 patients taking GBE, the number of side effects reported was extremely small. The most common side effect, gastrointestinal discomfort, occurred in only 21 cases, followed by headache (seven cases) and dizziness (six cases).[4-6] Due to its inhibition of PAF, many practitioners are concerned that ginkgo may increase bleeding risk when used concurrently with warfarin (Coumadin), aspirin, and other antiplatelet therapies. However, a study evaluating the use of ginkgo and warfarin concurrently revealed no change in the international normalized ratio, which is the blood test chosen to monitor the patient's possible bleeding risk in response to anticoagulation therapy.[71] Results from controlled studies consistently indicated that ginkgo did not significantly impact bleeding time or platelet aggregation nor adversely affect the safety of coadministered aspirin or warfarin.[72]

In contrast to the tolerance of the leaf extract, contact with or ingestion of the fruit pulp produced severe allergic reactions.[73,74] Contact with the ginkgolic acids in the fruit pulp causes erythema and edema, with the rapid formation of vesicles accompanied by severe itching. This is similar to an allergic reaction to the poison ivy-oak-sumac group, suggesting cross-reactivity between *G. biloba* fruit and this family. Ingestion of as little as two pieces of fruit pulp was reported to cause severe gastrointestinal irritation from the mouth to the anus. Because the ginkgo leaf does have a low level of irritative ginkgolic acids, animal studies were conducted to examine the possibility of adverse reactions from using ginkgo leaf extract. It was concluded that extracts of *G. biloba* taken orally were considered safe.[74]

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CHAPTER 94

Glucosamine

Michael T. Murray, ND

CHAPTER CONTENTS

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GENERAL DESCRIPTION

Glucosamine is a simple molecule, manufactured in the body from glucose and an amine. One of the primary physiologic roles of glucosamine is in the joints, where it stimulates the manufacture of glycosaminoglycans (GAGs), key structural components of cartilage. Glucosamine also promotes the incorporation of sulfur into cartilage. Because of this effect, glucosamine sulfate (GS) is thought to be the best source of glucosamine (Figure 94-1).

As some people age, they apparently lose the ability to manufacture sufficient levels of glucosamine. The result is that synthesis of GAGs does not keep up with degradation. The inability to manufacture glucosamine at an adequate rate has been suggested to be the major factor leading to osteoarthritis (OA).

There are no food sources of glucosamine. Commercially available sources of glucosamine are derived from chitin—the exoskeleton of shrimp, lobsters, and crabs.

AVAILABLE FORMS

Glucosamine is commercially available as GS, glucosamine hydrochloride, and *N*-acetylglucosamine (NAG). GS, the only form of glucosamine that has been the subject of more than 300 scientific investigations and more than 20 double-blind studies, is the preferred form. GS has also been used by millions of people worldwide and is registered as an aid in OA in 70 countries.

When authors or manufacturers discuss glucosamine hydrochloride or NAG, they often cite references of clinical studies that used GS or the combination of glucosamine hydrogen chloride (HCl) and chondroitin sulfate. On the basis of currently available clinical evidence, it appears that only GS provides proven clinical effectiveness when administered as an isolated agent (numerous studies showed the combination of glucosamine HCl and chondroitin sulfate to be effective). It does not appear to matter, however, if the GS is stabilized with either sodium or potassium.[1]

GLUCOSAMINE SULFATE VERSUS *N*-ACETYLGLUCOSAMINE

NAG differs from GS in that instead of a sulfur molecule, NAG has a portion of an acetic acid molecule attached to it. GS and NAG are different molecules and appear to be handled by the body differently. Companies marketing NAG claim that this form is better absorbed, more stable, and better used than GS. These contentions are without support in the scientific literature. Detailed human studies on the absorption, distribution, and elimination of orally administered GS show an absorption rate as high as 98% and that, once absorbed, it is then distributed primarily to joint tissues, where it is incorporated into the connective tissue matrix of cartilage, ligaments, and tendons.[2,3] In addition, there are impressive clinical studies on thousands of patients. In contrast, the only clinical study with NAG used was as a polymer that is not yet available commercially.[4] Polymerization is thought to be necessary due to the poor oral availability of unbound NAG.

Further evidence of the superiority of GS to NAG is offered by studies on laboratory animals. Several studies demonstrated that glucosamine absorption and utilization are at least twice that of NAG.[5-16] The researchers concluded that glucosamine was a more efficient precursor of macromolecular hexosamine (GAG) than NAG. It is possible that NAG does not penetrate the cell membranes and, as a result, is

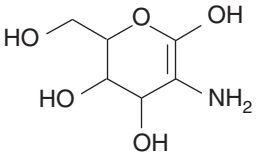


FIGURE 94-1 Glucosamine.

unavailable for incorporation into glycoproteins and mucopolysaccharides.[7] The body preferentially uses GS rather than NAG. This preference appears largely due to the active processes that enhance absorption of GS in the intestines.[17]

The absorption of NAG by humans is poor for several reasons:

- NAG is quickly digested by intestinal bacteria.
- NAG binds with dietary lectins in the gut, resulting in a lectin-NAG complex, which is excreted in the feces.
- A large percentage of NAG is metabolized by intestinal cells.

In addition to the question of absorption, several studies showed that the articular tissue cannot use NAG as well as it does glucosamine.[6,7] These absorption and utilization problems suggest NAG is highly unlikely to possess the same kind of antiarthritic and anti-inflammatory properties that GS has been shown to possess.

GLUCOSAMINE SULFATE VERSUS GLUCOSAMINE HYDROGEN CHLORIDE

Research showed that sulfur is an extremely important component in the therapeutic effect of GS, and its substitution is likely to decrease the efficacy of supplemental glucosamine.[18] Sulfur is an essential nutrient for joint tissue, where it functions in the stabilization of the connective tissue matrix of cartilage, tendons, and ligaments. Even healthy humans have low serum sulfate (0.3 to 0.4 mM) and synovial sulfur levels, but in OA these concentrations are even lower. As far back as the 1930s, researchers demonstrated that individuals with arthritis were commonly deficient in this essential nutrient.[19,20] Restoring sulfur levels brought about significant benefit to these patients.[19] In addition to sulfur playing a critical role in the manufacture of GAGs like chondroitin sulfate and keratan sulfate, sulfur was shown to inhibit the various enzymes that lead to cartilage destruction in OA (e.g., collagenase, elastases, and hyaluronidase).[18,21]

Because one of the primary effects of GS is to promote the manufacture of GAGs, a lack of the sulfur moiety may mean less GAG synthesis when glucosamine HCl is used. Therefore, it is unlikely that glucosamine HCl will show the same excellent clinical results achieved with GS, because it lacks this critical element.

Results from double-blind studies indicated that glucosamine HCl might be no more effective than a placebo in relieving OA. One double-blind, placebo-controlled, 10-week study examined the effects of glucosamine HCl in patients with OA of the knee.[22] Patients received either 500 mg of glucosamine HCl or a placebo three times daily. Forty-five patients received glucosamine HCl, whereas 53 received the placebo. The results indicated that 49% of patients who received glucosamine HCl felt they had improved compared with 45% of the placebo group, who said they felt improved. However, the difference between the two groups was not statistically significant. What these results call into question is the viability of glucosamine HCl as an effective form of glucosamine. Unfortunately several large, well-publicized studies utilized this form. For example, the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) study involved 1583 patients with symptomatic knee OA.[23] Patients were randomized to receive 1500 mg of glucosamine daily, 1200 mg of chondroitin sulfate daily, both glucosamine and chondroitin sulfate (same dosages as the single arms), 200 mg of celecoxib daily, or placebo for 24 weeks. Mean age of the patients was 59 years, and 64% were women. Overall, glucosamine and chondroitin sulfate were not significantly better than placebo in reducing knee pain by 20%. Compared with the rate of response to placebo (60.1%), the rate of response to glucosamine was 3.9% higher, the rate of response to chondroitin sulfate was 5.3% higher, and the rate of response to combined treatment was 6.5% higher. The rate of response in the celecoxib control group was 10.0% higher than that in the placebo control group. For patients with moderate-to-severe pain at baseline, the rate of response was significantly higher with combined therapy than with placebo (79.2% vs. 54.3%).

In an analysis of GAIT subjects with a radiographic confirmation of OA, the odds of achieving a 20% reduction in Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain score, compared with placebo, were celecoxib: 1.21, glucosamine: 1.16, combination glucosamine/chondroitin sulfate: 0.83, and chondroitin sulfate alone: 0.69. These rates were not statistically significant.[24,25]

CLINICAL APPLICATIONS

The primary use for GS is in the treatment of OA. This application has significant support in the medical literature because numerous double-blind studies have shown GS to produce much better results compared with non-steroidal anti-inflammatory drugs (NSAIDs), placebo, or acetaminophen in relieving the pain and inflammation of OA.[26-30] Although some of the studies comparing GS with NSAIDs or acetaminophen showed similar reduction in pain and symptom scores, only GS improved indexes of joint function or markers showing improvement of cartilage structure. Typically, the advantages of GS over these other treatments were seen after 2 to 4 weeks of use, but there is some evidence that the longer GS is used, the greater the therapeutic benefit.

Not all studies showed clear positive results, because a few exist that showed no greater benefit for GS over placebo in improving symptom scores.[31-36] However, it must be kept in mind that the placebo response in OA is quite high and may confound the true benefit of GS and other approaches to OA. Fortunately, there were several studies that showed objective improvements (discussed in the immediately following paragraphs).

The two longest placebo-controlled trials were 3 years in duration. The results from these studies showed, quite convincingly, that GS slowed down the progression of OA and in many cases produced regression of the disease, as noted by radiologic improvements, and significantly reduced the incidence of total joint replacement even after as much as 5 years after GS discontinuation.[36-39]

In the first long-term study, 212 patients with knee OA were randomly assigned 1500 mg oral GS or placebo once daily for 3 years. Weight-bearing anteroposterior radiographs of each knee in full extension were taken at enrollment and after 1 and 3 years. Mean joint-space width of the medial compartment of the tibiofemoral joint was assessed by digital image analysis, whereas minimum joint-space width (i.e., at the narrowest point) was measured by visual inspection with a magnifying lens. Symptoms were scored by the WOMAC OA index. The 106 patients on placebo had a progressive joint-space narrowing, with a mean joint-space loss after 3 years of –0.31 mm. No significant joint-space loss occurred in the 106 patients on GS (–0.06 mm). Similar results were reported with minimum joint-space narrowing. As assessed by WOMAC scores, symptoms worsened slightly in

patients on placebo compared with the clinical improvement observed in the group that received GS.

To investigate the relationship between baseline radiographic severity of knee OA and the importance of long-term joint-space narrowing in more detail, a subanalysis of data from the 3-year trial was performed.[40] Measurements of mean joint-space width, assessed by a computer-assisted method, were performed at baseline and after 3 years on weight-bearing anteroposterior knee radiographs. Those who received GS demonstrated a trend for significant reduction in joint-space narrowing in patients in the highest quartile of baseline mean joint-space width (>6.2 mm). In these patients, a joint-space narrowing of 14.9% occurred in the placebo group after 3 years, whereas patients from the GS group only experienced a narrowing of 6%.

Of 414 participants randomized in the two long-term studies, 319 were postmenopausal women. In a subset analysis, after 3 years, postmenopausal participants in the GS group showed no joint-space narrowing, whereas participants in the placebo group experienced a narrowing of –0.33 mm. Percent changes after 3 years in the WOMAC index showed an improvement in the GS group (–14.1%) and a trend for worsening in the placebo group (5.4%). These results indicated that postmenopausal women might be especially responsive to GS.[36]

Additional insight into who might best respond to GS was provided in another analysis from this 3-year study that examined the ability of GS to improve a biochemical marker of collagen type II degradation (CTX-II).[41] At baseline, the 212 patients had an average concentration of urinary CTX-II of 222.4 ng/mmol creatinine. This was significantly above the CTX-II levels measured in urine samples from 415 healthy controls (169.1 ng/mmol). Although there was no significant difference in the CTX-II response in the placebo group and the glucosamine-treated group, those with high cartilage turnover presented a significant decrease in CTX-II after 12-month glucosamine treatment.

The group with CTX-II concentrations above normal average plus 1 standard deviation decreased 15.5% after 12-month therapy. The change in CTX-II in these patients correlated with the change in average joint-space width observed after 36 months. Increased baseline levels of CTX-II in the placebo group were associated with a worsening of the WOMAC index. These data indicated that measurement of urinary collagen type II C-telopeptide fragments enabled the identification of patients with high cartilage turnover, who appeared to be most responsive to GS therapy.

In the second study, 202 patients with knee OA were randomized to receive oral GS (1500 mg once a day) or placebo. Changes in computed tomographic radiographic minimum joint-space width were measured in the medial compartment of the tibiofemoral joint, and symptoms were assessed using the Lequesne (an index of severity of osteoarthritis) and WOMAC. Although symptoms improved more significantly in the GS group, the most telling result was the fact that progressive joint-space narrowing with placebo use was –0.19 mm after 3 years, whereas there was no average change with GS use (an increase of 0.04 mm was the average).[38]

Another study sought to determine changes in levels of serum cartilage oligomeric matrix protein (COMP) and urine c-telopeptide of CTX-II as markers for cartilage turnover in patients with OA of the knee, in response to muscle strength training in combination with treatment with glucosamine, ibuprofen, or placebo. All three groups increased their muscle strength after 12 weeks of strength training. Glucosamine's reduction of serum COMP was statistically significant compared with both placebo and ibuprofen; the mean reduction with glucosamine was 13% versus placebo and 17% versus ibuprofen. This suggested an effect by glucosamine on the response of the OA cartilage to a period of joint loading in humans with knee OA. No effect was noted on CTX-II.[42]

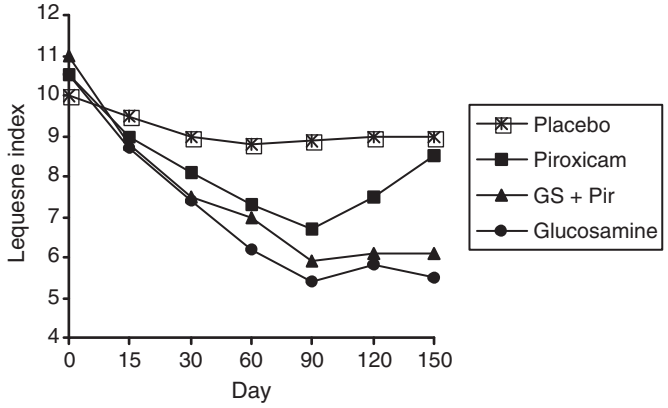


FIGURE 94-2 Symptom relief (Lequesne index) from glucosamine compared with piroxicam and placebo.

Several head-to-head, double-blind studies also showed that GS produced much better results compared with NSAIDs and analgesics in relieving the pain and inflammation of OA, despite the fact that GS exhibited little direct anti-inflammatory effect and no direct analgesic or pain-relieving effects.[43-47] Although NSAIDs and analgesics, like acetaminophen, offer purely symptomatic relief, and NSAIDs may actually promote the disease process, GS appears to address the cause of OA. By promoting cartilage synthesis, thus treating the root of the problem, GS not only relieves the symptoms but also helps the body to repair damaged joints. The clinical effect is impressive, especially when glucosamine's safety and lack of side effects are considered.

In one of the earlier comparative studies in which GS (1500 mg/day) was compared with ibuprofen (1200 mg/day), pain scores decreased faster in the first 2 weeks in the ibuprofen group. However, by week 4, the group that received GS experienced a significantly better improvement than the ibuprofen group.[43] Physicians rated the overall response as good in 44% of the GS-treated patients compared with only 15% of the ibuprofen group.

Additional studies designed to further evaluate the comparative effectiveness of GS to NSAIDs provided even better evidence.[44-46,48] One study consisted of 200 subjects with OA of the knee given either GS (500 mg three times daily) or ibuprofen (400 mg three times daily) for 4 weeks.[44] Consistent with previous studies, the ibuprofen group experienced quicker pain relief. However, by the end of the second week, the group taking GS experienced results as good as those in the ibuprofen group with one major exception—although the rate of side effects with glucosamine were mild and only affected 6% of the group, ibuprofen produced more significant side effects much more frequently, with 35% of the group experiencing them.

In another study, 329 patients were given 1500 mg GS, 20 mg piroxicam, both compounds, or a placebo for 90 days.[45] The main efficacy variable was represented by the Lequesne index, a standard method of assessing disease activity. As can be seen in Figure 94-2, the results of the study were strikingly in favor of GS alone.

These impressive results with GS were achieved without side effects. Patients on GS had fewer side effects than the placebo and no dropouts. (Table 94-1 provides the side effect and dropout values among the four groups.)

TABLE 94-1 **Side Effects and Dropouts from Glucosamine Compared with Piroxicam and Placebo**

	PLACEBO	GS	PIROXICAM	GS + PIROXICAM
Incidence of side effects	24.4%	14.8%	40.9%	5.9%
Dropouts	3	0	20	3

TABLE 94-2 **Results from a Double-Blind Study of Glucosamine Sulfate Versus Ibuprofen**

TIME	GLUCOSAMINE SULFATE	IBUPROFEN
Knee Pain (Average Score)		
Before treatment	8.42	8.46
Wk 2	5.54	5.63
Wk 4	3.60	4.18
2 wk after treatment	3.26	3.84
Knee Swelling (Average Score)		
Before treatment	1.43	1.48
Wk 2	0.77	0.89
Wk 4	0.47	0.48
2 wk after treatment	0.36	0.54

	Glucosamine sulfate		Ibuprofen	
CLINICAL IMPROVEMENT (EFFECTIVENESS)	AFTER 4 WK	AFTER 6 WK	AFTER 4 WK	AFTER 6 WK
Symptom free	45%	55%	32%	36%
Improved	39%	32%	45%	41%
Unchanged	11%	7%	15%	14%
Worsened	5%	6%	8%	9%

SIDE EFFECTS	GLUCOSAMINE SULFATE	IBUPROFEN
Side effects	6%	16%
Dropouts	0%	10%

Data from Qiu GX, Gao SN, Giacovelli G, et al. Efficacy and safety of glucosamine sulfate versus ibuprofen in patients with knee osteoarthritis. Arzneimittelforschung 1998;48:469-474.

In another study on OA of the knee (Table 94-2), GS showed comparable symptomatic relief, but was better tolerated and produced residual benefit after discontinuation.[46]

Another study showed an obvious advantage of GS over ibuprofen in patients diagnosed with temporomandibular joint (TMJ) OA. In the double-blind study, 40 women and 5 men received either GS (500 mg) or ibuprofen (400 mg) three times daily for 90 days. Fifteen patients taking GS (71%) and 11 taking ibuprofen (61%) improved, with positive clinical response taken as a 20% decrease in TMJ pain and function. Between-group comparison revealed that patients taking GS had a significantly greater decrease in TMJ pain with function, effect of pain, and acetaminophen used between days 90 and 120 compared with patients taking ibuprofen.[48]

In addition to showing benefit in double-blind studies, oral GS was shown to offer significant benefit in an open trial involving 252 doctors and 1506 patients in Portugal.[49] This large study provided valuable clinical information on the appropriate use of GS. The patients received 500 mg of GS three times a day over a mean period of 50 days. Symptoms of pain at rest, on standing, and on exercise, as well as limited active and passive movements, all improved steadily throughout the treatment period. Objective therapeutic efficacy was rated by doctors as "good" in 59% of the patients and "sufficient" in a further 36%. Although not a controlled study, a 95% response rate is impressive. The results with GS were rated by both doctors and patients as being significantly better than those obtained with previous treatment, including NSAIDs, vitamin therapy, and cartilage extracts. GS produced good benefit in a significant portion of patients who did not respond to any other medical treatment.

In the study, obesity was associated with a significant shift from good to fair. This finding may indicate that higher dosages may be required for obese individuals or that oral glucosamine is not enough to counteract the added stress of obesity on the joints. Patients with peptic ulcers and individuals taking diuretics were also associated with a shift from good to sufficient in efficacy, as well as tolerance. Individuals with peptic ulcers should take GS with foods. Individuals taking diuretics may need to increase the dosage to compensate for reduced effectiveness. The improvement with glucosamine lasted for 6 to 12 weeks after the end of treatment.



USE IN ATHLETES AND AS A PREVENTIVE MEASURE

GS may have a role as a preventive measure against the development of OA, especially in athletes subjected to joint strain, as well as an aid to recover from minor acute joint injuries (i.e., sprains and strains). One study investigated the chondroprotective action of GS on articular cartilage in athletes, the levels of biomarkers for CTX-II, and type II collagen synthesis (CPII) compared between soccer players and non-athlete controls before and after taking GS or placebo. CTX-II and CPII levels were substantially elevated in soccer players compared with those in controls, indicating that cartilage metabolism (CTX-II and CPII) was increased in soccer players. GS administration (1.5 and 3 g/day for 3 months) significantly decreased the CTX-II level; however, the effect disappeared after withdrawal of administration. In contrast, GS administration did not essentially affect the increased level of CPII. Furthermore, cartilage damage was evaluated using the ratio of CTX-II/CPII. The ratio in soccer players was significantly higher than that in controls, suggesting that CTX-II was relatively enhanced compared with CPII in soccer players than in control students. Of tremendous importance, the ratio was reduced by glucosamine administration but returned to the pre-administration level after GS supplementation ended. Together, these observations suggest that glucosamine is expected to exert a chondroprotective action in athletes (soccer players) by preventing CTX-II but maintaining CPII, although the effect is transient and disappears after stopping use.[51]

In a study designed to examine the effects of 4 weeks of glucosamine administration on the functional ability and the degree of pain intensity in competitive male athletes after acute knee injury, 106 patients with an acute knee injury were randomized to either take GS (1500 mg/day day) or a placebo for 28 days.[52] No significant difference was found between the glucosamine and placebo groups in mean pain intensity scores for resting and walking, and degree of knee swelling at the 7-, 14-, 21-, and 28-day assessment. There was no significant difference between passive knee flexibility at the 7-, 14-, and 21-day assessment, but after 28 days

of treatment, the patients from the glucosamine group demonstrated significant improvement in knee flexion and extension compared with the placebo group. These results showed modest benefits and suggest use, but certainly additional measures should be used to speed recovery.

DOSAGE

The standard dosage for GS is 1500 mg/day. It may be administered as a single or divided dosage with equal effectiveness. Obese individuals may need higher dosages on the basis of body weight (e.g., 20 mg/kg body weight daily). Individuals taking diuretics may also need to take higher dosages. Athletes or individuals who are subjecting their joints to greater wear and tear may need to increase the dosage to 3000 mg to maintain positive cartilage synthesis.

SIDE EFFECTS AND TOXICITY

GS has an excellent safety record in animal and human studies. On the basis of these studies, many experts have recommended that GS "be considered as a drug of choice for prolonged oral treatment of rheumatic disorders." Side effects, when they do appear, are generally limited to light to moderate gastrointestinal symptoms, including stomach upset, heartburn, diarrhea, nausea, and indigestion. If these symptoms occur, GS should be taken with meals.

Regarding people who are "sulfur sensitive," an important distinction must be made. When patients report they are allergic to sulfur, what they usually mean is that they are allergic to the so-called sulfa drugs or sulfite-containing food additives. It is impossible to be allergic to sulfur, as sulfur is an essential mineral. The sulfate form of sulfur is present in human blood. In short, GS is extremely well tolerated, and no allergic reactions have been reported.

Concern has been expressed that glucosamine may influence insulin secretion or action, or both, based primarily on in vitro studies with concentrations of glucosamine not possible to achieve with oral supplementation or at recommended dosages. Detailed human studies showed GS had no impact on insulin secretion or action in either healthy subjects, those with type 2 diabetes, or those with insulin resistance.[50,53-55] Long-term studies with GS actually produced a nonsignificant lowering of fasting blood glucose concentrations in all groups of subjects.[55]

DRUG INTERACTIONS

GS may potentiate the effect of warfarin (Coumadin). The World Health Organization's adverse drug reactions database documented 21 spontaneous reports of increased international normalized ratio associated with glucosamine use, 17 of which resolved when glucosamine was stopped. Two additional case reports also exist. Given the widespread use of GS, it does not appear to be a significant concern. Nonetheless, the use of warfarin and glucosamine may lead to an increased international normalized ratio, and physicians should monitor accordingly.[56]

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CHAPTER 95

Glutamine

Peter B. Bongiorno, ND, LAc

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Drug Interactions, *801*

INTRODUCTION

Glutamine (Figure 95-1) is the most abundant amino acid in blood and muscle tissue. It comprises approximately 6% of mixed whole body protein and is unique among amino acids in that it is a preferred fuel of rapidly dividing cells, such as intestinal and immune cells, and is important in maintaining pancreatic function.[1-3] Glutamine is involved in the transport of circulating amino nitrogen and is an important intermediary that allows for accelerated gluconeogenesis from amino acids that are released by the skeletal muscle during stress states.[4] In addition, glutamine is used as a precursor for DNA and glutathione synthesis.[5] As one of the principal fuels used by the cells of the intestinal lining, it accounts for 35% of enterocyte energy production.

Although readily available in the diet and synthesized in the body from glutamate and ammonia, supplementation is known to enhance the energy metabolism of the gastrointestinal mucosa, thus stimulating regeneration.[6] Although glutamine is not considered essential in healthy people, there is evidence that the increased need for glutamine in stressed states such as burns, septicemia, endotoxemia, intestinal failure, and critical illness may result in it being "conditionally essential."[3,7,8]

Food Sources

Typical food sources of glutamine include animal and plant proteins. Typical foods are cabbage, beef, chicken, fish, legumes, miso (a salty, fermented bean product), and dairy products.

Forms

The nomenclature of L-glutamine and glutamine are used interchangeably. D-glutamine is the stereoisomer of L-glutamine and does not have any known biological activity. L-glutamine is not soluble in water, and aqueous solutions are unstable at temperatures of 22° C to 24° C. As a result, the more soluble and more stable dipeptides such as alanyl-glutamine are used as delivery forms of L-glutamine in total parenteral nutrition solutions.[9,10]

Physiologic Effects

Intestinal Repair and Protection

Animal and human studies suggest that glutamine stimulates intestinal mucosal growth[11] and protects from mucosal atrophy. Glutamine prevents intestinal mucosal damage and was shown to decrease bacterial leakage across the intestines after they are damaged, presumably by stimulating repair.[12] Glutamine is thought to accomplish this by strengthening epithelial tight junctions and also by preventing paracellular permeabilities through an epidermal growth factor receptor–dependent mechanism.

In one tissue culture experiment, intestinal epithelium cells were treated with acetaldehyde to compromise barrier function. These cells were treated with L-glutamine, D-glutamine, L-asparagine, L-arginine, L-lysine, or L-alanine. Only the L-glutamine demonstrated a benefit by decreasing aldehyde effects on transepithelial resistance. Furthermore, L-glutamine–treated cells decreased permeability that was dose dependent. L-glutamine reduced the acetaldehyde-induced disturbance of transmembrane structures, such as occludin, zonula occludens-1,

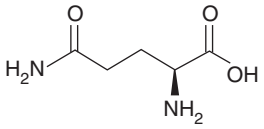


FIGURE 95-1 L-glutamine.

E-cadherin, and β-catenin from the intercellular junctions. Lastly, L-glutamine induced a rapid increase in the tyrosine phosphorylation of the epidermal growth factor receptor. No other amino acids demonstrated this effect.[13]

Acid Base Balance

Glutamine plays an important role in acid-base homeostasis.[14] Glutamine is synthesized from glutamate and the toxic alkaline waste product ammonia by the enzyme glutamine synthetase, which requires magnesium and adenosine triphosphate. When ammonia levels are elevated, the body effectively removes ammonia from the blood by synthesizing glutamine. Conversely, if the blood is too acidic, the glutamine can be broken down into glutamate and ammonia, which increases blood pH. Ammonia can bind hydrogen ions to produce ammonium cations, which are excreted in the urine along with chloride anions. Bicarbonate ions are simultaneously released into the bloodstream. Clinical studies showed that relatively small oral doses of glutamine can elevate plasma bicarbonate concentrations in healthy adults.

In one study, 2 g of glutamine were dissolved in a cola drink and ingested over a 20-minute period 45 minutes after a light breakfast. Control subjects were given soda only. Blood samples were taken 1 week before, at baseline, and subsequently at three separate 30-minute intervals after ingestion of the glutamine drink or placebo. Eight of nine subjects responded to the oral glutamine load with a significant increase in plasma glutamine at 30 and 60 minutes before returning to the baseline value at 90 minutes. Ninety minutes after the glutamine was administered, plasma bicarbonate concentration was found to be increased. Circulating plasma growth hormone concentration was elevated as well. Concomitant with enhanced renal acid secretion, glutamine ingestion also caused an increase in the glomerular filtration rate.[15]

The authors of this study explained that their results showed that it was unlikely L-glutamine was a direct precursor of bicarbonate. Instead, L-glutamine appeared to play an indirect role in accelerating acid secretion through mechanistic changes in the kidneys. Human studies showed that urinary ammonium excretion is altered by changes in glutamine intake.[16]

Chronic metabolic acidosis is a common clinical problem encountered in catabolic states such as sepsis, shock, and diabetes, and is a major factor in many biological derangements.[17] Because glutamine becomes an essential amino acid in catabolic states when the increased demand exceeds the body's capability to synthesize it,[18] glutamine supplementation may be quite useful to maintain pH homeostasis in patients with acidotic conditions.

Glutathione Repletion

Glutathione is a tripeptide consisting of glutamate, cysteine, and glycine. As a reservoir source for glutamate in the body, the availability of glutamine appears crucial for the regeneration of glutathione stores in the liver during hepatic injury; in skeletal muscle after major trauma, sepsis, or surgery; and in chemotherapy-injured heart muscle.[19-21] Glutamine can enhance intracellular repletion of glutathione, an important scavenger of reactive oxygen species.[22] Rat studies demonstrated that during 5-fluorouracil–induced free radical–mediated hepatic injury, glutamine increased glutathione biosynthesis and preserved the glutathione stores in hepatic tissue.[19] Seventeen patients who underwent a standardized surgical procedure were prospectively given 0.56 g/kg body weight/day of glutamine or a placebo. Using percutaneous muscle biopsies and blood samples, there were no significant decreases in total or reduced glutathione in the glutamine-supplemented group 24 and 72 hours after the operation. In contrast, the placebo group experienced total muscle glutathione losses of 47 ± 8% and 37 ± 11%, as well as reduced glutathione decreases of 53 ± 10% and 45 ± 16% at 24 and 72 hours, respectively.

Protein Sparing

Glutamine is a regulator of muscle proteolysis,[23] and supplementation can attenuate loss of protein in the muscle. Experiments using animal cancer models demonstrated decreased protein loss and simultaneous protection of immune and gut-barrier function during radiation therapy in patients with advanced cancer.[5] In children with severe muscle wasting, 5 hours of oral glutamine was shown to have protein-sparing effect (see later discussion on "Cachexia").[24]

Immune Support

Although poorly understood, it appears that glutamine has an immune-modulating effect by enhancing interleukin (IL)-6 levels[25] and lymphocyte function.[26] IL-6 plays an essential role in the final differentiation of β-cells into immunoglobulin-secreting cells, nerve cell differentiation, and acute phase reactants in hepatocytes. Exercise by itself is known to induce an eleven-fold increase in plasma IL-6. Glutamine supplementation further enhances IL-6 levels.[25] The ability of lymphocytes to proliferate and generate lymphokine-activated killer cell activity in vitro was found to be glutamine dependent.[27] Additionally, glutamine-enriched parental nutrition demonstrated enhanced lymphocyte activity in patients who received high doses of chemotherapy after stem cell transplantation for hematologous malignancy.

CLINICAL APPLICATIONS

Intestinal Permeability–Related Conditions

A number of conditions are linked to intestinal permeabilities, including chronic urticaria,[28] inflammatory bowel disease (Crohn's disease),[29-31] celiac disease,[32] liver and biliary cirrhosis and cases of portal hypertension,[33,34] systemic sclerosis,[35] diabetes,[36] rheumatologic disorders,[37,38] cystic fibrosis,[39] alcohol overuse,[40] adult and child asthma,[41] human immunodeficiency virus (HIV)/acquired immune deficiency syndrome,[42] nonsteroidal antiinflammatory drug–treated arthritis patients,[43] moderate to major burn injuries,[44] corticosteroid use,[45] cardiopulmonary bypass patients,[46,47] and acute metal toxicities.[48] To evaluate these permeabilities, sucrose serves as a marker for gastroduodenal permeability and the urinary lactulose/mannitol ratio for intestinal permeability, after administration of these sugars.[28] From a naturopathic perspective, the underlying cause of many of these conditions may stem from food allergies that contribute first to chronic inflammation in the intestinal tract[28] and then to systemic endotoxemia. Certain conditions such as cardiopulmonary bypass can cause intestinal ischemia,[49] which is then the primary insult that causes permeabilities in these patients. The use of glutamine can help heal these permeabilities, thus removing a mode of pathogenesis in these variegated conditions.

Infectious Diarrhea

Animal models showed the usefulness of glutamine in diarrhea to augment sodium and water absorption and to enhance blood glucose and body weight.[50] A rat model of cholera toxin–induced diarrhea showed that glutamine was able to improve water and electrolyte intestinal absorption even better than traditional glucose solutions.[10] One placebo-controlled, double-blind, randomized trial human study evaluated glutamine to treat acute diarrhea in 128 otherwise healthy children. Of these 6- to 24-month-olds, 63 received 0.3 g/kg per day of glutamine and 65 controls received a placebo for 7 days. The average duration of diarrhea in the glutamine-treated group was significantly shorter than that of the placebo group (3.40 ± 1.96 vs 4.57 ± 2.48 days, respectively). However, no differences in serum IL-8 and secretory immunoglobulin-A were found between groups at the beginning of treatment or 1 week later.[51]

Clearly, glutamine holds promise for enhancing repair of mucosal injury caused by a wide range of infections or toxic agents and thus has great potential as a nutritional therapeutic for patients with enteric infection.[52]

Postsurgical Complications of the Gastrointestinal Tract

Patients undergoing abdominal surgeries such as gastrectomies, sigmoidectomies, cholecystectomies, colectomies, and rectal resections are at risk for the development of intestinal failure or short bowel syndrome (SBS). In SBS, a serious malabsorption of fluid, electrolytes, and other nutrients can occur, placing the patient at higher morbidity and mortality risk.[53] Trauma from abdominal surgery may also compromise the intestinal mucosa to the point where bacteria and endotoxins can easily transfer through the intestinal wall and invade tissue and blood in an event called bacterial translocation. Through inflammatory mechanisms, bacteria, and endotoxic septic conditions, the intestinal mucosal barrier can be adversely affected and cause further damage, thus forming a vicious circle. Severe cases result in systemic inflammatory response syndrome and multiple organ dysfunction syndrome.[54]

In a regimen that includes growth hormone and diet changes, glutamine can help difficult cases to enhance bowel adaptation. In one study of 10 patients with SBS who previously failed to adapt to enteral nutrients, 8 subjects received exogenous growth hormone, supplemental glutamine, and a modified high-carbohydrate, high-fiber diet. Two patients were treated with the modified diet alone. Three weeks of treatment with growth hormone, glutamine, and a modified diet significantly increased total caloric absorption from approximately 60% to 75%, protein absorption from 49% to 63%, and carbohydrate absorption from 60% to 82%. Water absorption increased from 46% to 65%, and sodium from 49% to 69%. Fat absorption did not change. Diet alone did not influence nutrient absorption or stool output. After 28 days of therapy, the patients were discharged and instructed to continue the diet and glutamine treatment.[55] It is unknown whether glutamine and diet changes alone, without concomitant growth hormone administration, would have the same positive effect.

In a second study, 20 patients who underwent abdominal surgery were randomized into two groups receiving oral administration of 30 g of glutamine or a placebo in divided doses for 7 days. Serum glutamine concentration was significantly decreased in the placebo group and increased in the glutamine group after 7 days. Markers of intestinal permeability were significantly increased in the placebo group and decreased in the glutamine group. Additionally, the serum markers of endotoxin, diamine oxidase, and malondialdehyde concentrations were significantly decreased in the glutamine group compared with those in the placebo group. Temperatures, heart rates, and white blood cell counts were also significantly lower in the glutamine group.[54]

Ischemia reperfusion of the gut is also a common event in various clinical conditions, such as trauma, burn, septic shock, cardiac or aortic surgery, and liver or small bowel transplantation, and is associated with a high death rate. Intestinal ischemia reperfusion can cause edema and disruption of the structural integrity and function of the intestinal mucosa and associated vascular tissue. It may set the stage for endotoxemic translocation of a number of bacterium, including *Escherichia coli, Enterococcus, Pseudomonas, Proteus,* and *Staphylococcus*. Studies of animal models demonstrated that glutamine, when supplemented as total parenteral nutrition, protected the intestines from morphologic and functional mucosal injury after intestinal ischemia reperfusion. Furthermore, intestinal permeabilities and the incidence of bacterial translocation in intestinal ischemia reperfusion animals were also prevented in a dose-dependent manner by glutamine supplementation.[56,57]

The gastrointestinal tract is susceptible to SBS, severe intestinal permeabilities, ischemia perfusion damage, systemic inflammatory response during trauma, various medical conditions, and abdominal postoperative periods. Glutamine can decrease intestinal permeability, maintain an intestinal barrier, and attenuate systemic inflammatory response in early postoperative patients.

Chemotherapy and Radiation Side Effects

Standard cancer therapies often include the use of chemotherapy and radiation, which can injure rapidly dividing intestinal cells. It was shown that during chemotherapeutic and radiotherapy insult, glutamine reduced degeneration of intestinal mucosa in rats, prevented intestinal mucosal injury,[56] protected liver function through enhanced glutathione biosynthesis and storage in hepatic tissue, increased immune function, and reduced permeability of the gut.[19,26]

In one investigation, 70 patients with colorectal cancer were randomly assigned to oral glutamine at 18 g/day or placebo before the first regimen of 5-fluorouracil and folinic acid administered intravenously for 5 days. Glutamine was given 5 days before, during, and after chemotherapy. Using D-xylose urinary excretion and cellobiose/mannitol evaluation, damage to the intestines was assessed at baseline, as well as 4 and 5 days after the end of the first cycle of chemotherapy. After one cycle of chemotherapy, the reduction in D-xylose absorption and reduction of mannitol was significantly greater in the placebo group (7.1% vs 3.8% and 9.2% vs 4.5%, respectively). Urinary recovery of cellobiose was not different between the study arms. Accordingly, the cellobiose/mannitol ratio increased more in the placebo treatment group. Furthermore, diarrhea parameters, as well as the average number of antidiarrheal opiate loperamide tablets needed, were reduced in the glutamine arm, thus supporting the positive clinical effect of this low-cost supplement.[11]

Oropharyngeal mucositis, or mouth sores, and accompanying swallowing difficulty are other untoward results of radiotherapy and can be a major source of suffering in patients with head and neck cancer. Glutamine during and after chemotherapy appears to be an excellent way to safely decrease the incidence of mouth sores. One investigation of 17 patients with head and neck cancer who received primary or adjuvant mouth irradiation for 5 days a week were randomized to either adjunctive glutamine suspension of 16 g in 240 mL normal saline or a saline placebo. Patients were instructed to swish the test solutions (30 mL) four times daily. The duration of

objective oral mucositis was significantly shorter in the glutamine arm.[58] A second randomized, double-blind crossover trial observed 24 patients who were given a glutamine or placebo suspension to swish and swallow on days of chemotherapy administration and for at least 14 days after therapy. Significant improvement was observed in the glutamine group. Additionally, the duration of mouth pain was 4.5 days less in chemotherapy courses with concomitant glutamine supplementation. The severity of oral pain was reduced so significantly when glutamine was used that a patient could venture past soft foods 4 days sooner compared with placebo.[59]

Glutamine studies validating its use are also beginning to emerge in other areas of oncology. In a study of esophageal cancer patients, 13 patients were randomized into two groups, controls and a group that received oral glutamine supplemented at a dosage of 30 g/day for 4 weeks. It was observed that supplementation of glutamine enhanced lymphocyte mitogenic function and reduced permeability of the gut during radiochemotherapy.[5] Patients who underwent bone marrow transplant and myelosuppressive chemotherapy for acute myeloid leukemia also found that parenteral glutamine therapy could improve neutrophil recovery, although no change in neutropenic fever was shown.[60] Given that glutamine improves the structure and function of the gut, it is understandable that multiple parameters and markers of healthy physiologic function will improve with its use.

It should be noted that glutamine's efficacy may depend on a number of other factors, including the specific chemotherapeutic prescribed and dosage. A study of 65 patients with advanced breast cancer receiving doxifluridine were prescribed 30 g/day of glutamine in three divided doses of 10 g each or a placebo for 8 consecutive days during each interval between chemotherapy, which was administered from days 1 to 4. In this case, there was no statistical difference with regard to diarrhea morbidity, nor did glutamine affect the severity and duration of tumor growth.[61] Interestingly, a study of bone marrow transplantation patients found that allogeneic transplantation patients (those receiving bone marrow from another individual) did not have the same beneficial mouth pain reduction that autologous transplantation patients (those who donated their own marrow) experienced when receiving glutamine support. However, in the work mentioned previously, the amounts of glutamine were less than those used in other studies.

It was also theorized that methotrexate use in the allogeneic patients might have been responsible for the decreased protection. Nevertheless, in the allogeneic patients, the 28-day survival was still increased.[62] A third multicenter study of 129 patients found no protection against diarrhea when used adjunctively with pelvic radiation therapy. These patients received 4 g of glutamine or a placebo by mouth, which was also a significantly lower dose than the more successful studies employed.[63]

Although intestinal function is greatly compromised with chemotherapy and radiation treatment, cardiac function is commonly affected as well. The use of doxorubicin therapy for breast cancer is often limited by cardiomyopathic heart changes that often result in congestive heart failure. One rat study simulated doxorubicin treatment with and without glutamine support and found that oxidative damage to the heart was diminished in the glutamine-treated group, probably as a result of glutamine's ability to maintain cardiac tissue glutathione levels (see later discussion on "Cardiac Disease").[21]

Cachexia

Cancer-related cachexia is caused by a diverse combination of accelerated protein breakdown and slowed protein synthesis.[64] There has been considerable interest in giving supplemental glutamine to cancer patients because glutamine is taken up by the growing tumor, and any subsequent deficiency of glutamine in the host may cause cancer cachexia.[5]

One animal study found that glutamine levels in plasma and skeletal muscle were decreased in tumor-bearing rats, whereas glutamine production and the conversion of arginine to glutamine were increased. In rats supplemented with glutamine, total parenteral nutrition demonstrated a reduced whole body protein breakdown rate during chemotherapy.[5] A clinical study of patients with Stage IV solid malignancies who had weight loss of at least 5% were randomly assigned in a double-blind fashion to either a control mixture of nonessential amino acids or treatment of 14 g/day of glutamine, along with the leucine metabolite β-hydroxy-β-methylbutyrate (3 g/day) and L-arginine (14 g/day). Within 4 weeks, the patients supplemented with the glutamine mixture gained 0.95 ± 0.66 kg of body mass, whereas control subjects lost 0.26 ± 0.78 kg during the same period. This effect continued over the 24 weeks, with no negative effect of treatment on the incidence of adverse effects or quality of life measures.[64]

Because the glutamine derived from skeletal muscle is trapped by the tumor, there is a theoretic concern that glutamine supplementation in cancer patients could potentially encourage tumor growth. One research group, however, showed that glutamine supplementation does not appear to enhance DNA content in tumor cells.[5,65] Additionally, some tissue culture studies provided evidence that glutamine might even inhibit cancer promotion.[66] Although research is necessary to clarify this point, given the immediate risk of mortality due to protein loss in cancer patients, it still would seem prudent to administer glutamine to those patients at greater immediate risk of cachexia-related death.

Human Immunodeficiency Virus

Loss of body cell mass and drug-associated gastrointestinal problems often occur in patients with HIV infection. In these cases, the patient's ability to survive can be affected in the long term. Given the role glutamine plays in cachexic body mass loss (see previous section on "Cachexia"), reversal of malabsorption,[67] and protection of the small intestine,[68] glutamine deficiency is a probable causal factor in HIV-associated wasting.[69]

Preliminary clinical studies suggested improvements in HIV-positive patients dosed at 8 g/day with regard to intestinal permeability and intestinal absorption. The authors of this study correctly suggested that at least 20 g/day might be necessary for more significant improvements.[70] A double-blind, placebo-controlled trial of 26 patients with greater than 5% weight loss since their disease onset used a glutamine and antioxidant regimen, including 40 g/day of glutamine in divided doses or 40 g of a glycine placebo for 12 weeks. Over 3 months, the glutamine/antioxidant group gained 2.2 kg in body weight (3.2%), whereas the control group gained only 0.3 kg (0.4%).

The glutamine-antioxidant group gained 1.8 kg in body cell mass, whereas the control group gained 0.4 kg. Of note, the intracellular water increased in the glutamine-antioxidant group but not in the control group.[71] Glutamine can help HIV patients decrease the severity of iatrogenic diarrhea. Twenty-five patients suffering for more than a month from nelfinavir-associated diarrhea were randomized in a double-blind, placebo-controlled, crossover trial to receive L-glutamine at 30 g/day or a placebo for 10 days. In this study, the L-glutamine significantly reduced the severity of nelfinavir-associated diarrhea and produced improved quality of life compared with placebo.[72]

Peptic Ulcers

Cabbage juice, a key source of glutamine, has been well documented as having remarkable success in treating peptic ulcers. One liter per day of the fresh juice, taken in divided doses, resulted in total ulcer healing in an average of only 10 days. Further research showed that the high glutamine content of the juice is probably responsible for the efficacy of cabbage in treating these ulcers. In a double-blind clinical study of 57 patients, 24 using 1.6 g/day of glutamine and the rest using conventional therapy (antacids, antispasmodics, milk, and bland diet), glutamine proved to be the more effective treatment. Half of the glutamine patients showed complete healing (according to radiographic analysis) within 2 weeks, and 22 of the 24 showed complete relief and healing within 4 weeks.[22] Although the mechanism for these results is unknown, it was postulated by the authors to be due to the role of glutamine in the biosynthesis of the hexosamine moiety in certain mucoproteins. These moieties may stimulate mucin synthesis, which would benefit peptic ulcer patients.

Severe Burns

Plasma glutamine levels were demonstrated to be profoundly decreased after severe burns in adults. This may at least partially explain the impaired cellular immunity that is seen in burn patients. Burn victims given glutamine showed better intestinal repair, a higher quality of wound healing, and reduced hospitalization. In one study, 48 severe burn patients were randomly divided into two groups: a control group that took a placebo and a glutamine-treated group that received 0.5 g of glutamine/kg body weight/day, both for 14 days. After taking glutamine for 14 days, plasma glutamine concentration was significantly increased in the glutamine group compared to the control group. In addition, a greater quality of wound healing as well as shorter hospital stays were experienced in the glutamine-treated burn patients.[73]

In another study, dosage of L-glutamine at 0.6 g/kg per day did not result in an immediate whole body protein gain (an important factor in a burn patient's convalescence) and resulted in an insignificant increase in plasma glutamine.[4] However, this study measured only the first 48 hours, which might not have been enough time to show a long-term benefit.

Another study of 45 severely burned adults found that those randomized to receive enteral glutamine experienced a reduction in blood infection by a factor of three, and mortality risk was lowered.[74] Another investigation of burned patients whose total body surface burns ranged from 50% to 80% and third-degree burns ranged from 20% to 40%, but who did not have respiratory injuries found improved gut permeability, initially decreased plasma endotoxin levels, and reduced hospitalization.[75]

Low-Birth-Weight Infants

Infants with a birth weight of less than 1000 to 1500 g may be especially susceptible to glutamine depletion, as nutritional supply of glutamine is limited in the first weeks after birth. This may increase morbidity by contributing to problems with gut integrity, as well as immune suppression.[3] One study of 35 ill preterm neonates of less than 1000 g were randomized to receive either glutamine-supplemented parenteral nutrition or standard parenteral nutrition. Although there were no significant differences between the groups in white cell count, differential white cell count, blood urea nitrogen, plasma ammonia, lactate, pyruvate, plasma glutamine, or glutamate, the median time to achieving full enteral nutrition was shorter in the glutamine group (13 versus 21 days). Parenteral glutamine was well tolerated and considered safe for these preterm neonates.[76]

However, other studies found that formula supplemented with glutamine in growing preterm infants was entirely metabolized in the gut and did not have a discernable effect on whole-body protein and nitrogen kinetics.[77] A large multicenter, double-blind, randomized trial of infants with a birth weight of 401 to 1000 g were given either a control or 20% isonitrogenous solution by parenteral nutrition for up to either 120 days of age, death, or discharge from the hospital. Of the 721 infants who were assigned to glutamine supplementation, 370 (51%) died or developed late-onset sepsis, compared with 343 of the 712 infants (48%) assigned to control. Although no adverse effects were noted as a result of being given glutamine, this study demonstrated that glutamine did not decrease mortality. This study and others also found no reduction in the incidence of sepsis in these young patients.[78,79]

Exercise and Weight Lifting

Glutamine is considered to have an anabolic effect on skeletal muscle. Given the benefits on glutathione reserves, protein catabolism, and intestinal integrity, some glutamine enthusiasts believe that glutamine supplementation may be useful for exercise and strength training as well. One small study suggested that oral glutamine increases growth hormone release.[15] Even so, clinical trials studying glutamine as an exercise performance enhancer are not encouraging.

A double-blind, placebo-controlled, crossover study had six resistance-trained men lift weights after the ingestion of glutamine or glycine at 0.3 g/kg body weight or a placebo. One hour after ingestion, subjects performed four total sets of exercise to momentary muscular failure, including two sets of leg presses at 200% of body weight and two sets of bench presses at 100% of body weight. Despite glutamine's possible role in exercise, there were no actual differences in the average number of maximal repetitions performed in the leg press or bench press exercises among these three groups.[80] Other studies using 0.3 to 0.9 g/kg of body weight also demonstrated no changes in exercise performance, body composition, or muscle protein degradation in young healthy adults.[81,82] It is possible that beneficial effects of glutamine are best detected only in patients with chronic illness and those with compromised physiology instead of normal, healthy individuals.

Cardiac Disease

Cardiac disease is a recognized stress on the physiology of the gastrointestinal and immune system. Animal studies supported the notion that glutamine can help recovery from cardiac ischemia and help the heart recover after reperfusion injury.[83,84] As noted earlier, glutamine can protect the heart from damage due to chemotherapy regimens by its glutathione-replenishing effect (see earlier discussion on "Chemotherapy and Radiation Side Effects").[19] The benefits to the gastrointestinal system in those heart patients experiencing ischemic gut episodes after cardiac bypass were also previously noted.[46,47] Animal research showed that greater levels of plasma glutamine also prevented decreases in the ratio between adenosine triphosphate to adenosine diphosphate in myocardial tissue.[84]

Unfortunately, little research has been done to evaluate the clinical use of glutamine in various cardiac situations. One investigation of patients with chronic stable angina received a single 80 mg/kg oral dose of glutamine or a placebo in a double-blind, random

fashion 40 minutes before a standard exercise test. This single dose of glutamine significantly increased plasma glutamine concentration from 419 to 649 µmol/L. Moreover, the glutamine appeared to encourage positive changes in ST depression on the echocardiogram.[84] Clearly, more research is required, but given that heart disease is the leading reason for mortality, natural and safe treatments like glutamine should be further explored.

Other Conditions

A number of other medical conditions, such as alcoholism, pancreatitis, and brain injury will further adversely affect the health of a patient who already has protein and energy needs and is more susceptible to infection. Although more studies are necessary, the following includes a few interesting conditions not mentioned earlier.

In alcoholics, glutamine supplementation (1 g/day) was shown to reduce voluntary alcohol consumption in uncontrolled human studies and experimental animal studies.[85-88] Despite the fact that this research is about 50 years old, there has never been any follow-up to these preliminary studies. This is unfortunate, because the results were quite promising, finding glutamine to be safe and relatively inexpensive. Related to alcoholism in many patients, individuals with acute pancreatitis also benefited from parenteral glutamine treatment with improvement in immune function, decreased systemic inflammation, and a trend toward shorter hospital stays.[1]

In an interesting study of 20 brain injury patients, 10 subjects were randomized to receive either an early enteral diet or the same formula with glutamine and probiotic added for a range of 5 to 14 days. The infection rate was found to be 100% in the control group, but only 50% in the glutamine group. The median number of infections per patient was significantly greater in the control group compared with the study group. Critical care stay and ventilation requirements were more than halved in the treatment group (10 vs 22 days, and 14 vs 7 days, respectively). Interestingly, probiotics were also used in the treatment group. This synergistic enhancement in gut flora may be useful to augment the already known benefits of glutamine.[89]

DOSAGE

The typical minimum oral dosage of glutamine is 100 mg three times a day, although the delivery method and actual effective dosage should be condition specific, meaning dosages are often much higher. The following points serve as guidelines:

- Severe burns: enteral dosage for individuals with severe burns was approximately 0.5 g/kg per day in most studies.
- Preventing and treating the side effects of chemotherapy involves the following:
 - Patients treated with 5-fluorouracil received up to 18 g/day 5 days before, then during, and 5 days after treatment.[11]
 - High-dose chemotherapy after stem cell transplantation: total parenteral nutrition enriched with glutamine 20 g.[26]
- Oral mucositis: 16 g mixed with 240 mL normal saline, and 30 mL is swished four times a day.[58]
- Esophageal cancer radiotherapy was given with a successful adjunctive oral glutamine supplement of 30 g/day for 4 weeks.[5]
- Cachexia patients were tested with dosages of 14 g/day combined with other amino acids.[64]
- Pediatric oncology patients: 0.65 g/kg was found to be a safe dose of glutamine to use in a clinical study in pediatric oncology patients.[90]
- Children with acute diarrhea: 0.3 g/kg per day was used successfully.[51]
- Peptic ulcers: drinking 1 L a day in divided doses was sufficient or 1.6 g/day for 1 month.[23]
- HIV patients: 30 to 40 g/day of glutamine to prevent medication-associated diarrhea and to improve intestinal permeability[71,72]; coadministration of antioxidants might also be helpful.
- Postabdominal surgeries: glutamine can be dissolved in warm water and taken orally or by gastric tube after the operation at 30 g/day for 7 days.[54]

TOXICITY

Glutamine, even at high doses, is without apparent side effects and is well tolerated.[4,52] Glutamine is synthesized from glutamate and the toxic alkaline waste product ammonia. If the blood is too acidic, the glutamine can be broken down into glutamate and ammonia, which will increase blood pH. Glutamate levels in the blood can increase slightly with high doses of supplemental glutamine administration (around 15 g in a single dose), but not with moderate doses (of about 5 g in a single dose). The higher doses may contribute to glutamate levels, and should be used with caution in patients with neurodegenerative diseases such as amyotrophic lateral sclerosis and multiple sclerosis.[91] In one pediatric oncology patient, a single dose of 0.75/kg was found to raise the blood ammonia level to an unacceptably high limit. Related to this, it was difficult to disperse the glutamine adequately at this dose, resulting in the suspension being found unpalatable.

DRUG INTERACTIONS

In cancer treatment, glutamine does not appear to change the efficacy of cancer drugs, rate of relapse, or progression of malignancy.[62] Some animal studies suggested that glutamine supplementation might even preferentially increase tumor retention of methotrexate, thus increasing the therapeutic window of this drug.[92] Many antiseizure medications, including phenobarbital, phenytoin, carbamazepine, primidone, and valproic acid, work to block glutamate activity in the brain. Because glutamine can convert to glutamate, clinicians should be cautious when using glutamine in patients using these medications.

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CHAPTER 96

Glycyrrhiza glabra (Licorice)

Michael T. Murray, ND

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Glycyrrhiza glabra (family: Leguminosae)
Common names: licorice, glycyrrhiza

GENERAL DESCRIPTION

Glycyrrhiza glabra is a perennial, temperate zone herb or subshrub, 3 to 7 feet high, with a long, cylindrical, branched, flexible, and burrowing rootstock with runners. The parts used are the dried runners and roots, which are collected in the fall.

CHEMICAL COMPOSITION

The major active component of licorice root is the triterpenoid saponin glycyrrhizin (also known as glycyrrhizic acid or glycyrrhizinic acid; Figure 96-1), which is usually found in concentrations ranging from 6% to 10%. The intestinal flora is believed to hydrolyze glycyrrhizin, yielding the aglycone molecule (glycyrrhetinic acid) and a sugar moiety, resulting in absorption of both.[1]

A processed licorice extract, deglycyrrhizinated licorice (DGL), which is used in the treatment of peptic and aphthous ulcers, is made by removing the glycyrrhizin molecule. The active components of DGL are flavonoids. These compounds demonstrated impressive protection against chemically-induced ulcer formation in animal studies.[2]

Other active constituents of licorice include isoflavonoids (e.g., isoflavonol, kumatakenin, licoricone, glabrol); chalcones; coumarins (e.g., umbelliferone, herniarin); triterpenoids; and sterols, lignins, amino acids, amines, gums, and volatile oils.[3]

HISTORY AND FOLK USE

The medicinal use of licorice in both Western and Eastern cultures dates back several thousand years. It was used primarily as a demulcent, expectorant, antitussive, and mild laxative. Licorice is one of the most popular components of Chinese medicines. Its traditional uses include treating peptic ulcers, asthma, pharyngitis, malaria, abdominal pain, insomnia, and infections.[3]

PHARMACOLOGY

Licorice is known to exhibit many pharmacologic actions, including the following[3]:

- Estrogenic
- Aldosterone-like action
- Anti inflammatory (cortisol-like action)
- Antiallergic
- Antibacterial, antiviral, and antitrichomonas
- Antihepatotoxic
- Anticonvulsive
- Choleretic
- Anticancer
- Expectorant
- Antitussive activities

The majority of these actions are discussed individually later. Although much of the pharmacology focuses on glycyrrhizin and glycyrrhetinic acid, it is worth

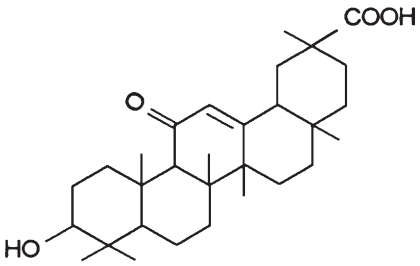


FIGURE 96-1 Glycyrrhizinic acid.

remembering that licorice has many other components, such as flavonoids, which may have significant pharmacologic effects.

Estrogenic Activity

Most herbalists generally believe that glycyrrhiza exhibits alterative action on estrogen metabolism (i.e., when estrogen levels are too high, it inhibits estrogen action, and when estrogens are too low, it potentiates estrogen action when used in greater amounts).[4] Glycyrrhetinic acid has been shown to antagonize many of the effects of estrogens, particularly exogenous estrogens.[5] The estrogenic action of glycyrrhiza is due to its isoflavone content, as many isoflavone structures (e.g., daidzein and genistein from soy) are known to possess estrogenic effect. The estrogenic activity of the isoflavones appears to be more significant than the estrogen antagonism of glycyrrhetinic acid.[6] Interestingly, these same components inhibit breast cancer cell growth.[7]

Pseudoaldosterone Activity

Long-term ingestion of glycyrrhiza in large doses leads to a well-documented pseudoaldosteronism syndrome (i.e., hypertension, hypokalemia, sodium and water retention, low plasma renin activity, and suppressed urine and serum aldosterone levels).[8-13] In normal subjects, the amount of glycyrrhizin needed to produce these side effects is between 0.7 and 1.4 g, which corresponds to approximately 10 to 14 g of the crude herb.[9] Although glycyrrhiza possesses mineralocorticoid activity (about four orders of magnitude lower than aldosterone) and binds to aldosterone receptors, it is largely without effect in adrenalectomized animals or in patients with severe adrenocorticoid insufficiency. Therefore, it can be concluded that its primary effects are largely as a result of glycyrrhetinic acid inhibiting the breakdown of aldosterone in the liver.[14] Glycyrrhizin and glycyrrhetinic acid were shown to suppress 5-β-reductase, the main enzyme in humans responsible for inactivating cortisol, aldosterone, and progesterone. These effects can be put to good use in the treatment of Addison's disease, a severe disease of adrenal insufficiency.[13]

Antiinflammatory and Antiallergic Activity

Glycyrrhiza has significant antiinflammatory and antiallergic activity.[15,16] Although both glycyrrhizin and glycyrrhetinic acid bind to glucocorticoid receptors, and much of glycyrrhiza's antiinflammatory activity has been explained by its "cortisol-like effects," many of the effects of glycyrrhiza actually antagonize or counteract cortisol.[17] Antagonism to such actions of cortisol include activation of tryptophan oxygenase, accumulation of hepatic glycogen, stimulation of hepatic cholesterol synthesis, inhibition of thymus atrophy, and inhibition of adrenocorticotropic hormone synthesis and secretion. Glycyrrhizin does, however, reinforce cortisol's inhibition of antibody formation, stress reaction, and inflammation. Like its mineralocorticoid effect, glycyrrhiza's major influence on glucocorticoid metabolism is probably related to its suppression of 5-β-reductase activity, thus increasing the half-life of cortisol. Glycyrrhetinic acid can also increase the conversion of cortisol to the more powerful cortisone.[18]

Glycyrrhiza's major cortisol-like effect relates to its ability to inhibit phospholipase A_2.[19] This enzyme is responsible for cleaving lipids from biomembranes for eicosanoid metabolism. In addition to this effect, glycyrrhizin was also shown to inhibit cyclic adenosine monophosphate phosphodiesterase, thereby raising cyclic adenosine monophosphate levels and prostaglandin formation by activated peritoneal macrophages from rats.[20,21] Glycyrrhizin was shown to inhibit experimentally induced allergenic reactions, such as the Arthus phenomenon, the Shwartzman phenomenon, and Forssman anaphylaxis, and to be an antidote against many toxins, including diphtheria, tetanus, and tetrodotoxin.[21,22]

Glycyrrhizin exerts antithrombotic effects but does not potentiate the inhibitory activity of antithrombin III or heparin cofactor II toward thrombin.[23]

Immunostimulatory and Antiviral Effects

Glycyrrhizin and glycyrrhetinic acid were shown to induce interferon.[24] The induction of interferon leads to significant antiviral activity, because interferons bind to cell surfaces, where they stimulate synthesis of intracellular proteins that block the transcription of viral DNA. The induction of interferon is also followed by activation of macrophages and augmentation of natural killer cell activity.

Glycyrrhizin was shown to directly inhibit the growth of several DNA and RNA viruses in cell cultures (vaccinia, Epstein-Barr, Herpes simplex, Newcastle disease, vesicular stomatitis viruses, severe acute respiratory syndrome [SARS]-associated coronavirus, and HIV) and to inactivate herpes simplex virus 1 (HSV-1) irreversibly.[25-28] Administration of glycyrrhizin to mice with herpetic encephalitis increased their survival rate on average about 2.5 times, whereas it reduced HSV-1 replication in the brain to 45.6% of the controls.[29] Glycyrrhizin, as stated earlier, also inhibited the thymolytic and immunosuppressive action of cortisone. Other licorice components exerted immunomodulatory effects as well.[30]

Anticancer Effects

Licorice components exert a wide range of anticancer effects.[31] The most active appear to be the flavonoids and coumarins. For example, isoliquiritigenin was shown to suppress colon cancer in mice via markedly decreasing both prostaglandin E_2 and nitric oxide production in mouse macrophage cells.[32] Isoliquiritigenin was also shown to significantly inhibit the proliferation of prostate and breast cancer cell lines in dose- and time-dependent manners.[7,33] Isoliquiritigenin also significantly reduced pulmonary metastasis in mouse renal cell carcinoma and prevented the leukocytopenia caused by administration of 5-fluorouracil.[34] A coumarin compound, identified as licocoumarone, was shown to be the factor in licorice that induces apoptosis.[35]

Antibacterial Activity

Alcohol extracts of glycyrrhiza displayed antimicrobial activity in vitro against *Helicobacter pylori, Staphylococcus aureus* (including antibiotic resistant strains), *Streptococcus mutans*, *Mycobacterium smegmatis*, *Bacillus subtilis*, *S. pyogenes, Haemophilus influenzae, Moraxella catarrhalis,* and *Candida albicans*.[36-39]

The majority of the antimicrobial effects are due to isoflavonoid components, with the saponins having a lesser antibacterial effect.

Antihepatotoxic Activity

Glycyrrhetinic acid inhibits carbon tetrachloride and galactosamine-induced liver damage. The mechanism of action is prevention of nonenzymatic lipid peroxidation and inhibition of the production of free radicals by the enzymatic action of nicotine adenine disphosphonucleotide, reduced–cytochrome P450 reductase on CCl4.[40]

Memory-Enhancing Effect

Licorice may exert some memory-enhancing effects. In a study in mice, licorice was shown to enhance learning and memory in mice as determined by the elevated plus-maze and passive avoidance paradigm. Furthermore, licorice significantly reversed the amnesia induced by diazepam and scopolamine. Although anti-inflammatory and antioxidant properties may contribute favorably to the memory-enhancement effect, because scopolamine-induced amnesia was reversed as well, it is possible that the beneficial effect on learning and memory was due to facilitation of cholinergic transmission.[41]

Antinephritic Activity

Glabridin, an isoflavan isolated from *G. glabra*, improved urinary protein excretion, total cholesterol, serum creatinine, and blood urea nitrogen levels after its oral administration to mice with glomerular disease.[42]

CLINICAL APPLICATIONS

Licorice is a component of more traditional Chinese and Japanese herbal formulas than any other herb. Although extremely pharmacologically diverse, the current clinical applications of licorice can be divided into four main categories:

- Use of DGL
- Use of oral licorice preparations containing glycyrrhizin
- Use of licorice flavonoid oil (LFO)
- Use of topical preparations containing glycyrrhetinic acid

The key use of DGL is in ulcerative conditions of the gastrointestinal tract (e.g., peptic ulcers, canker sores, inflammatory bowel disease), whereas the key uses of oral licorice containing glycyrrhizin include viral infections (e.g., the common cold, HIV and AIDS, viral hepatitis); premenstrual syndrome (PMS) and menopause; acute intermittent porphyria; Addison's disease; inflammation; syndrome X; and as a sweetening agent. Topical preparations containing glycyrrhetinic acid can be used in eczema, psoriasis, herpes, and melasma.

DEGLYCYRRHIZINATED LICORICE

Although glycyrrhetinic acid was the first drug proven to promote healing of gastric and duodenal ulcers,[43] most physicians using licorice in the treatment of peptic ulcers now use DGL. DGL was actually shown to be more effective than glycyrrhetinic acid, without side effects.[44]

DGL's mode of action is different than that of current drugs, such as antacids and H_2-receptor antagonists, which focus on reducing gastric acidity. Although effective, these treatments can be expensive, carry some risk of toxicity, disrupt normal digestive processes, and alter the structure and function of the cells that line the digestive tract. The latter factor is just one of the reasons why peptic ulcers develop again if antacids, cimetidine, ranitidine, and similar drugs are used.

Rather than inhibit the release of acid, DGL stimulates the normal defense mechanisms that prevent ulcer formation and stimulate healing of the damaged mucous membranes. Specifically, DGL increases the following[45,46]:

- The blood supply to the damaged mucosa
- The number of cells producing the mucus that protects the mucous membranes
- The amount of mucus the cells produce
- The life span of the intestinal cell

In addition, several flavonoid components of *G. glabra* have shown significant activity against *H. pylori,* including antibiotic-resistant strains.[38]

Gastric Ulcers

Numerous clinical studies over the years found DGL to be an effective antiulcer compound. DGL was shown to be extremely effective in the treatment of gastric ulcers.[47-51] In one study, 33 gastric ulcer patients were treated with either DGL (760 mg, three times a day) or a placebo for 1 month.[50] There was a significantly greater reduction in ulcer size in the DGL group (78%) than in the placebo group (34%). Complete healing occurred in 44% of those receiving DGL, but only in 6% of the placebo group.

In several head-to-head comparison studies, DGL was shown to be more effective than cimetidine (Tagamet), ranitidine (Zantac), or antacids in both short-term treatment and maintenance therapy of peptic ulcers.[47,48,52] However, although these drugs are associated with significant side effects (see preceding section), DGL is extremely safe and is only a fraction of the cost.

Subsequent studies showed DGL to be as effective as Tagamet and Zantac for both short-term treatment and maintenance therapy of gastric ulcer.[47-49] For example, in a head-to-head comparison with Tagamet, 100 patients received either DGL (760 mg, three times a day between meals) or Tagamet (200 mg, three times a day, and 400 mg at bedtime).[48] The percentage of ulcers healed after 6 and 12 weeks were similar in both groups. Although Tagamet is associated with some toxicity, DGL is extremely safe to use.

Gastric ulcers are often a result of using alcohol, aspirin, or other nonsteroidal anti-inflammatory drugs, caffeine, and other factors that decrease the integrity of the gastric lining. Because DGL was shown in human studies to reduce the gastric bleeding caused by aspirin, DGL is strongly indicated for the prevention of gastric ulcers in patients requiring long-term treatment with ulcerogenic drugs such as aspirin, nonsteroidal anti-inflammatory agents, and corticosteroids.[51]

Duodenal Ulcers

DGL is also effective in duodenal ulcers. This is perhaps best illustrated by one study in patients with severe duodenal ulcers: 40 patients with chronic duodenal ulcers of 4 to 12 years' duration and more than six relapses during the previous year were treated with DGL.[53] All of the patients were referred for surgery because of relentless pain, sometimes with frequent vomiting, despite treatment with bed rest, antacids, and anticholinergic drugs. Half of the patients received 3 g/day of DGL for 8 weeks; the other half received 4.5 g/day for 16 weeks. All 40 patients showed substantial improvement, usually within 5 to 7 days, and none required surgery during the 1-year follow-up. Although both dosages were effective, the higher dosage was significantly more effective than the lower dosage.

In another more recent study, the therapeutic effect of DGL was compared with that of antacids or cimetidine in 874 patients with confirmed chronic duodenal ulcers.[52] Ninety-one percent of all ulcers healed within 12 weeks; there was no significant difference in healing rate in the groups. However, there were fewer relapses in the DGL group (8.2%) than in those receiving cimetidine (12.9%) or antacids (16.4%). These results, coupled with DGL's protective effects, suggest that DGL is a superior treatment of duodenal ulcers.

Aphthous Ulcers

Recurrent aphthous stomatitis (canker sores) is a common problem. DGL may be effective in promoting healing. In one study, 20 patients were instructed to use a solution of DGL as a mouthwash (200 mg powdered DGL dissolved in 200 mL warm water) four times daily.[54] Fifteen of the 20 (75%) patients experienced 50% to 75% improvement within 1 day, followed by complete healing of the ulcers by the third day. DGL in tablet form may produce even better results.

ORAL LICORICE PREPARATIONS CONTAINING GLYCYRRHIZIN

The most popular use of oral licorice preparations containing glycyrrhizin is in the treatment of viral illnesses, particularly the common cold. Licorice has long been used in this application. This historical use is justified by its immune-enhancing and antiviral effects. In addition, licorice components were shown to exert antibacterial action against the common pathogens *S. pyogenes, Haemophilus influenzae,* and *Moraxella catarrhalis*.[55]

Another popular use of licorice is in the treatment of gynecologic issues, primarily PMS and menopause. Regarding PMS, because glycyrrhizin and glycyrrhetinic acid possess antiestrogenic effects and suppress the breakdown of progesterone, administration of licorice 2 weeks before the onset of menstruation (the midluteal phase) may help to reduce PMS symptomatology. Clinical trials showed that taking licorice containing herbal combinations was useful in dysmenorrhea.[56] Isoflavones from glycyrrhiza showed an ability to inhibit serotonin reuptake, and therefore, might also exhibit some antidepressant effects in PMS.[57]

Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome

Glycyrrhizin-containing preparations are showing promise in the treatment of HIV-related diseases, including AIDS. Although much of the research featured intravenous administration, this route of administration might not be necessary, as glycyrrhizin and glycyrrhetinic acid are easily absorbed orally and are well tolerated. This was most evident in a recent double-blind study on the clinical effectiveness of glycyrrhizin by long-term oral administration to 16 hemophiliac patients with evidence of HIV infection.[58] Patients received daily doses of 150 to 225 mg of glycyrrhizin for 3 to 7 years.

Helper and total T-lymphocyte numbers, other immune system parameters, and glycyrrhizin and glycyrrhetinic acid levels in the blood were monitored. The results indicated that orally administered glycyrrhizin was converted into glycyrrhetinic acid, which was detected in sera, without manifesting any side effects. None of the patients given the glycyrrhizin had progression of immunologic abnormalities or development to AIDS. In contrast, the group not receiving glycyrrhetinic acid showed decreases in helper and total T-cell counts and antibody levels. Two of the 16 patients in the control group developed AIDS.

In another study, 10 HIV positive patients without AIDS took 150 to 225 mg/day of glycyrrhizin.[59] After 1 to 2 years, none developed symptoms associated with AIDS or AIDS-related complex, whereas 1 of 10 patients of a matched control group developed AIDS-related complex, and 2 progressed to AIDS and subsequently died.

The result of glycyrrhizin in HIV-positive and AIDS patients is almost immediate improvement in immune function. In one study, nine symptom-free HIV-positive patients received 200 to 800 mg/day of glycyrrhizin intravenously. After 8 weeks, the groups had increased T-helper cells, improved helper/suppressor ratios, and improved liver function.[60]

In another study, six AIDS patients received 400 to 1600 mg/day of glycyrrhizin intravenously.[61] After 30 days, five of the six showed a reduction or disappearance of the P24 antigen, which indicates active disease. The results of these studies and others in HIV-positive and AIDS patients are encouraging.

Hepatitis

Some studies of HIV patients used an intravenous glycyrrhizin-containing product, Stronger Neo-Minophagen C (SNMC), consisting of 0.2% glycyrrhizin, 0.1% cysteine, and 2.0% glycine in physiologic saline solution. This product is used in Japan primarily for the treatment of hepatitis. The other components, glycine and cysteine, appear to modulate glycyrrhizin's actions. Glycine was shown to prevent the aldosterone effects of glycyrrhizin, whereas cysteine aids the liver in detoxification reactions.

In addition to AIDS, SNMC demonstrated beneficial results in treating chronic hepatitis B and C, often difficult infections for the body to clear.[22,62-64] Specifically, SNMC was shown to improve liver function and lower levels of liver enzymes. Glycyrrhizin therapy appears particularly helpful in patients with chronic hepatitis C who fail to respond to interferon and in those who cannot be treated with it for various reasons.

Acute Intermittent Porphyria

This disorder of heme biosynthesis is characterized by recurrent attacks of neurologic and psychiatric dysfunction. The symptoms include the following:

- Abdominal complaints of nausea, vomiting, and colicky pain, occasionally severe enough to present as an acute abdomen without fever or leukocytosis
- Variable neurologic signs and symptoms (e.g., paresthesia, hypesthesia, neuritic pain, wrist or foot drop, loss of deep tendon reflexes)
- Variable mental and emotional disturbances, typically restlessness, disorientation, and visual hallucinations (seen in one third of patients)

Because estrogens are known to exacerbate or induce acute intermittent porphyria (AIP), it is quite possible that some of the so-called PMS symptoms are exacerbations of AIP due to the midcycle estrogen surge.

A partial (50%) deficiency of uroporphyrinogen I synthase results in increased inducibility of aminolevulinic acid synthase by drugs and foreign chemicals and by 5-β-reductase steroid metabolites (potent inducers of aminolevulinic acid synthase). AIP is also associated with a marked deficiency in the activity of 5-α-reductase, resulting in increased 5-β-reductase activity.[65] Glycyrrhetinic acid and glycyrrhizin were shown to significantly reduce 5-β-reductase while increasing 5-α-reductase.[66] (Lead also increases 5-β-reductase

activity, resulting in a presenting picture similar to AIP.[66] Chronic or acute lead toxicity must be ruled out in these patients.)

Obesity and Metabolic Syndrome

Preparations containing glycyrrhetinic acid may be effective in reducing various issues related to syndrome X or metabolic syndrome. For example, in a preliminary study, 15 normal-weight subjects (7 males, 22 to 26 years old, and 8 females, 21 to 26 years old), who consumed 3.5 g/day of a commercial preparation of licorice containing glycyrrhetinic acid for 2 months, had reduced body fat mass of 1.2% in men and 2.8% in women.[67] This weight loss might have been mediated not only via suppressing renin activity and aldosterone levels via inhibition of 11-β-hydroxysteroid dehydrogenase, but also via improving blood glucose control—a key goal in syndrome X.[68-70]

In another study, supplementation of a licorice root extract to moderately hypercholesterolemic patients for 1 month reduced plasma susceptibility to oxidation (by 19%). It also increased resistance of plasma low-density lipoprotein against three major atherogenic modifications: oxidation (by 55%), aggregation (by 28%), and retention (by 25%). It reduced plasma cholesterol levels (by 5%), which were due to a 9% reduction in plasma low-density lipoprotein cholesterol levels, and reduced (by 14%) plasma triglyceride levels. Licorice extract supplementation also reduced systolic blood pressure by 10%.[71]

Addison's Disease

As described in "Pseudoaldosterone Activity", licorice exerts an aldosterone-like effect that is useful in treating Addison's disease.

Inflammation

Virtually any inflammatory or allergic condition may be reduced by licorice by the mechanisms discussed earlier in the section on "Pharmacology". Historically, licorice was successfully used for treating asthma and other atopic conditions.[3,15]

Licorice was shown to enhance the action of corticosteroids like prednisone and prednisolone, as well as the levels of the body's own corticosteroids.[72,73] In one study, six subjects received an intravenous dose of prednisolone with or without 200 mg glycyrrhizin. Glycyrrhizin was found to significantly increase the concentration of total and free prednisolone by inhibiting its breakdown. Furthermore, the effects of prednisolone appeared to be potentiated by glycyrrhizin.[73]

One interesting application shown with positive clinical results in a double-blind study was reduction of postoperative sore throat.[74] Forty adults who underwent elective lumbar laminectomy were randomized into two groups of 20 patients each. One group received water (Group C); the other received 0.5 g licorice in water (Group L). Both groups gargled 5 minutes before anesthesia. Postoperative sore throat incidence and severity as well as postextubation cough were reduced for all time points in the licorice group compared with the water group at rest and on swallowing. Postextubation cough was reduced in Group L compared with Group C (P <0.05). There was no difference in side effects between groups (P >0.05).

Sweetening Agent

Because glycyrrhizin is 50 to 100 times sweeter than sucrose, licorice can be used as a sweetening or flavoring agent to mask the bitter taste of other medications.[3]

TABLE 96-1 **Body Weight and Mass Compared with Baseline After Licorice Flavonoid Oil Treatment**

GROUP	BASELINE	4 WEEKS	8 WEEKS
		Body Weight (kg)	
Placebo	73.13	73.07	73.39
900 mg	72.79	72.20	72.05
		Body mass index (kg/m^2)	
Placebo	26.51	26.49	26.59
900 mg	26.22	26.01	25.97

LICORICE FLAVONOID OIL

LFO shows promise as an antiobesity and weight loss agent. It is standardized to contain 30% polyphenols with glabridin standardized at 3%. The flavonoids are extracted with ethanol and then solubilized in medium chain triglycerides oil (hence, 70% of LFO is medium chain triglycerides). The extracted licorice flavonoids are hydrophobic compounds and virtually free of the hydrophilic compounds glycyrrhizin and glycyrrhizinic acid (there is less than 0.005% glycyrrhizic acid in LFO).

LFO decreases the activity of acetyl coenzyme A carboxylase and fatty acid synthase, the rate-limiting enzymes in the fatty acid synthetic pathway, while increasing the enzymatic activity of acyl coenzyme A dehydrogenase, the rate-limiting enzyme in the fatty acid oxidative pathway. These effects are thought to be responsible for the reduction in abdominal fat in animal and human studies.[75-78]

In a double-blind study, 56 men and 28 postmenopausal women, aged 40 to 60 years with body mass indexes of 24 to 30 kg/m^2, were randomized into 4 groups: the placebo group took three placebo capsules per day, the low-dose group took one LFO capsule and two placebos per day (300 mg/day LFO), the middle-dose group took two LFO capsules and one placebo per day (600 mg/day LFO), and the high-dose group took three LFO capsules per day (900 mg/day LFO). The subjects in the 900 mg LFO group experienced significant decreases from baseline in body weight and body mass index compared with the placebo group (Table 96-1).[78]

The subjects in all 3 LFO groups, but not the placebo group, had significantly lower body fat masses compared with baseline after 8 weeks of treatment. Computed tomographic scans showed that visceral fat mass decreased significantly compared with baseline in the 900 mg LFO group (122.37 to 113.02 cm^2).

A safety study demonstrated that LFO is safe when administered once daily up to 1200 mg/day.[79] There were no clinically noteworthy changes in hematologic or related biochemical parameters.

TOPICAL APPLICATIONS

Eczema and Psoriasis

Glycyrrhetinic acid exerts an effect similar to that of topical hydrocortisone in the treatment of eczema, contact and allergic dermatitis, and psoriasis.[80-84] In several studies, glycyrrhetinic acid was shown to be superior to topical cortisone, especially in chronic cases. For example, in one study of patients with eczema, 93% of the patients applying glycyrrhetinic acid demonstrated improvement compared with 83% using cortisone.[85] In another study, a topical gel containing 2% glycyrrhetinic acid was shown to be

effective for treatment of atopic dermatitis and was more effective than preparations containing 1% glycyrrhetinic acid in reducing the scores for erythema, edema, and itching over 2 weeks.[80]

Glycyrrhetinic acid can also be used to potentiate the effects of topically applied hydrocortisone by inhibiting 11-β-hydroxysteroid dehydrogenase, which catalyzes the conversion of hydrocortisone to an inactive form.[81,82] It also increases the permeation of topically applied steroids. In one study, glycyrrhetinic acid in a concentration of 0.1% in gel increased diclofenac sodium flux value ten-fold compared with a control gel.[83]

Herpes Simplex

Clinical studies showed topical glycyrrhetinic acid and derivatives to be quite helpful in reducing the healing time and pain associated with cold sores and genital herpes.[86,87] As mentioned previously, glycyrrhizin inactivates HSV-1 irreversibly and stimulates the synthesis and release of interferon.[25]

Melasma

Two components, glabrene and isoliquiritigenin, can inhibit tyrosinase—a key enzyme in melanin biosynthesis.[88] Dermatologic disorders such as melasma, age spots, and sites of actinic damage arise from the accumulation of melasma. Glabrene and isoliquiritigenin may serve as candidates for skin-lightening agents.

DOSAGE

The dosage of licorice for most clinical applications is based on the content of glycyrrhetinic acid. The exception is in the treatment of peptic ulcer. In this application, DGL is preferred, as it produces equally effective results compared with glycyrrhetinic acid but is free from any side effects.

For most purposes, the goal is to achieve a high level of glycyrrhetinic acid in the blood without producing side effects (discussed in "Toxicology"). In general, the following doses three times a day are safe and effective in raising glycyrrhetinic acid levels:

- Powdered root: 1 to 2 g
- Fluid extract (1:1): 2 to 4 mL
- Solid (dry powdered) extract (4:1): 250 to 500 mg

In the treatment of AIDS, pure glycyrrhetinic acid products or extracts standardized for glycyrrhetinic acid are recommended. Toxicity can become a problem for patients taking licorice for any period longer than 1 month (see "Toxicology" and "Drug Interactions").

Dosage Instructions for Deglycyrrhizinated Licorice

To be effective in healing peptic ulcers, it appears that DGL must mix with saliva. DGL may promote the release of salivary compounds, which stimulate the growth and regeneration of stomach and intestinal cells. DGL in capsule form has not been shown to be effective.[89,90]

The standard dosage for DGL is two to four 380-mg chewable tablets between or 20 minutes before meals. Taking DGL after meals is associated with poor results.[91] DGL should be continued for 8 to 16 weeks, depending on the response.

Dosage Instructions for Licorice Flavonoid Oil

The standard dosage for LFO is 900 mg/day usually administered as 300 mg three times a day.

TOXICOLOGY

The main hazards of licorice administration are due to the aldosterone-like effects of glycyrrhetinic acid. If ingested regularly, licorice root (>3 g/day for more than 6 weeks) or glycyrrhizin (>100 mg/day) may cause sodium and water retention, hypertension, and hypokalemia.[8,9,92-94] Individuals with existing hypertension may be more predisposed to this effect via increased sensitivity to the inhibition of 11-β-hydroxysteroid-dehydrogenase by glycyrrhetinic acid.[18,82,95] Monitoring of blood pressure and electrolytes and increasing dietary potassium intake is suggested, as the pseudoaldosterone effects can be quite significant. The maximal effect on blood pressure with long-term ingestion is observed after 2 weeks of use.[96]

There is great individual variation in the susceptibility to the symptom-producing effects of glycyrrhizin, primarily due to differences in pharmacokinetics and conversion to the more potent glycyrrhetinic acid (100 to 200 times more active in suppressing 11-β-hydroxysteroid-dehydrogenase).[97] Adverse effects are rarely observed at levels below 100 mg/day, whereas they are quite common at levels above 400 mg/day.[9] However, some persons may be susceptible to long-term dosages at even lower levels, especially if the more potent glycyrrhetinic acid is available in free form. One study determined a no-effect level of glycyrrhetinic acid as 2 mg/kg, from which an acceptable daily intake of 0.2 mg/kg body weight can be extrapolated with a safety factor of 10. This translates to a consumption of 12 mg/day of glycyrrhetinic acid for a person with a body weight of 60 kg.[98]

Prevention of the side effects of glycyrrhizin may be possible by following a high-potassium, low-sodium diet. Although no formal trial has been performed, patients who normally consume high-potassium foods and restrict sodium intake, even those with high blood pressure and angina, have been reported to be free from the aldosterone-like side effects of glycyrrhizin.[99]

Licorice should probably not be used in patients with a history of hypertension or renal failure or in those who currently use digitalis preparations.

Licorice preparations containing glycyrrhizin may reduce serum and salivary testosterone levels in men. In one study, men consuming the equivalent of 500 mg of glycyrrhizin experienced a drop of 26% in serum testosterone levels.[100] However, in another study, no significant effect was noted.[101]

Licorice intake during pregnancy is generally regarded as safe, unless hypertension becomes an issue. There was one detailed study on maternal consumption of glycyrrhizin and how it affected birth weight.[102] Glycyrrhizin intake was calculated from detailed questionnaires on licorice consumption. Glycyrrhizin exposure was grouped into three levels: low (<250 mg/week), moderate (250 to 499 mg/week), and heavy (≥500 mg/week). Birth weight and gestational age (from ultrasound measurements) were obtained from hospital records. Babies with heavy exposure to glycyrrhizin were not significantly lighter at birth, but they were significantly more likely to be born earlier—2.52 days earlier. No other associations could be made.

DRUG INTERACTIONS

No significant reports of drug interactions have appeared, although on theoretic grounds, licorice components have shown considerable interactions with various enzyme systems. Licorice root extract and purified glabridin were shown to inhibit P450 3A4, the major human drug metabolizing P450 enzyme, in time- and concentration-dependent manners, thereby potentiating the

action of many drugs.[103] Glycyrrhizin intake may be problematic for people on digitalis, diuretics, or antihypertensive medications. Also, individuals using oral hypoglycemic drugs or insulin need to monitor blood sugar levels closely when using glycyrrhiza.

Glycyrrhetinic acid can reduce the prevalence of side effects related to the diuretic activity of spironolactone. In a study of 32 women with polycystic ovarian syndrome, women who received 3.5 g of licorice a day with spironolactone eliminated symptoms related to volume depletion, and the activation of the renin-aldosterone system was significantly lower during spironolactone plus licorice than with spironolactone alone. The prevalence of metrorrhagia was also lower with the combined therapy.[104]

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CHAPTER 97

Hydrastis canadensis (Goldenseal) and Other Berberine-Containing Botanicals

Michael T. Murray, ND

Hydrastis canadensis (family: Ranunculaceae)
Common names: goldenseal, yellow root, Indian turmeric, eye root, jaundice root
Berberis vulgaris (family: Berberidaceae)
Common name: barberry
Berberis aquifolium (family: Berberidaceae)
Common names: Oregon grape, trailing mahona
Coptis chinensis (family: Ranunculaceae)
Common name: goldthread

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INTRODUCTION

The plants goldenseal *(Hydrastis canadensis),* barberry *(Berberis vulgaris),* Oregon grape *(Berberis aquifolium),* and goldthread *(Coptis chinensis)* share similar indications and effects due to their high content of berberis alkaloids. The chief berberis alkaloid, berberine, has been studied extensively in both experimental and clinical settings. Its pharmacologic effects are reviewed later. The general description, history and folk use, chemical composition, and specific clinical indications for each plant are presented here. The pharmacology of these plants is primarily discussed in terms of the activity of berberine.

GENERAL DESCRIPTION

Hydrastis canadensis

Goldenseal is native to eastern North America and is cultivated in Oregon and Washington. It is a perennial herb with a knotty yellow rhizome from which arises a single leaf and an erect hairy stem. In early spring, it bears two five- to nine-lobed rounded leaves near the top, which are terminated by a single greenish-white flower. The parts used are the dried rhizome and roots.[1,2]

Berberis vulgaris

The common barberry is a deciduous spiny shrub that may reach 16 ft in height. Native to Europe, it has been naturalized in eastern North America. Parts used are the barks of the stem and root.[1,2]

Berberis aquifolium

The Oregon grape is an evergreen, spineless, ornamental shrub, 3 to 7 ft in height. It is native to the Rocky Mountains from British Columbia to California. Parts used are the rhizome and roots.[1,2]

Coptis chinensis

Goldthread is a perennial herb native to China. The parts used are the rhizomes and root.[3]

CHEMICAL COMPOSITION

The chemical structure of berberine is shown in Figure 97-1.

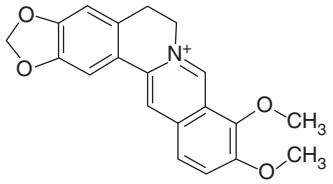


FIGURE 97-1 Berberine.

Hydrastis canadensis

Alkaloids isolated from hydrastis include the following:
- Hydrastine (1.5% to 4%)
- Berberine (0.5% to 6%)
- Berberastine (2% to 3%)
- Canadine
- Candaline
- Hydrastinine
- Other related alkaloids

Other constituents include meconin, chlorogenic acid, phytosterins, and resins.[1,2]

Berberis vulgaris

Barberry contains several alkaloids in its roots:
- Jatrorrhizine
- Berberine
- Berberubine
- Berbamine
- Bervulcine
- Palmatine
- Columbamine
- Oxyacanthine

It also contains chelidonic, citric, malic, and tartaric acids.[1,2]

Berberis aquifolium

Oregon grape contains the alkaloids berbamine, berberine, canadine, corypalmine, hydrastine, isocorydine, mahonine, and oxyacanthine. Resins and tannins have also been reported.[1,2]

Coptis chinensis

Goldthread root contains berberine (5% to 8%) and other alkaloids similar to those found in goldenseal.[3]

HISTORY AND FOLK USE

Hydrastis canadensis

Native to North America, hydrastis was used extensively by American Indians as an herbal medication and clothing dye. Its medicinal use centered around its ability to soothe the mucous membranes of the respiratory, digestive, and genitourinary tracts in inflammatory conditions induced by allergy or infection. The Cherokee and other Indian tribes used hydrastis in disorders of the eye and skin.[1,2]

Berberis vulgaris

This plant is native to most of Europe. Similar species are found in North Africa and Asia. Barberry's historic use is as an antidiarrheal agent, bitter tonic, antipyretic, and antihemorrhagic.[1,2]

Berberis aquifolium

Oregon grape's historic and folk use is similar to that of hydrastis. In addition, Oregon grape was used in the treatment of chronic skin conditions such as acne, psoriasis, and eczema.[1,2]

Coptis chinensis

In China, goldthread was used in the traditional medicine system to "drain fire." It was used primarily in infectious conditions, similar to the historic use of goldenseal. Specific uses included fever, dysentery, gastrointestinal infection, furuncles, boils, and eye infections.[3]

PHARMACOLOGY

The medicinal value of hydrastis, barberry, Oregon grape root, and goldthread is thought to be due to their high content of isoquinoline alkaloids, of which berberine has been the most widely studied. Berberine demonstrates antibiotic, immunostimulatory, anticonvulsant, sedative, hypotensive, uterotonic, choleretic, and carminative activity. Berberine's pharmacologic activities support the historic use of the berberine-containing herbs.

Antimicrobial Activity

Perhaps the most celebrated of berberine's effects has been its antibiotic activity. Although not as potent as many prescription antibiotics, berberine exhibits a broad spectrum of antibiotic activity. Berberine has shown antimicrobial activity against bacteria, protozoa, and fungi, including the following[1-13]:
- *Staphylococcus spp.*
- *Streptococcus spp.*
- *Chlamydia spp.*
- *Corynebacterium diphtheriae*
- *Escherichia coli*
- *Salmonella typhi*
- *Vibrio cholerae*
- *Diplococcus pneumoniae*
- *Pseudomonas spp.*
- *Shigella dysenteriae*
- *Entamoeba histolytica*
- *Trichomonas vaginalis*
- *Neisseria gonorrhoeae*
- *Neisseria meningitidis*
- *Treponema pallidum*
- *Giardia lamblia*
- *Leishmania donovani*
- *Candida albicans*

Its action against some of these pathogens is actually stronger than that of the prescription antibiotics commonly used for these pathogens. Berberine's action in inhibiting *Candida*, as well as other pathogenic bacteria, prevents the overgrowth of yeast that is a common side effect of antibiotic use. Table 97-1 lists the in vitro sensitivity of various organisms to berberine sulfate.

The antimicrobial activity of berberine increases with pH in all organisms studied.[5] At a pH of 8, its antimicrobial activity in vitro is typically two to four times greater than it is at pH 7, which in turn is one to four times greater than at pH 6. This suggests that alkalinization will improve its clinical efficacy, particularly in the treatment of urinary tract infections.

TABLE 97-1 **In Vitro Sensitivity of Microorganisms to Berberine Sulfate**

ORGANISM	INHIBITORY CONCENTRATION (mg/mL)*
Bacteria	
Bacillus cereus	25
B. subtilis	25
Corynebacterium diphtheriae	6.2
Enterobacter aerogenes	2500.05
Escherichia coli	600.05
Klebsiella spp.	>100
Klebsiella pneumoniae	25
Proteus spp.	>100
Pseudomonas mangiferae	>100
P. pyocyanea	>100
Salmonella paratyphi	>100
S. typhimurium	>100
Shigella boydii	12.5
Staphylococcus aureus	6.2-50
Streptococcus pyogenes	12.5
Vibrio cholerae	25
Fungi	
Candida utilis	12.5
C. albicans	12.5
Cryptococcus neoformans	150†
Microsporum gypseum	50†
Saccharomyces cerevisiae	100†
Sporothrix schenckii	6.2
Trichophyton mentagrophytes	100†
Other	
Entamoeba histolytica	200
Erwinia carotovora	100
Leishmania donovani	5.08
Mycobacterium tuberculosis	200†
Xanthomonas citri	3.1

*Minimum concentration that totally inhibits growth in a liquid medium at pH 8. Maximum concentration tested was 100 mg/mL, unless otherwise noted.
†Tested in a solid medium, which typically requires a 4 to 10 times greater concentration for the same level of inhibition.
Data from references 5, 6, and 9.

Antiinfective Activity

Researchers investigated berberine's ability to inhibit the adherence of group A streptococci to host cells on the basis that the therapeutic effect of berberine appeared to be greater than its direct antibiotic effects.[14] Recent studies showed that certain antimicrobial agents can block the adherence of microorganisms to host cells at doses much lower than those needed to kill cells or to inhibit cell growth.

Berberine's ability to inhibit the adhesion of streptococci to host cells has several modes of action. First, berberine causes streptococci to lose lipoteichoic acid. Lipoteichoic acid is the major substance responsible for adhesion of the bacteria to host tissues. Another important action of berberine is preventing the adhesion of fibronectin to the streptococci, as well as eluting already bound fibronectin.

The results of this study are quite profound. The results raise many questions and force researchers and practitioners to look at the treatment of bacterial infections in a new light. Is it better to use a substance with bactericidal or bacteriostatic action over a substance that prevents the adherence of bacteria to host cells? Is the true value of botanicals with "antiinfective" actions a multifactorial effect on all aspects of infections from immune stimulation to antimicrobial and antiadherence actions?

The results of the study indicate that berberine interferes with infections due to group A streptococci not only by inhibiting streptococcal growth but also by blocking these organisms to host cells. The study implies that berberine-containing plants may be ideal in the treatment of "strep throat," a condition historically treated with goldenseal by American naturopathic physicians. Berberine's action in inhibiting *C. albicans* prevents the overgrowth of yeast, which is a common side effect of antibiotic use.

Immunostimulatory Activity

Berberine was shown to increase the blood supply to the spleen.[15] This improved blood supply may promote optimal activity of the spleen by increasing the release of compounds, such as tuftsin, that potentiate immune function. Berberine was also shown to activate macrophages, via both enhanced priming and triggering.[16]

Anticancer Effects

Berberine exhibits potent anticancer activity both directly by killing tumor cells and indirectly by stimulating white blood cells.[16-20] The most impressive effect was noted in a study demonstrating antitumor activity against human and rat malignant brain tumors.[18] Several experimental approaches were used in the study. In vitro studies were performed on a series of six human malignant brain tumor cell lines and rat 9L brain tumor cells. Berberine used alone at a dose of 150 mg/mL showed an average cancer cell kill of 91%. This kill rate was more than twice that of 1,3-*bis*(2-chloro-ethyl)-1-nitrosourea (BCNU), the standard chemotherapeutic agent for brain tumors, which had a cell kill rate of 43%. Studies in rats harboring solid 9L brain tumors also showed that berberine had antitumor effects. Rats treated with berberine, 10 mg/kg, had an 81% cell kill. However, the combination treatment of berberine and BCNU exhibited additive effects on killing cancer cells. These results indicate that berberine may prove to be more effective than BCNU or, at the least, a valuable therapeutic addition in the treatment of difficult brain cancers.

Berberine also exhibited unique antioxidant and antimutagenic effects.[21,22]

Antipyretic Activity

Historically, berberine-containing plants were used as febrifuges. Berberine produces an antipyretic effect three times as potent as aspirin in a pyretic model in rats.[23] However, although aspirin suppresses fever through its action on prostaglandins, berberine appears to lower fever by increasing the immune system's handling of fever-producing compounds from microorganisms.

Antidiabetic Actions

Berberine was shown to possess a wide range of antidiabetic effects, including an ability to increase insulin receptor expression and improve glucose utility both in vitro and in animal models,

reduce insulin resistance through protein kinase C–dependent upregulation of insulin receptor expression, stimulate insulin secretion, block glucose absorption via inhibition of α-glucosidase and epithelial glucose transport, and reduce serum lipid levels in animal models of impaired glucose tolerance.[24-26]

CLINICAL APPLICATIONS

The broad antimicrobial effects of berberine, combined with its antiinfective and immune-stimulating actions, support the historic use of berberine-containing plants in infections of the mucous membranes. Berberine-containing plants may also be useful as an adjunct to standard cancer therapy. Lastly, clinical research on use of berberine in the treatment of type 2 diabetes and the metabolic syndrome is extremely promising.[27]

Infectious Diarrhea

Berberine showed significant success in the treatment of acute diarrhea in several clinical studies. It was found to be effective against diarrheas caused by *E. coli* (traveler's diarrhea), *Shigella dysenteriae* (shigellosis), *Salmonella paratyphi* (food poisoning), *Klebsiella species*, *G. lamblia* (giardiasis), and *V. cholerae* (cholera).[28-38] Studies in hamsters and rats showed that berberine also had significant activity against *Entamoeba histolytica*, the causative organism of amebiasis.[7,8]

It appears that berberine is effective in treating the majority of common gastrointestinal infections. Clinical studies produced results with berberine comparable to standard antibiotics in most cases. In several studies, results were better.

For example, in a study of 65 children younger than 5 years of age with acute diarrhea caused by *E. coli*, *Shigella*, *Salmonella*, *Klebsiella* or *Faecalis aerogenes,* those given berberine tannate (25 mg/6 h) responded better than those treated with standard antibiotic therapy.[33]

In another study, 40 children, who were 1 to 10 years old and infected with the parasite *Giardia,* received either berberine (5 mg/kg body weight each day), the drug metronidazole (10 mg/kg body weight each day), or a placebo of vitamin B syrup in three divided doses.[34] After 6 days, 48% of patients treated with berberine were symptom free and, on stool analysis, 68% were giardia free. In the metronidazole (Flagyl) group, 33% of patients were without symptoms and, on stool analysis, all were giardia free. In comparison, 15% of patients on placebo were asymptomatic and, on stool analysis, 25% were giardia free. These results indicated that berberine was actually more effective than metronidazole in relieving symptoms at half the dose, but less effective than the drug in clearing the organism from the intestines.

Finally, in a study of 200 adult patients with acute diarrhea, the subjects were given standard antibiotic treatment with or without berberine hydrochloride (150 mg/day). The patients receiving berberine recovered quicker.[35] An additional 30 cases of acute diarrhea were treated with berberine alone. Berberine arrested diarrhea in all of these cases, with no mortality or toxicity.

Despite these results, because of the serious consequences of an ineffectively treated infectious diarrhea due to highly pathogenic organisms, the best approach may be to use berberine-containing plants as an adjunct to standard antibiotic therapy.

Much of berberine's effectiveness is undoubtedly due to a combination of its direct antimicrobial activity, inhibition of microbial attachment to mucous membranes, and blocking of the action of toxins produced by several pathogenic bacteria.[39-41] The toxin-blocking effect is most evident in diarrheas caused by enterotoxins (e.g., *V. cholerae, E. coli*), cholera, and traveler's diarrhea, respectively.[36-39]

Although cholera is a serious disorder that needs standard antibiotic therapy, traveler's diarrhea is usually self-limiting. Good results with berberine in the treatment of traveler's diarrhea have been obtained. In one study, patients with traveler's diarrhea randomly received 400 mg of berberine sulfate in a single dose or served as controls.[36] In treated patients, the mean stool volumes were significantly less than those of controls during three consecutive 8-hour periods after treatment. At 24 hours after treatment, significantly more treated patients stopped having diarrhea compared with controls (42% vs 20%).

For people planning to travel to an underdeveloped country or an area of poor water quality or sanitation, the prophylactic use of berberine-containing herbs 1 week before, during, and 1 week after visiting may be useful.

Trachoma

Water extracts of berberine-containing plants have been employed to treat various eye complaints, including infectious processes by cultures throughout the world. Recently, berberine showed remarkable effect in the treatment of trachoma.[42,43] Trachoma, an infectious eye disease due to the organism *Chlamydia trachomatis*, is a major cause of blindness and impaired vision in underdeveloped countries. It affects approximately 500 million people worldwide and results in blindness in 2 million.

The drug sulfacetamide is currently the most widely used antitrachoma drug. In clinical trials comparing berberine (0.2%) and sulfacetamide (20% solution), sulfacetamide showed the best improvement (decrease in conjunctival discharge, edema, and papillary reactions), but the conjunctival scrapings of all patients receiving sulfacetamide were still positive for *C. trachomatis*. These patients had a high rate of recurrence of symptoms. In contrast, patients treated with the berberine solution showed mild ocular symptoms, which disappeared more gradually, but their conjunctival scrapings were always negative for *C. trachomatis*. These patients did not have relapse even 1 year after treatment, which suggests that berberine is probably curative for trachoma.[42,43]

Berberine's efficacy is believed to be due to stimulation of some host defense mechanism, rather than simply a direct action on the organism. Because the berberine concentration used in these studies was 100 times less than the concentration of sulfacetamide, and berberine is much cheaper, it may be more cost-effective than other treatments for trachoma. Berberine (0.2% solution) is an appropriate therapy for many types of conjunctivitis.

Cholecystitis and Cirrhosis of the Liver

Berberine was shown in several clinical studies to stimulate the secretion of bile (choleretic effect) and bilirubin.[44-46] In one study of 225 patients with chronic cholecystitis, oral berberine doses of 5 to 20 mg three times a day before meals caused, over a period of 24 to 48 hours, a disappearance of clinical symptoms, a decrease in bilirubin level, and an increase in the bile volume of the gall bladder.

Berberine was shown to correct the hypertyraminemia of patients with liver cirrhosis. It prevented the elevation of serum tyramine after oral tyrosine load by inhibiting the enzyme tyrosine decarboxylase found in bacteria in the large intestine.[46] Berberine inhibits tyrosine decarboxylase and tryptophanase activities of *Streptococcus faecalis* and *E. coli,* but not those of animal enzymes. Tyramine is believed to be responsible for some of the cardiovascular and neurologic complications of liver disease, such as hepatic

encephalopathy. The accumulation of tyramine and its derivatives may cause lowering of peripheral resistance, with resultant high cardiac output, reduction in renal function, and cerebral dysfunction. Berberine, by lowering plasma tyramine levels, helps prevent the complications of cirrhosis. This tyramine-lowering effect of berberine may have significance in other conditions as well.

Cancer

Berberine and another alkaloid found in berberine-containing plants, berbamine, were shown to exert beneficial effects as adjuncts in cancer therapy. Berbamine has been used in China since 1972 in the treatment of depressed white blood cell (WBC) counts due to chemotherapy and radiation.

In one study, 405 patients with WBC counts less than 4000 were given 150 mg/day of berbamine (50 mg orally three times daily) for 1 to 4 weeks. Berbamine was viewed as "significantly effective" if WBC count increased to greater than 4000 after 1 week or increased to greater than 1000 after 2 weeks; "effective" if WBC count increased to greater than 4000 after 2 weeks or increased greater than 1000 after 4 weeks; and "ineffective" if there was no change in WBC count after 4 weeks of treatment. The overall results for the 405 patients were as follows:

- Significantly effective in 163 cases (40.2%)
- Effective in 125 cases (38.8%)
- Ineffective in 117 cases (29%)

The total effective rate was 71%. However, WBC count before therapy was related to overall effectiveness. The effective rate was only 54.8% in 31 cases in which WBC count was less than 1000 and 82.7% in cases in which WBC count was between 3100 and 3800.[47]

Congestive Heart Failure

Berberine-containing plants may exert beneficial effects in chronic congestive heart failure (CHF). In one double-blind study, 156 patients with CHF and more than 90 ventricular premature complexes (VPCs) or nonsustained ventricular tachycardia, or both, on 24-hour Holter monitoring were randomly divided into two groups. All patients were given conventional therapy for CHF, consisting of angiotensin-converting enzyme inhibitors, digoxin, diuretics, and nitrates. Patients were given berberine 1.2 to 2 g/day or a placebo. Symptoms, a 6-minute walk test, left ventricular ejection fraction (LVEF), frequency and complexity of VPCs, and quality of life were assessed after 8 weeks of treatment and during a mean 24-month follow-up.

After treatment with berberine, there was a significantly greater increase in LVEF, exercise capacity, improvement of the dyspnea-fatigue index, and a decrease of frequency and complexity of VPCs compared with the control group. There was also a significant decrease in mortality in the berberine-treated patients during long-term follow-up (7 patients receiving treatment died vs 13 on placebo). There were no apparent side effects in the berberine group. Researchers concluded that berberine improved quality of life and decreased VPCs and mortality in patients with CHF.[48]

Type 2 Diabetes

Human clinical studies validated the antidiabetic effects noted in in vitro and in vivo models because they showed berberine (500 mg three times a day) significantly lowered fasting blood glucose, hemoglobin A_{1C} (HbA_{1c}), triglycerides, and insulin levels in patients with type 2 diabetes mellitus.[49-51] The fasting blood glucose and HbA_{1c} lowering efficacies of berberine were similar to those of metformin and rosiglitazone. For example, in one study, berberine reduced HbA_{1c} from 9.5% to 7.5%, fasting blood glucose from 10.6 to 6.95 mmol/L, postprandial blood glucose from 19.8 to 11.1 ± 0.9 mmol/L, and plasma triglycerides from 1.13 to 0.89 mmol/L.[54] In another study, berberine at a dosage of 1.0 g/day for 3 months decreased fasting blood glucose from 7.0 to 5.6 mmol/L, HbA_{1c} from 7.5% to 6.6%, triglycerides from 2.51 to 1.61 mg/dL, total cholesterol from 5.31 to 4.35 mg/dL, and low-density lipoprotein (LDL) cholesterol from 3.23 to 2.55 mg/dL.[51]

Consistent with the in vitro and in vivo models, the berberine-treated patients experienced a statistically significant increase in the percentages of peripheral blood lymphocytes that express insulin receptor expression.[49] In patients with chronic viral hepatitis (B and C), liver function was improved greatly by showing reduction of liver enzymes. Additional mechanisms of value to patients with type 2 diabetes include the ability to inhibit aldose reductase, lower blood lipids levels (including the ability to reduce free fatty acid levels), and protect and improve endothelial function.[52] In a lipid-lowering trial in 32 hypercholesterolemic patients for 3 months, berberine (500 mg three times daily) reduced serum cholesterol by 29%, triglycerides by 35%, and LDL cholesterol by 25%.[53] Berberine lowers LDL by upregulating hepatic LDL receptor expression through a mechanism of mRNA stabilization.[54]

DOSAGE

Since no detailed clinical studies have differentiated which berberine-containing herb to use for specific conditions, the following is offered only as a guideline based on experimental studies and historical use. In general, the plants can be viewed as interchangeable.

H. canadensis:

- Infective, congestive, and inflammatory states of the mucous membranes
- Digestive disorders
- Gastritis
- Peptic ulcers
- Colitis
- Anorexia
- Painful menstruation

Berberis vulgaris: The treatment of gallbladder disease, including gallstones, and as a less expensive form of berberine in the treatment of the conditions listed earlier for hydrastis.

Berberis aquifolium: Best used in the treatment of chronic skin diseases and in the conditions listed earlier for hydrastis.

Coptis chinensis: Can be used in the treatment of infective, congestive, and inflammatory states of the mucous membranes, fever, and infectious disorders of the skin.

The dosage should be based on berberine content. Because there is a wide range of quality in goldenseal preparations, standardized extracts are recommended. In one study of 20 products purchased at local pharmacies or health food stores, 17 were labeled as containing goldenseal root and 3 contained goldenseal herb as the sole active herbal ingredient.[55] The berberine concentration varied from 0.82% to 5.86%, whereas the hydrastine concentration ranged from 0% to 2.93%. Only 10 of 17 products met proposed U.S. Pharmacopeia standards for the hydrastine and berberine content of goldenseal root. Five products contained little or no hydrastine, unusual berberine-to-hydrastine ratios, and additional peaks not observed with other products.

Dosages three times a day are as follows:

- Dried root or infusion (tea): 2 to 4 g
- Tincture (1:5): 6 to 12 mL (1.5 to 3 tsp)
- Fluid extract (1:1): 2 to 4 mL (0.5 to 1 tsp)

- Solid (powdered dry) extract (4:1 or 8% to 12% alkaloid content): 250 to 500 mg
- Berberine sulfate: see dosage levels used in clinical studies referenced above (e.g., in type 2 diabetes: 500 mg two to three times a day)

TOXICITY

Berberine and berberine-containing plants are generally nontoxic at the recommended dosages. However, berberine-containing plants are not recommended for use during pregnancy, and higher dosages may interfere with B vitamin metabolism. Berberine is excreted via hepatobiliary mechanisms.[56]

The oral median lethal dose in rats for berberine is greater than 1000 mg/kg body weight, indicating that the toxicity is extremely low.[57]

DRUG INTERACTIONS

Berberine-containing plants may interfere with the absorption of tetracycline and related antibiotics. In one double-blind study, giving subjects 100 mg of berberine at the same time as 500 mg of tetracycline four times daily led to a reduction in the efficacy of tetracycline in subjects with cholera.[34] However, another double-blind study showed no interaction.[36] Nonetheless, simultaneous use is not recommended until this issue is clarified.

Berberine produces significant inhibition of CYP3A enzymes in humans.[54,58] Because most drugs are metabolized by these enzymes, berberine may decrease the clearance of many medications. CYP3A is involved in the metabolism of approximately half the drugs that are used today, including acetaminophen, codeine, ciclosporin, diazepam, and erythromycin. Sometimes this inhibitory effect of berberine on CYP3A may be useful for improving a therapeutic benefit. For example, the combined use of cyclosporine with berberine markedly increased the blood concentration of cyclosporin in heart transplantation recipients, reduced the dosage of cyclosporine required, and showed no obvious adverse reaction.[59] Berberine also increases the effectiveness of statin drugs to lower cholesterol; in one study, the effect of a simvastatin and berberine combination was 30% greater than simvastatin alone.[60]

Berberine-containing plants may enhance the effects of oral hypoglycemic drugs through its multitude of antidiabetic effects. Patients on oral hypoglycemic drugs should monitor blood glucose levels if taking berberine-containing plants. Adjustment of drug dosage may be required.

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CHAPTER 98

5-Hydroxytryptophan

Michael T. Murray, ND

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INTRODUCTION

5-Hydroxytryptophan (5-HTP) (Figure 98-1) is the intermediate between tryptophan and serotonin.[1] Although the use of 5-HTP may be relatively new to most clinicians, it has been available through pharmacies for several years and has been intensely researched for the past three decades. It has been used clinically since the 1970s.

TRYPTOPHAN AND 5-HYDROXYTRYPTOPHAN METABOLISM

Once tryptophan is absorbed from the intestines, it is carried by the blood to the liver, along with other amino acids consumed during the meal. Ingested tryptophan can pass into the general circulation, metabolize into blood proteins, or convert to kynurenine (which then goes on to form nicotinic acid, picolinate, and other important metabolites) in the liver. After conversion to kynurenine, it cannot be converted to serotonin. The same is likely true if the tryptophan is incorporated into blood proteins. Unchanged tryptophan can be converted to 5-HTP and then to serotonin. However, if this conversion occurs outside the brain, brain chemistry will not be influenced. Even under the best-case scenario, only 3% of a dosage of L-tryptophan in supplemental or dietary form is likely to be converted to serotonin in the brain.[2]

The manufacture of serotonin from tryptophan within the brain is highly dependent on the level of tryptophan or 5-HTP that crosses the blood–brain barrier. Although 5-HTP easily crosses the blood–brain barrier, the delivery of tryptophan into the brain depends on several factors. The first factor of importance is the level of free tryptophan in the blood. In a number of situations the liver's conversion of tryptophan to kynurenine occurs at an elevated rate (i.e., stress, elevated cortisol levels, low B vitamin status, and high doses of L-tryptophan [greater than 2000 mg]). All of these situations lead to increased activity of tryptophan oxidase and kynurenine formamidase, which convert tryptophan to kynurenine. Elevated levels of kynurenine block the entry of tryptophan into the brain and lower brain serotonin levels. Increasing tryptophan intake makes matters worse when tryptophan oxidase activity is increased.

Unlike 5-HTP, which easily enters the brain, the transport of tryptophan across the blood–brain barrier involves the binding of tryptophan to a transport molecule. As tryptophan shares this transport vehicle with several other amino acids, when the ratio of tryptophan to these other amino acids is low, little tryptophan is transported into the brain. The protein in almost all foods contains relatively small amounts of tryptophan and larger proportions of other amino acids. This generally leads to low serotonin levels with a high-protein intake. The opposite occurs with a high-carbohydrate meal.

PHARMACOLOGY

Several pharmacokinetic studies showed that about 70% of a dose of 5-HTP taken orally is delivered to the bloodstream.[3,4] The remaining 30% is metabolized by intestinal cells.

Ample evidence from these pharmacokinetic studies, as well as clinical studies, indicates that once absorbed, 5-HTP is delivered to the brain, resulting in increased formation of not only serotonin but also other brain chemicals (e.g., the monoamines

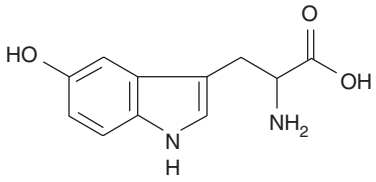


FIGURE 98-1 5-Hydroxytryptophan.

melatonin, endorphins, dopamine, and norepinephrine). By raising brain serotonin levels, as well as by other effects, 5-HTP showed positive effects in the various conditions associated with low serotonin levels.

Besides raising serotonin and melatonin levels, 5-HTP was shown to raise β-endorphin levels. Many pain-relieving and mood-elevating benefits of 5-HTP might be related more to its ability to enhance endorphin levels than to its ability to increase serotonin levels. This endorphin-increasing action is useful for both migraine and tension headache, fibromyalgia, and other painful situations. In addition, raising endorphin levels produces significant effects on mood and behavior.

By raising serotonin, melatonin, and β-endorphin levels, 5-HTP has a significant impact on helping to regulate and improve brain chemistry. 5-HTP was also shown to raise the levels of other important neurotransmitters, such as dopamine and norepinephrine.[5] The ability of 5-HTP to increase both serotonin (and other indolamines) and catecholamines is quite significant and unique to 5-HTP. It is an effect that 5-HTP does not share with L-tryptophan. The effective treatment of depression requires more than simply raising serotonin levels; catecholamine levels must also be increased. 5-HTP provides the brain with both sets of tools.

5-Hydroxytryptophan Versus L-Tryptophan

Nutrition-oriented physicians have long used precursor therapy for affecting brain chemistry. Unfortunately, L-tryptophan produced inconsistent results. These inconsistent results were likely due to its inconsistent elevation of brain serotonin levels.

In a head-to-head comparison study of 5-HTP and L-tryptophan in the treatment of depression, 5-HTP proved superior.[6] The proposed reason is the fact that 5-HTP easily crosses the blood–brain barrier and is not affected by competing amino acids. 5-HTP affects brain chemistry in a broader and more positive fashion. L-Tryptophan is often effective in cases of low serotonin, especially insomnia, but 5-HTP is more broadly effective.

There are many advantages of 5-HTP over L-tryptophan. Chief among them is that 5-HTP easily crosses the blood–brain barrier and is one step further on the path to serotonin synthesis. The conversion of tryptophan to 5-HTP by tryptophan hydrolase is the most important step in the manufacture of serotonin. This enzyme is inhibited by a number of factors, including the following:

- Stress
- Vitamin B_6 insufficiency
- Low magnesium levels
- Insensitivity to insulin
- Various hormones
- Genetic factors

In addition, as noted earlier, these same factors and others are known to increase the activity of tryptophan oxygenase, increasing the conversion of L-tryptophan to kynurenine.

Perhaps the biggest advantage of 5-HTP over L-tryptophan is that it is safer.[7] Although L-tryptophan is safe if properly prepared and free of the contaminants linked to eosinophilia myalgia syndrome (EMS), 5-HTP is inherently safer. The reasons are that taking L-tryptophan to produce positive effects in the treatment of depression, insomnia, and other low serotonin conditions requires a relatively high dose (e.g., a minimum of 2000 mg in insomnia and 6000 mg in depression). At high doses such as these, L-tryptophan is potentially problematic, because more L-tryptophan will be shunted toward the kynurenine pathway, and L-tryptophan promotes oxidative damage. Excessive levels of dietary tryptophan or high doses of L-tryptophan result in tryptophan actually acting as a free radical.[8] In contrast, 5-HTP is an antioxidant.[9] This antioxidant difference is due to the additional molecule of oxygen and hydrogen in 5-HTP. This simple change in molecular structure allows the phenolic ring structure to effectively accept or quench the unpaired electron of a free radical.

BOX 98-1 Conditions Associated with Low Serotonin Levels

- Depression
- Anxiety
- Obsessive compulsive disorder
- Obesity
- Carbohydrate craving
- Bulimia
- Insomnia
- Narcolepsy
- Sleep apnea
- Migraine headaches
- Tension headaches
- Chronic daily headaches
- Premenstrual syndrome
- Fibromyalgia
- Epilepsy
- Myoclonus
- Chronic pain disorders

CLINICAL APPLICATIONS

A massive amount of evidence suggests that low serotonin levels are a common consequence of modern living. The lifestyle and dietary practices of many people living in this stress-filled era result in lowered levels of serotonin within the brain. As a result, many people are overweight, crave sugar and other carbohydrates, experience bouts of depression, get frequent headaches, and have vague muscle aches and pains. All of these maladies are correctable by raising brain serotonin levels. The primary therapeutic applications for 5-HTP are low serotonin states, as listed in Box 98-1.

Depression

Some of the first clinical studies on 5-HTP for the treatment of depression began in the early 1970s in Japan. The first study involved 107 patients with either unipolar depression or manic bipolar depression.[10] These patients received 5-HTP at dosages ranging from 50 to 300 mg/day. The researchers observed a quick response (within 2 weeks) in more than half of the patients. Seventy-four of the patients either experienced complete relief or significantly improved, and none experienced significant side effects. These promising results were repeated in several other Japanese studies. An interesting aspect in two of these studies was the fact that 5-HTP was shown to be effective in some patients (50% in

one study, 35% in another) who had not responded positively to any other antidepressant agent.[11,12]

The most detailed of the Japanese studies was conducted in 1978.[13] The study enrolled 59 patients with depression (30 males and 29 females). The groups were mixed, in that both unipolar and bipolar depressions were included, along with a number of other subcategories of depression. The severity of the depression in most cases was moderate to severe. Patients received 5-HTP in dosages of 50 or 100 mg three times a day for at least 3 weeks.

The antidepressant activity and clinical effectiveness of 5-HTP was determined using a rating scale developed by the Clinical Psychopharmacology Research Group in Japan. The improvements among the various patients are detailed in Table 98-1. These results indicated that 5-HTP was helpful in 14 of 17 patients with unipolar depression and 12 of 21 patients with bipolar depression. The degree of improvement in most cases ranged from excellent to very good.

The results achieved in this open study were quite good, given how rapidly they were achieved. Thirty-two of the 40 patients who responded to 5-HTP did so within the first 2 weeks of therapy. Typically, in most studies with antidepressant drugs, the benefits are not apparent until after 2 weeks to 1 month of use. For this reason, the length of study when assessing antidepressant drugs should be at least 6 weeks, because it may take that long to significantly affect brain chemistry in a positive manner. In contrast, many of the studies with 5-HTP were shorter than 6 weeks because statistically significant results were achieved so soon (Table 98-2). However, the longer 5-HTP is used, the better the results. Some people may need to be on 5-HTP for at least 2 months before they experience benefits.

The only major side effect noted in this study was mild nausea. The occurrence of nausea due to 5-HTP is actually less frequent than that experienced with other antidepressant drugs (roughly 10% of subjects taking 5-HTP at a daily dose of more than 300 mg experience nausea compared with about 23% taking Prozac) and about the same as that which occurs with a placebo. In double-blind studies, about 10% or so of people taking the placebo typically complain of nausea. Nonetheless, mild nausea may be a natural consequence of elevated serotonin levels with 5-HTP. About 30% of the 5-HTP taken orally is converted to serotonin in the intestinal tract. This can lead to a mild case of nausea. Fortunately, this effect wears off after a few weeks of use.

A 5-HTP dosage of 150 to 300 mg/day is sufficient in most cases. For example, in one study, it was shown that 13 of 18 subjects with depression given 5-HTP at a level of 150 or 300 mg/day experienced good to excellent results.[14] This percentage of responders is quite good, but if the level of serotonin in the blood is viewed as a rough indicator of brain serotonin levels, some interesting conclusions can be made (Table 98-3). In some cases, a higher dosage may be necessary.

The measurements in Table 98-3 suggest that serotonin levels in depressed individuals are considerably lower than those found in normal subjects, and that individuals who respond to 5-HTP show a rise in serotonin to levels consistent with normal subjects. The level of serotonin in those who do not respond to 5-HTP remains quite low. These results imply that nonresponders may require higher doses to raise serotonin levels or that additional support may be necessary. When prescribing higher doses, it is important that the 5-HTP be taken in divided doses not only to reduce the problem with nausea, but also because the rate of brain cell uptake of 5-HTP is limited.

The first studies of 5-HTP were open trials.[15] The antidepressive effects of 5-HTP were also compared with L-tryptophan in the early 1970s.[6] In one study, 45 subjects with depression were given L-tryptophan (5 g/day), 5-HTP (200 mg/day), or a placebo. The patients were matched in clinical features (e.g., age, sex) and severity of depression. The main outcome measure was a rating scale called the Hamilton Depression Scale (HDS), the most widely used assessment tool in clinical research on depression.

TABLE 98-1 **Improvement in Various Subtypes of Depression**

	Improvement*						
SUBTYPE	1	2	3	4	5, 6, 7	8	1 + 2 + 3/TOTAL†
First-episode depression	1	1	0	1	0	0	2/3
Unipolar depression	3	8	3	1	2	0	14/17
Bipolar depression	6	4	2	3	3	3	12/21
Mixed depression	0	1	0	1	0	0	1/2
Presenile or senile depression	3	2	0	3	1	0	5/9
Neurotic depression	0	1	2	1	0	0	3/4
Reactive depression	0	1	1	0	0	0	2/2
Schizophrenic depression	0	1	0	0	0	0	1/1
Total	13	19	8	10	6	3	40/59
% of total	22	32.2	13.6	16.9	10.2	5.1	67.8

*Improvement: 1, marked improvement; 2, moderately improved; 3, slightly improved; 4, unchanged; 5, 6, 7, felt worse; 8, dropped out.
†The number of subjects that improved (improvement scores 1, 2, or 3) compared with the total number of subjects in that subtype.

TABLE 98-2 **Day When Improvements Were First Noticed**

IMPROVEMENT GROUP	Day					
	1	2	3	4-7	8-14	15
Marked	1	3	2	5	2	0
Moderate	0	1	13	1	4	0
Slight	0	2	2	2	1	1
Total	1	6	17	8	7	1

TABLE 98-3 **Level of Serotonin in Blood (nanograms per milliliter): Controls, Responders, and Nonresponders**

	BEFORE	AFTER 1 Wk (150 OR 300 mg/day 5-HTP)
Normal subjects	150	
Responders	78	148
Nonresponders	56	77

5-HTP, 5-Hydroxytryptophan.

TABLE 98-4 **Hamilton Depression Scale from a Comparative Study of 5-Hydroxytryptophan (5-HTP), L-Tryptophan, and Placebo**

	5-HTP	L-TRYPTOPHAN	PLACEBO
Beginning of the study	26	25	23
End of the study (30 days)	9	15	19

The HDS score is determined by having the test subject complete a series of questions in which he or she rates the severity of symptoms on a numerical basis, as follows:

- 0—not present
- 1—present but mild
- 2—moderate
- 3—severe
- 4—very severe

Symptoms assessed by the HDS include depression, feelings of guilt, insomnia, gastrointestinal symptoms and other bodily symptoms of depression (e.g., headaches, muscle aches, heart palpitations), and anxiety. The HDS is popular in research because it provides a good assessment of the overall symptoms of depression. Table 98-4 shows the results of the study.

A review of head-to-head comparison studies showed that 5-HTP, at a dosage of 200 mg/day, produced therapeutic success on a par with tricyclic antidepressant drugs.[16] Research also showed that combining 5-HTP with clomipramine and other types of antidepressant drugs produced better results than any of the compounds given alone.[17-22] For example, in one study, 5-HTP combined with a monoamine oxidase inhibitor demonstrated significant advantages compared with the monoamine oxidase inhibitor alone (Table 98-5).[21]

This line of research suggests that 5-HTP might also be used in conjunction with St. John's wort extract and *Ginkgo biloba* extract, two herbal medicines with proven antidepressant activity.

Because 5-HTP was expensive in 1972, researchers developed a test to determine who was most likely to respond to it, so that it would not be wasted on people who were unlikely to respond.[15,23] The test involved the patients first having a spinal tap to measure the level of 5-hydroxyindoleacetic acid (5-HIAA, the breakdown product of serotonin) in the cerebrospinal fluid (CSF). The drug probenecid, which prevents the transport of 5-HIAA from the CSF to the bloodstream, was administered for the next 3 days. As a result of this blocking action, the amount of serotonin produced over a 4-day period could be calculated by a repeat spinal tap on day 4. Because the 5-HIAA could not leave the CSF, it accumulated and provided a measure of serotonin manufacture.

The researchers discovered that the average level of 5-HIAA after 3 days of probenecid was significantly lower in depressed individuals than in controls matched for age, sex, and weight. This low level of serotonin reflected a decreased rate of manufacture within the brain. 5-HTP was most effective in patients with a low 5-HIAA response to 3 days of probenecid.[23-25] In other words, 5-HTP is most effective as an antidepressant when the amount of serotonin manufactured in the brain is reduced.

As stated earlier, 5-HTP often produces good results in patients who are unresponsive to antidepressant drugs. One of the more impressive studies involved 99 patients described as having "therapy-resistant" depression.[26] These patients did not respond to any previous therapy, including all available antidepressant drugs and electroconvulsive therapy. These therapy-resistant patients received 5-HTP at dosages averaging 200 mg/day but ranging from 50 to 600 mg/day. Complete recovery was seen in 43 of the 99 patients, and significant improvement was noted in 8 more. Such significant improvement in patients with long-standing, unresponsive depression is quite impressive, prompting the author of another study to state the following[27]:

> *L-5-HTP merits a place in the front ranks of antidepressants instead of being used as a last resort. I have never in 20 years used an agent that (1) was effective so quickly; (2) restored patients so completely to the persons they had been and their partners had known; and (3) was so entirely without side effects.*

TABLE 98-5 **Change in Hamilton Rating Scale for Depression**

	5-HTP + MAO	MAO + PLACEBO
Initial measurement	28.67	26.33
After 8 days	16.67	19.23
After 15 days	11.77	6.03

5-HTP, 5-hydroxytryptophan; MAO, monoamine oxidase.
Modified from Alino JJ, Gutierrez JL, Iglesias ML. 5-Hydroxytryptophan (5-HTP) and a MAOI (nialamide) in the treatment of depressions. A double-blind controlled study. Int Pharmacopsychiatry 1976;11:8-15.

A 1987 review article on 5-HTP in depression highlighted the need for well-designed, double-blind, head-to-head studies of 5-HTP versus standard antidepressant drugs.[28] Although 5-HTP was viewed as an antidepressant agent with few side effects, the authors of this review felt that the big question to answer was how 5-HTP compared with the new breed of antidepressant drugs, the selective serotonin reuptake inhibitors (SSRIs) like Prozac, Paxil, and Zoloft. In 1991, a double-blind study comparing 5-HTP with an SSRI was conducted in Switzerland.[29] 5-HTP was compared in the study with the SSRI fluvoxamine (Luvox). Fluvoxamine is used primarily in the United States as a treatment for obsessive compulsive disorder, an anxiety disorder characterized by obsessions and compulsions affecting an estimated 5 million Americans. Fluvoxamine exerts antidepressant activity comparable to (if not better than) other SSRIs like Prozac, Zoloft, and Paxil.

In the study, subjects received either 5-HTP (100 mg) or fluvoxamine (50 mg) three times a day for 6 weeks. The assessment methods used to judge effectiveness included the HDS, self-assessment depression scale (SADS), and physician's assessment (Clinical Global Impression). As indicated in Table 98-6, the percentage decrease in depression was slightly better in the 5-HTP group (60.7% versus 56.1%). 5-HTP was quicker acting than the fluvoxamine, and a higher percentage of patients responded to 5-HTP than to fluvoxamine.

The advantages of 5-HTP over fluvoxamine are evident when looking at the subcategories of the HDS: depressed mood, anxiety, physical symptoms, and insomnia. For depressed mood, 5-HTP produced a 65.7% reduction in severity compared with 61.8% for fluvoxamine; for anxiety, 5-HTP produced a 58.2% reduction in severity compared with 48.3% for fluvoxamine; for physical symptoms, 5-HTP produced a 47.6% decrease in severity compared with 37.8% for fluvoxamine; and for insomnia, 5-HTP produced a 61.7% decrease in severity compared with a 55.9% decrease for fluvoxamine. However, perhaps more important than simply relieving insomnia was 5-HTP's ability to improve the quality of sleep. In contrast, antidepressant drugs greatly disrupt sleep processes. On the SADS, 5-HTP produced a 53.3% drop in SADS values compared with a drop of 47.6% for the fluvoxamine group. A drop greater than 50% is an excellent result. A 50% drop is the best SSRIs generally produce.

5-HTP is equal to or better than standard antidepressant drugs, and the side effects are much less severe (Table 98-7). In the study

TABLE 98-6 **5-Hydroxytryptophan (5-HTP) Versus Fluvoxamine in Percentage Changes in the Hamilton Depression Scale (HDS)**

	DECREASE IN HDS	5-HTP (n = 34)	FLUVOXAMINE (n = 29)
After 2 wks	Mean decrease (%)	23	18.9
	<35% decrease	20	19
	35%-50% decrease	10	8
	50%-75% decrease	4	2
After 4 wks	Mean decrease (%)	46.2	46.1
	<35% decrease	2	8
	35%-50% decrease	7	3
	50%-75% decrease	12	13
	>75% decrease	3	5
After 6 wks	Mean decrease (%)	60.7	56.1
	<35% decrease	4	5
	35%-50% decrease	8	3
	50%-75% decrease	12	8
	>75% decrease	10	13

TABLE 98-7 **5-Hydroxytryptophan (5-HTP) Versus Antidepressant Drugs: Comparison of Side Effects**

	Percentage of Patients Experiencing Side Effects		
SIDE EFFECTS	5-HTP	TRICYCLICS	SSRIs
Nausea	9	15	23
Headache	5	16	20
Nervousness	2.5	11	16
Insomnia	2.5	7	17
Anxiety	2.5	9	14
Drowsiness	7	23	11
Diarrhea	2.5	4	12
Tremor	0	18	11
Dry mouth	7	64.5	12
Sweating	2.5	15	9
Dizziness	5	25.5	7
Constipation	5	25	5.5
Vision changes	0	14.5	4

SSRIs, selective serotonin reuptake inhibitors.

comparing 5-HTP with fluvoxamine, this is how the physicians described the differences among the two groups: Whereas the two treatment groups did not differ significantly in the number of patients sustaining adverse events, the interaction between the degree of severity and the type of medication was highly significant: fluvoxamine predominantly produced moderate to severe side effects; oxitriptan (5-HTP) produced primarily mild forms of adverse effects.

Fourteen (38.9%) of the patients receiving 5-HTP reported side effects compared with 18 patients (54.5%) in the fluvoxamine group. The most common side effects with 5-HTP were nausea, heartburn, and gastrointestinal problems (flatulence, feelings of fullness, and rumbling sensations). These side effects were rated as being very mild to mild. In contrast, most of the side effects experienced in the fluvoxamine group were of moderate to severe intensity. The only subject to drop out of the 5-HTP group did so after 35 days (5 weeks), whereas four subjects in the fluvoxamine group dropped out after only 2 weeks. On the basis of studies on weight loss, the longer that 5-HTP is used (e.g., after 4 to 6 weeks of use), the less the problem with mild nausea.

5-HTP has been shown to have "equipotency" with SSRIs and tricyclic antidepressants in terms of effectiveness, but offers several advantages in that it is better tolerated and associated with fewer and much milder side effects. In addition, many people prefer to use a natural substance like 5-HTP over synthetic drugs.

L-Tyrosine: An Adjunct to 5-Hydroxytryptophan

In the early 1970s, researchers discovered that, in about 20% of patients who responded well to 5-HTP, the results tended to decrease after 1 month of treatment. The antidepressant effects of 5-HTP in these subjects began to wear off gradually after the first month despite the fact that the level of 5-HTP in the blood, and presumably the level of serotonin in the brain, remained at the same level as when they were experiencing benefits.[8]

The researchers discovered that although serotonin levels appeared to stay at the same levels after 1 month of treatment, the levels of the other important monoamine neurotransmitters, dopamine and norepinephrine, declined.[28] As discussed earlier, when depressed patients are treated with 5-HTP, they experience a rise not only in serotonin but also in catecholamines like dopamine and norepinephrine. In about 20% of subjects, the catecholamine-enhancing effects of 5-HTP tended to wear off. Providing these patients with L-tyrosine, the amino acid precursor to the catecholamines, helped to reestablish the efficacy of 5-HTP.[8,30] The dosage was 200 mg/day for 5-HTP and 100 mg/kg body weight for L-tyrosine. This dosage for L-tyrosine is quite high and requires substantial clinical supervision.

Anxiety and Panic Disorder

5-HTP showed an ability to relieve anxiety in studies in depressed individuals. Lowering the availability of serotonin to the brain by tryptophan depletion increased the vulnerability of panic disorder patients for an experimental carbon dioxide panic challenge, and increasing the availability of serotonin inhibited the response to such a challenge. When 5-HTP or placebo was given to 24 panic disorder patients and 24 healthy volunteers before panic challenge, 5-HTP significantly reduced the reaction to the panic challenge in panic disorder patients regarding subjective anxiety, panic symptom score, and number of panic attacks, as opposed to placebo.[31] These results indicate that 5-HTP might be helpful in relieving panic attacks.

Weight Loss

A considerable body of scientific evidence documents the major role serotonin in the brain plays in influencing eating behavior. A key finding is that when animals and humans are fed tryptophan-free diets, appetite is significantly increased, resulting in binge eating—carbohydrates would be preferable, but animals binge on whatever is available.[2,3] A diet low in tryptophan leads to low brain serotonin levels; as a result, the brain senses it is starving and stimulates the appetite control centers in a powerful way. This stimulation results in a preference for carbohydrates.

Researchers discovered that when animals or humans are fed a carbohydrate meal, more tryptophan is delivered to the brain, resulting in more serotonin being manufactured. This scenario led to the idea that low serotonin levels lead to "carbohydrate craving" and play a major role in the development of obesity, as well as bulimia.[32]

Cravings for carbohydrates can be mild or quite severe. They may range in severity from the desire to nibble one piece of bread or cookie to uncontrollable binging. At the upper end of the spectrum of carbohydrate addiction is bulimia, a potentially serious eating disorder characterized by binge eating and purging of the food through forced vomiting or the use of laxatives. The serotonin theory of bulimia is that low serotonin levels trigger binge eating, which leads to a rush of serotonin being produced and released in the brain.[33,34] This increased serotonin effect produces a brief reduction in feelings of stress and tension. This serotonin "fix" is short-lived and followed by feelings of guilt and low self-esteem. The current medical treatment for bulimia is the use of drugs that enhance the effects of serotonin. Although there are no reports in the medical literature of 5-HTP being used in the treatment of bulimia, given its effects on serotonin levels, it merits consideration.

5-HTP may help to prevent the decline in serotonin levels associated with a reduced calorie intake. Concentrations of tryptophan in the bloodstream and subsequent brain serotonin levels plummet with dieting.[35] In response to severe drops in serotonin levels, the brain puts out a strong message to eat. This situation sets up the scenario to explain why most diets do not work.

As far back as 1975, researchers demonstrated that giving 5-HTP to rats who were genetically bred to overeat and be obese resulted in a significant reduction in food intake.[36] It turns out that these rats bred to be fat had decreased activity of the enzyme that converts tryptophan to 5-HTP and subsequently to serotonin.

There is circumstantial evidence that many humans are genetically predisposed to obesity. This predisposition may involve the same mechanism as rats genetically predisposed to obesity. By providing preformed 5-HTP, this genetic defect is bypassed and more serotonin is manufactured.

The early animal studies with 5-HTP as a weight-loss aid were followed by a series of three human clinical studies. The first study involved 19 significantly overweight female subjects with a body mass index ranging from 30 to 40 kg/m^2.[37] Analysis of the pretreatment dietary intake concluded that these women tended to overeat carbohydrates. Food intake and eating behavior were assessed using a 3-day diet diary at the beginning and end of the two treatment periods. All food was carefully weighed before meals and weighed again if there were any leftovers. Participants also filled out a self-evaluation of appetite and satiety twice a week, and mood was evaluated using standard psychological tests.

The daily dosage of 5-HTP used in the study was 8 mg/kg body weight. Patients were given either 5-HTP or placebo 20 minutes before meals for 5 weeks, and after a 1-week interval were switched to receive the other treatment. No dietary restrictions were prescribed because the researchers wanted to answer the question, "Does 5-HTP reduce appetite and promote weight loss without any conscious effort?" To make sure that the women actually took the 5-HTP, researchers measured the level of the serotonin breakdown product, 5-HIAA, in the urine. Table 98-8 lists the results of the study.

These results with 5-HTP were achieved without the women making any conscious effort to reduce food consumption. The average amount of weight loss during the 5-week period of 5-HTP supplementation was a little more than 3 lb, compared with less than 1 lb of total weight loss during the placebo period.

TABLE 98-8 **The Effect of 5-Hydroxytryptophan (5-HTP) on Food Intake**

	FOOD INTAKE (calories/day)	PROTEIN INTAKE (g/day)	CARBOHYDRATE INTAKE (g/day)
Pretreatment	2903	101	274
Placebo	2327	85	223
5-HTP	1819	79	176

TABLE 98-9 **Impact of 5-Hydroxytryptophan (5-HTP) on Weight Loss**

	PLACEBO	5-HTP
Weight (lb)		
Baseline	207.68	229.46
After 6 wks	206.58	225.94
After 12 wks	205.4	219.12
Total weight loss (lb)		
After 6 wks	1.1	3.52
After 12 wks	2.28	10.34

Interestingly, evaluation of the various self-tests indicated that appetite or degree of initial hunger did not differ between the two groups. What differed was satiety. In other words, the 5-HTP did not reduce appetite before a meal, but after consuming an adequate amount of food, the satiety centers in the brain were stimulated, and the women did not feel hungry. As a result, their caloric intake was dramatically reduced.

The level of 5-HIAA, the breakdown product of serotonin, in the group receiving the 5-HTP increased by more than fifty-fold over the control group. This increase provided two things: (1) it assured researchers that subjects actually took the 5-HTP, and (2) it clearly indicated that 5-HTP increased serotonin manufacture.

The next study sought to determine if 5-HTP helped overweight individuals adhere to dietary recommendations.[38] Fourteen overweight female subjects with a body mass index between 30 and 40 kg/m^2 were enrolled in the double-blind study.[10] Again, analysis of the pretreatment dietary intake concluded that these women tended to overeat. The women were randomly assigned to receive either 5-HTP (300 mg) or placebo 30 minutes before meals. The 12-week study was divided into two 6-week periods. For the first 6 weeks, there were no dietary recommendations, and for the second 6 weeks the women were placed on a 1200-calorie diet.

The women were seen every 2 weeks to evaluate body weight, diet diaries, self-evaluations of appetite, and satiety. The women were also asked if they experienced the presence of meat aversion; taste or smell alterations; early satiety; and nausea or vomiting, or both. To verify patient compliance, urinary measurement of 5-HIAA was again determined. As shown in Table 98-9, the women taking the placebo lost 2.28 lb, whereas the women taking the 5-HTP lost 10.34 lb.

Like the previous study, 5-HTP appeared to promote weight loss by promoting satiety. Although some women reported some aversion to meat or altered taste and smell, each woman (100%) reported early satiety (Table 98-10). Most of the women receiving

TABLE 98-10 **Impact of 5-Hydroxytryptophan (5-HTP) on Appetite and Satiety**

	5-HTP		PLACEBO	
	WK 1-6	WK 7-12	WK 1-6	WK 7-12
Taste alteration	2/7	1/7	0/7	0/7
Smell alteration	2/7	1/7	0/7	0/7
Meat aversion	3/7	1/7	0/7	0/7
Early satiety	7/7	6/7	2/7	2/7
Nausea	5/7	0/7	1/7	2/7

5-HTP also experienced mild nausea during the first 6 weeks of the trial, but during the last 6 weeks none complained of nausea. The fact that weight loss was accelerated during the second 6-week period makes it highly unlikely that 5-HTP promoted weight loss as a result of producing nausea.

One study with 5-HTP enrolled overweight women with a body mass index ranging between 30 and 40 kg/m^2 and an overactive appetite.[39] The 28 subjects of the study were given either 5-HTP (300 mg three times daily before meals) or a placebo. For the first 6 weeks, there were no dietary restrictions, and for the second 6 weeks, the women were placed on a diet of 1200 calories/day. Carbohydrates contributed 53% of the calories, fats comprised 29%, and proteins provided 18%. No carbohydrate-rich foods were permitted between meals. Subjects were examined every 2 weeks to evaluate food intake and body weight. Routine blood measurements were also performed at the beginning, at 6 weeks, and at the end of the study. To verify patient compliance, urinary measurement of 5-HIAA was determined.

The results from this study were even more impressive than the previous studies for several reasons. The group receiving the 5-HTP lost an average of 4.39 lb after the first 6 weeks and an average of 11.63 lb after 12 weeks. In comparison, the placebo group lost an average of only 0.62 lb after the first 6 weeks and 1.87 lb after 12 weeks. The lack of weight loss during the second 6-week period in the placebo group obviously reflected the fact that the women had difficulty adhering to the diet.

Early satiety was reported by 100% of the subjects during the first 6-week period. During the second 6-week period, even with severe caloric restriction, 90% of the women taking 5-HTP reported early satiety. Once again, many of the women receiving the 5-HTP reported mild nausea during the first 6 weeks of therapy. However, the symptom was never severe enough for any of the women to drop out of the study. No other side effects were reported.

On the basis of the urinary measurements of 5-HIAA, the women took their 300 mg of 5-HTP with meals and, as a result, achieved weight loss. The amount of weight loss was amplified by a better capability to adhere to a 1200-calorie diet. The structure of the dietary changes reflected primarily a reduction in pasta, bread, and other carbohydrate-rich foods (the study was conducted in Rome).

In the latest study, 25 overweight non–insulin-dependent diabetic outpatients were enrolled in a double-blind, placebo-controlled study and randomized to receive either 5-HTP (750 mg/day) or placebo for 2 consecutive weeks, during which no dietary restrictions were prescribed.[40] Results again indicated that patients receiving 5-HTP significantly decreased their daily energy intake by reducing carbohydrate and fat intake and reduced their body weight.

Insomnia

Several clinical studies showed 5-HTP produced good results in promoting and maintaining sleep in normal subjects, as well as in those experiencing insomnia.[39-46] One of the key benefits with 5-HTP in the treatment of insomnia is its ability to increase sleep quality. This effect is evident by its ability to increase rapid eye movement (REM) sleep (typically by about 25%) while simultaneously increasing deep sleep stages 3 and 4 without increasing total sleep time.[39,42] The sleep stages that are reduced by 5-HTP to compensate for the increases are non-REM stages 1 and 2, the least important stages of sleep. In one of the studies, the subjects receiving 200 mg of 5-HTP increased their amount of REM sleep by 15.5 minutes during the five-night study.[39] Subjects taking 600 mg of 5-HTP increased REM sleep time by an average of 20 minutes for the five-night study. These results indicated that 5-HTP increased the amount of dream time by about 3 to 4 minutes a night.

Although there was a clear dose-related effect, the lower dosage is sufficient in most cases. In addition, taking too much 5-HTP may increase REM sleep to an abnormal level, leading to an increased risk for nightmares. That said, 5-HTP might prove effective in sleep terrors in children. To test this hypothesis, an open trial in a group of children with sleep terrors was compared with a group of children with the same disorder but without 5-HTP treatment.[47] 5-HTP was administered (2 mg/kg per day) at bedtime to 31 randomly selected patients for 20 consecutive days. After 1 month of treatment, 29 of 31 (93.5%) patients showed a positive response. In the comparison group without drug therapy, after 1 month, the episodes disappeared only in four children (28.6%), whereas ten children (71.4%) showed persistence of episodes with the same frequency as before. After 6 months, 26 of 31 (83.9%) children treated with 5-HTP were sleep terror–free, whereas in five children (16.1%) sleep terror episodes persisted. Of the children in the comparison group, 10 (71.4%) continued to show sleep terrors at 6-month follow-up. These results represent preliminary evidence that treatment with 5-HTP is able to modulate the arousal level in children and to induce a long-term improvement of sleep terrors.

Migraine and Tension Headache

The relationship of serotonin and headaches is fully described in Chapter 190. Because migraine patients have low levels of serotonin in their tissues, some researchers refer to migraine as a "low serotonin syndrome."[46] Although the primary benefit of 5-HTP in the prevention of both migraine and tension headache is related to its ability to normalize underlying imbalances in the serotonin system, it also influences the endorphin system in a positive way.

Several clinical studies on using 5-HTP for headaches, both vascular and nonvascular, showed excellent results. In particular, the use of 5-HTP in the prevention of migraine headache offers considerable advantages over drug therapy. Although a number of drugs were shown to be useful in the prevention of migraine headaches, all of them carry significant side effects.

The problem with drug therapy in the prevention of migraine headaches is perhaps best exemplified by one of the most commonly used drugs, methysergide (Sansert). Methysergide therapy for the prevention of migraine attacks is effective in about 60% to 80% of cases. However, this effectiveness is not without a high price, since side effects are quite common and can be severe. Retroperitoneal fibrosis, pleuropulmonary fibrosis, and fibrotic thickening of cardiac valves may occur in patients receiving long-term

TABLE 98-11 **5-Hydroxytryptophan (5-HTP) Versus Methysergide: Clinical Effects of Treatment in 124 Patients**

	METHYSERGIDE	5-HTP
No attacks (100% reduction)	35%	25%
Improvement (>50% reduction)	40%	46%
No improvement	12.5%	29%
Withdrawal due to side effects	12.5%	0%

methysergide maleate therapy. Therefore, this preparation must be reserved for prophylaxis in patients whose vascular headaches are frequent or severe and uncontrollable, and for those who are under close medical supervision.

Several studies compared 5-HTP with methysergide in the prevention of migraine headaches. In one of the largest double-blind studies, 124 patients received either 5-HTP (600 mg/day) or methysergide (3 mg/day) in identical pills for 6 months.[48] Treatment was determined successful if there was a reduction higher than 50% in the frequency of attacks or in the number of severe attacks. Although 75% (30 of the remaining 40 patients) taking methysergide demonstrated significant improvement compared with 71% (32 of the 45 patients), this difference was not viewed as statistically significant (Table 98-11). The advantage of 5-HTP over methysergide was demonstrated when researchers looked at side effects. Side effects were more frequent in the group receiving methysergide than in the 5-HTP group. Five patients in the methysergide group withdrew during the trial because of side effects.

Two other studies comparing 5-HTP with drugs used in the prevention of migraine headaches (pizotifen and propranolol) demonstrated that 5-HTP compared quite favorably in terms of effectiveness.[49,50] Although these drugs have significant side effects, 5-HTP is extremely well tolerated even at dosages as high as 600 mg/day. One of the other key differences noted in these studies between 5-HTP and the drugs was 5-HTP's ability to improve mood and relieve feelings of depression.

In a double-blind study of 5-HTP in chronic tension headache, 78 patients with chronic tension-type headaches were treated with 5-HTP (300 mg/day) or placebo for 8 weeks.[48] In comparison with the group treated with placebo, there were no statistically significant changes in the number of days with headache or in headache intensity in the group treated with 5-HTP; however, there was a significant decrease in the consumption of analgesics.[51] During the 2 weeks after treatment, there was also a significant decrease in the number of days with headache. Subjective opinion during this latter period was also favorable to 5-HTP.

Juvenile Headache

One of the best uses of 5-HTP is in chronic headaches in children. These headaches are a big problem because of the tremendous risk for side effects of the current drugs used to treat, as well as prevent, them. Several studies of 5-HTP in the treatment of chronic headaches in children and adolescents showed excellent results.[52-54] Given the risks of current drugs used in chronic childhood headaches, a trial of 5-HTP for 2 months certainly seems reasonable. If the headaches are also accompanied by sleep disorders, 5-HTP appears to be especially well suited.

In one study, 48 elementary and junior high students with recurrent headaches (at least one headache every 2 weeks) and sleep disorders, including difficulty in getting to sleep, frequent awakenings, sleep walking, nightmares, and bedwetting, were divided into two groups.[52] Group A was given 5-HTP for 2 months, followed by a placebo for 2 months, whereas group B received just the opposite. It was necessary to divide group A into a nine-patient subgroup, Group C. These nine patients did so well on the 5-HTP that they did not want to switch over to the other medication, although they had no idea whether they were, in fact, taking 5-HTP or were on a placebo. The dosage of 5-HTP was based on the child's weight (4.5 mg/kg per day).

The headache index was reduced by about 70% when the kids were taking 5-HTP compared with an 11.5% drop when they were taking the placebo. In the nine patients in group C, there was an 81.8% decrease in the headache index after the second month. Interestingly, these same patients only exhibited an 18.2% reduction after the first month. These results indicated that evaluation of the benefits of 5-HTP in the treatment of headaches required at least a 2-month trial. The failure to show benefit with 5-HTP in some studies in headaches might be due to the fact that they lasted less than 2 months. The 25 patients experienced a modest reduction in frequent awakenings, nightmares, sleep walking, and talking while asleep, and no change in difficulty falling asleep or in bedwetting.

Overall, this study demonstrated very good effects in these children. Perhaps the most impressive aspect to consider, however, was the fact that these benefits were achieved without side effects. Not a single child reported a side effect while taking 5-HTP. Interestingly, for some reason, children rarely experience even mild nausea from 5-HTP.

The possible benefits of using 5-HTP in children with recurrent headaches or sleep disorders, or both, is far-reaching. Evaluation of the 48 children in the trial demonstrated inadequate school progress compared with their classmates. The children were shown to be of normal intellectual capacity but demonstrated inattentiveness similar to that observed in depression. Many of the children might have had depression. The unwillingness of the nine subjects in Group C to switch to the other unknown medication (which was the placebo) is a strong indicator that these children and their parents noted some rather dramatic improvements beyond simply a reduction in headaches or improved sleep.

The manner in which 5-HTP may be of benefit in migraine headaches may not simply be the overcoming of some defect in serotonin synthesis. As noted previously, part of the clinical benefit of 5-HTP may be via an ability to increase the levels of β-endorphin. A decrease in β-endorphin level in migraine, as well as tension headache patients, was demonstrated by several investigators.[55,56]

A clinical trial measured the effects of 5-HTP on serotonin and β-endorphin levels in 20 juvenile patients with migraine or tension-type headaches.[57] Patients were monitored and evaluated for frequency and intensity of headache attacks for 3 months before 5-HTP treatment and 3 months of therapy. The researchers reported a statistically significant reduction in the headache score with 5-HTP treatment in both migraine and tension-type patients. These improvements were likely due to increased β-endorphin levels, as noted in Table 98-12. However, the level of β-endorphins achieved with 5-HTP, especially as measured in the white blood cell, was still far less than that observed in control patients without recurrent headache. These results imply that longer periods of 5-HTP supplementation may be required before there is a normalization of β-endorphin levels in children prone to headaches.

TABLE 98-12 **Serotonin and β-Endorphin Levels in Juvenile Patients with Headaches Before and After Administration of 5-Hydroxytryptophan (5-HTP)**

	SEROTONIN (SERUM, mg/L)	BETA-ENDORPHIN (PLASMA, pmol/L)	BETA-ENDORPHIN (WHITE BLOOD CELLS, pmol/10^6 GB/L)
Migraine (13 subjects)			
Before	104.6	16.2	110.5
After	115.7	19.4	120.3
Tension-type (7 subjects)			
Before	90.7	14.5	142.3
After	97.2	17.6	152.4
Total (20 subjects)			
Before	100.5	15.7	129.3
After	108.3	18.4	140.4
Controls (17 subjects)			
	96	21.3	359.3

These results may indicate that 5-HTP alone is not able to raise β-endorphin levels sufficiently to reduce or eliminate headaches, suggesting that other therapies designed to increase β-endorphin levels should be used along with 5-HTP. Examples of other therapies that have been shown to raise β-endorphin levels are exercise, acupuncture, and biofeedback.

Fibromyalgia

The history of the development of 5-HTP as an effective treatment for fibromyalgia began with studies on the drug fenclonine.[58] This drug blocks the enzyme that inhibits the conversion of tryptophan to 5-HTP and, as a result, blocks serotonin production. During the late 1960s and early 1970s, it was thought that increased serotonin formation might promote migraine headaches (the opposite of what was later proved, i.e., increasing serotonin levels reduced migraine headache occurrence). The researchers discovered that providing headache patients with fenclonine resulted in severe muscle pain. This effect was the exact opposite of what was expected, but led to some important advances in the understanding of fibromyalgia—a way to induce its severe symptoms of (as well as symptoms nearly identical to) EMS, the condition caused by contaminated L-tryptophan. The researchers also discovered that migraine patients had a greater reaction to the drug than non-headache subjects. In most normal subjects, fenclonine produced no fibromyalgia. These occurrences highlighted just how sensitive migraine patients are to low serotonin levels.

Migraine headaches and fibromyalgia share a common feature: both are low serotonin syndromes.[59] After more than 25 years of research, one of the lead researchers stated: "In our experience, as well as in that of other pain specialists, 5-HTP can largely improve the painful picture of primary fibromyalgia."[60]

A double-blind study in 50 patients with fibromyalgia found that 100 mg of 5-HTP three times per day significantly improved their symptoms.[61] As shown in Table 98-13, 5-HTP was rated substantially better than placebo by subjects and evaluating physicians. Improvements were noted in all symptom categories: number of painful areas, morning stiffness, sleep patterns, anxiety, and fatigue. In another study, 100 mg of 5-HTP taken three times a day demonstrated maximum results by day 30 of the 90-day trial.[62]

TABLE 98-13 **Patients' and Physicians' Opinions on the Effectiveness of 5-Hydroxytryptophan (5-HTP) Versus Placebo in Fibromyalgia**

RESPONSE	5-HTP	PLACEBO
Good	11	1
Fair	8	5
Poor	4	8
None	0	9

One of the primary benefits with 5-HTP in fibromyalgia may be its ability to improve sleep quality. A key finding in patients with fibromyalgia is a reduced REM sleep and an increase in non-REM sleep.[63] In addition, the deeper levels (stages III and IV) are not achieved for long enough periods. As a result, people with fibromyalgia wake up feeling fatigued and in pain. The severity of the pain of fibromyalgia correlates with the rating of sleep quality. For example, a study of 50 women with fibromyalgia syndrome recorded their sleep quality, pain intensity, and attention to pain for 30 days, using palm-top computers programmed as electronic interviewers.[64] They described their previous night's sleep quality within 30 minutes of awakening each day and at randomly selected times in the morning, afternoon, and evening rated their present pain. The researchers found that a night of poor sleep was followed by a significantly more painful day, and a more painful day was followed by a night of even poorer sleep. 5-HTP might help to break the cycle by addressing the low serotonin level, as well as by promoting a restful sleep.

Parkinson's Disease

The use of 5-HTP in Parkinson's disease provides some benefit, but only if used in combination with the drug Sinemet (the combination of L-dopa with the decarboxylase inhibitor carbidopa). Although brain levels of serotonin are decreased in Parkinson's disease, the reduction in dopamine receptors is more severe. Increasing serotonin levels with 5-HTP in patients not taking Sinemet is associated with worsening of symptoms, especially rigidity.[65]

One of the key benefits of taking 5-HTP in Parkinson's disease is that it can help to counteract the negative effects that the L-dopa in the Sinemet has on sleep and mood.[66-68] In addition, 5-HTP was also shown to improve the physical symptoms of Parkinson's disease.

About 9 of 10 people with Parkinson's disease have depression. The degree of depression in Parkinson's disease is a reflection of their serotonin levels. The lower the level of serotonin, the more severe is their depression. One study examined the effect of 5-HTP in seven Parkinson's disease patients, all of whom were on Sinemet.[65] The initial dosage of 5-HTP was 75 mg, which was increased by 25 mg every 3 days until the patients reported a relief of their depression, or up to a maximum of 500 mg/day for 4 months. The impressive results obtained in these patients are shown in Table 98-14.

Six of seven patients responded to 5-HTP. It should be noted that the doses of 5-HTP in five of the six patients who responded ranged from only 75 to 125 mg. The only patient who did not respond took 500 mg of 5-HTP.

TABLE 98-14 **The Effect of 5-Hydroxytryptophan (5-HTP) on Depression in Parkinson's Disease**

PATIENT NO.	L-DOPA (mg/day)	CARBIDOPA (mg/day)	5-HTP (mg/day)	HDS	
				BEFORE	AFTER
1	1000	175	125	22	11
2	300	75	75	14	3
3	400	150	100	21	13
4	1000	100	100	12	6
5	500	125	500	18	22
6	1125	112.5	300	18	7
7	500	50	100	17	13

HDS, Hamilton Depression Scale.

Seizure Disorders

Most of the recent research on 5-HTP focused on its use in the treatment of several seizure disorders.[69-73] 5-HTP showed good results in most (but not all) studies in patients with diseases characterized by myoclonus, with the exception of epilepsy, which is not helped by 5-HTP.

The best response to 5-HTP for myoclonus occurs in people who have intention myoclonus, which is most often produced as a result of ischemic damage to the brain.[35] Intention myoclonus can be a problem after a stroke or heart attack, overdosage of a drug such as heroin, a severe asthma attack, or an adverse reaction to anesthesia or another chemical. Improvements with 5-HTP were demonstrated in patients with intention myoclonus. 5-HTP also produced good results in patients with progressive myoclonus epilepsy, essential myoclonus, palatal myoclonus, and Friedreich's ataxia.[74]

In a 1983 article, one researcher of 5-HTP stated: "Some helpless bedridden patients dramatically improved to the extent that they could walk again and resume independent living."[75] Because of the phenomenal results, 5-HTP was the first compound to be evaluated as an orphan drug by the Pharmaceutical Manufacturing Associations Commission on Drugs for Rare Diseases.

DOSAGE

Enteric-coated preparations are required to avoid nausea. The dosage should be started at 50 mg three times daily. If the response is inadequate after 2 weeks, increase the dosage to 100 mg three times daily. This recommendation will greatly reduce the mild symptoms of nausea often experienced during the first few weeks of 5-HTP therapy. Because 5-HTP does not rely on the same transport vehicle as L-tryptophan, it can also be taken with food. Because the half-life of 5-HTP is relatively short (3 to 4 hours with peak serum levels achieved at 1 to 2 hours), more frequent dosing may be more effective than single higher doses.

For insomnia, the general recommendation is 100 to 300 mg, 30 to 45 minutes before retiring. Start with the lower dose for at least 3 days before increasing dose.

TOXICOLOGY

The major concern with 5-HTP is a possible link to L-tryptophan and EMS. However, an important distinction must be made in the manufacturing process. Although L-tryptophan is produced via bacterial fermentation and filtration, 5-HTP is commercially available through an extraction process from the seed of *Griffonia simplicifolia*, an African plant. 5-HTP extracted from this natural source avoids the contamination problem associated with past manufacturing of L-tryptophan.

Detailed analyses of all evidence by the Centers for Disease Control and Prevention and other experts led to the conclusion that the cause of the EMS epidemic could be traced to a single Japanese manufacturer, Showa Denko.[76,77] Of the six Japanese companies that supplied L-tryptophan to the United States, Showa Denko was the largest (50% to 60% of all the L-tryptophan). The L-tryptophan was used not only as a nutritional supplement but also in infant formulas and nutrient mixtures for intravenous feeding.

A single case report linked 5-HTP to a condition similar to EMS in 1980.[78] However, this case involved the use of high dosages of 5-HTP (1400 mg) over a 20-month period. Further examination of the patient indicated a defect in tryptophan metabolism that resulted in elevations in kynurenine. Such defects in tryptophan metabolism are common in patients with scleroderma, which shares many common features with EMS. It appeared that either the 5-HTP might have contained a contaminant to which this man was sensitive or that taking such high doses of 5-HTP over a prolonged period of time aggravated his abnormal handling of L-tryptophan.

There was also a report of a 28-year-old woman, her husband, and her two sons, 33 and 13 months old, who developed an EMS-like illness in response to contaminated 5-HTP.[76] The young boys inherited the inability to convert tryptophan to 5-HTP. As a result, they required daily administration of 5-HTP (5 to 7 mg/kg). Both boys received the 5-HTP almost from birth.

The mother was not taking 5-HTP, but she prepared it for the young boys by opening the capsules, mixing the powder in juice or water, and giving it to them orally with a syringe. She never took the 5-HTP; she only touched it with her hands as she emptied the capsules.

When the second boy was about 9 months old, the mother began experiencing symptoms of EMS. After consulting a physician in July 1991, it was noted that her eosinophil count was well over 30%. She continued to worsen and was hospitalized in August 1991 with a tentative diagnosis of EMS. At this time, she was referred to the National Institutes of Health for further evaluation.

Because of the possible link between the mother's symptoms and the 5-HTP, the boys and the father were also evaluated. The older boy had an eosinophil count of 9% (normal is 1% to 4%), and the younger boy had a count of 6%. The father had no abnormalities.

The 5-HTP that the boys used was analyzed by high pressure liquid chromatography and found to contain an impurity not found in the 5-HTP that the National Institutes of Health used in its studies for ataxia and myoclonus. Switching the boys to the contaminant-free 5-HTP brought about normalization of eosinophil counts. The mother's case was interesting because she was the most severely affected, and she only came into contact with the contaminated 5-HTP through her skin.

In 1998, researchers at the Mayo Clinic identified trace levels of a compound termed "peak X" as the key contaminant using a sensitive laboratory technique.[79] As a result, manufacturers of 5-HTP now screen for the presence of this compound to ensure that all of the 5-HTP on the marketplace is free from peak X as outlined in current Food and Drug Administration methodology. A minor chromatographic peak (peak X) reported in some 5-HTP samples lacks credibility due to chromatographic artifacts and

infinitesimal concentrations, and has raised undue speculations concerning its chemistry and toxicity. It might also be a moot point since extensive analyses of several sources of 5-HTP showed no toxic contaminants similar to those associated with L-tryptophan, nor the presence of any other significant impurities.[80]

There have been no reports of a single person developing EMS from 5-HTP despite its popularity over the last 20 years. Nonetheless, to be on the safe side, some experts recommend that long-term continual use of 5-HTP be monitored by regular (every 6 months) eosinophil determination.

Evidence that uncontaminated 5-HTP does not cause EMS is also provided by researchers who have been using 5-HTP for more than 25 years. They state that: "EMS has never appeared in the patients of ours who received only uncontaminated L-tryptophan or 5-hydroxtryptophan (5-HTP)."[81] Furthermore, researchers at the National Institutes of Health studying the effects of uncontaminated 5-HTP on various metabolic conditions have not observed a single case of EMS, nor has a case of elevated eosinophils been attributed to 5-HTP in these studies.[82] In short, there has never been a report of uncontaminated 5-HTP causing EMS.

Although there has never been a single person developing EMS from 5-HTP products proven to be free from the contaminants, long-term continual use of 5-HTP should be monitored by regular (every 6 months) eosinophil determination. For any person with scleroderma due to the problem with tryptophan metabolism noted in these patients, an eosinophil determination after the first month of 5-HTP use is indicated, especially if dosages are greater than 500 mg/day. In addition is the following advice:

- Do not use 5-HTP during pregnancy or lactation.
- Do not use 5-HTP in Parkinson's disease unless the patient is on Sinemet.
- Do not use 5-HTP in patients with scleroderma.



DRUG INTERACTIONS

Because 5-HTP is the direct precursor to serotonin, it should not be used by individuals taking antidepressant drugs without close medical supervision. Although 5-HTP has been used safely in combination with prescription antidepressant drugs in clinical studies, taking this combination could result in too much serotonin in the body. The result is a condition known as the "serotonin syndrome," characterized by confusion, fever, shivering, sweating, diarrhea, and muscle spasms.

5-HTP may antagonize the effects of drugs used in migraine headaches like methysergide and cyproheptadine, which block serotonin effects.

The drug carbidopa greatly enhances the half-life and produces an apparent clearance at least 14 times smaller, as well as a 15.4 times greater area under the curve, compared with 5-HTP 100 mg given without carbidopa.[83] By combining 5-HTP with carbidopa, increased bioavailability for brain penetration and decreased peripheral side effects would be expected, due to reduced peripheral decarboxylation of 5-HTP to serotonin. However, in a double-blind study in healthy male volunteers, nausea and vomiting occurred dose-dependently as the most frequent side effects, resulting in dose-related dropout of 6.6% at 100 mg and 45.5% at 300 mg 5-HTP.[80]

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CHAPTER 99

Hypericum perforatum (St. John's Wort)

Peter B. Bongiorno, ND, LAc, and Michael T. Murray, ND

Hypericum perforatum (family: Hypericaceae)
Common names: St. John's wort, Klamath weed, hypericum

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GENERAL DESCRIPTION

Likely the most well-studied botanical of all time, St. John's wort *(Hypericum perforatum)* is a shrubby perennial plant with numerous bright yellow flowers. It is commonly found in dry, gravelly soils, fields, and sunny places. St. John's wort is native to many parts of the world, including Europe, Asia, and the United States. It grows especially well in northern California and southern Oregon.[1]

The plant is glabrous throughout, green or sometimes glaucescent; the stems are erect, branched at the top, and 30 to 100 cm long. The leaves are (1) oval or elliptic; (2) oblong-ovate or rather narrow, oblong-linear, subobtuse, and flat; or (3) more or less revolute—marginated with numerous pellucid and a few black granular dots. The yellow flowers are numerous, forming a broad, paniculate, almost corymbose inflorescence, 7 to 11 cm long and 5 to 11 cm broad. The lanceolate bracts are 0.5 cm long and acute. The calyx is deeply parted, 5 mm long, and about two to three times shorter than the corolla. The sepals are lanceolate or narrow lanceolate 4 to 5 mm long, 1 mm broad, as long as the ovary, acute or acuminate, sparingly furnished with black oval dots, with a smooth or sparsely toothed margin. The petals are oblong to oblong-elliptic, 1.2 to 1.5 cm long and 0.5 to 0.6 cm broad, with or without numerous black granular dots and lines on the margin in the upper part, whereas the surface is full of yellow glandular dots, thin lines, and stripes. The three-bundled stamens are numerous; the ovary is ovoid, 3 to 5 mm long. The seed is 1 mm long, cylindric, brown, and minutely pitted longitudinally.[1]

The whole plant is used medicinally. Harvesting time is generally July through August. The plant must be dried immediately to prevent degradation of active principles.[1]

CHEMICAL COMPOSITION

The major compounds of interest are hypericin (Figure 99-1) and pseudohypericin. These compounds are typically found in low concentrations, ranging from 0.0095% to 0.466% in the leaves and as much as 0.24% in the flowers.[1]

More recently, researchers have been interested in the other chemical constituents (especially the various flavonoids and xanthones). The interest in these other components stems largely from pharmacologic studies with commercially available extracts demonstrating effects and benefits beyond hypericin and pseudohypericin. For example, amentoflavone was shown to bind to benzodiazepine receptors and to act as a modulator of γ-aminobutyric acid, which may be a major anxiolytic mechanism.[2] The active components include[1,3]:

- Flavonoids (flowers 16%, leaves 12%, and whole herb 9%)
- Xanthones
- Phenolic carboxylic acids (caffeic, chlorogenic, ferulic, and gentisic acids)
- Essential oils (whole herb content 0.13%)
- Carotenoids
- Alkanes
- Phloroglucinol derivatives
- Phytosterols
- Medium-chain fatty acid alcohols

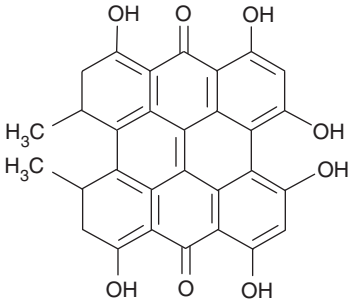


FIGURE 99-1 Hypericin.

HISTORY AND FOLK USE

St. John's wort has a long history of folk use. Dioscorides, the foremost physician of ancient Greece, as well as Pliny and Hippocrates, used St. John's wort in the treatment of many illnesses. Its Latin name, *H. perforatum,* is derived from Greek and means "over an apparition," a reference to the belief that the herb was so obnoxious to evil spirits that a whiff of it would cause them to depart.

The naming of St. John's wort has its origins in folk traditions. One claims that the red spots, symbolic of the blood of St. John, appeared on the leaves of the plant on the anniversary of the saint's beheading. Another comes from a common medieval belief that if one slept with a piece of the plant under a pillow on St. John's Eve, "the Saint would appear in a dream, give his blessing, and prevent one from dying during the following year."

Many people from the time of the ancient Greeks through the Middle Ages believed St. John's wort to have magical powers. Recent research on St. John's wort appears to offer some explanation of this "magical" power. On the basis of a long history of use as a mood-elevating substance and preliminary in vitro experiments and clinical studies, in 1984, the German Commission E permitted the medicinal use of St. John's wort for depression, anxiety, or nervous excitement.

The Commission E evaluates efficacy of herbal medicines on the basis of a doctrine of reasonable certainty, in contrast to the U.S. Food and Drug Administration's doctrine of absolute proof. Herbal products can be marketed with drug claims if they are proven to be safe and effective. Whether the herbal product is available by prescription or over the counter is based on its application and safety of use. Herbal products sold in German pharmacies are reimbursed by insurance if they are prescribed by a physician.

Because the German system allowed companies to market their products according to the guidelines of the Commission E, many companies achieved success with their products, allowing them to fund the necessary research to gain greater acceptance within mainstream conventional medicine. St. John's wort extract in the treatment of depression is a perfect case in point to illustrate how the Commission E monographs fueled the science of botanical medicine. For example, it was originally thought that hypericin acted as an inhibitor of the enzyme monoamine oxidase (MAO), thereby resulting in the increase of central nervous system (CNS) monoamines such as serotonin and dopamine. However, newer information indicated that St. John's wort possesses no in vivo inhibition of MAO. Apparently, the antidepressant activities are related more to modulating the relationship between the immune system and mood, as well as by inhibiting serotonin reuptake. In addition, it appears that although hypericin is an important marker, other compounds such as flavonoids are thought to play a major role in the pharmacology of St. John's wort.

More than 27 double-blind randomized trials, involving more than 2200 patients with mild to moderately severe depression, showed that St. John's wort extracts standardized for hypericin had excellent results in the treatment in depression, with far fewer side effects than standard antidepressant medications.[4] For patients with preexisting conductive heart dysfunction or elderly patients, high-dose hypericum extract is safer with regard to cardiac function than tricyclic antidepressants.[5] It is no coincidence that St. John's wort extracts became among the most widely used antidepressants in Germany, with a market share of more than 25% in 1997.[6,7]

PHARMACOLOGY

St. John's wort extracts (primarily of the flowering tops) have shown a wide variety of effects in experimental and clinical studies. Some of the activities demonstrated include the following[1,3]:

- Antidepressant effects
- Antiviral effects
- Antibiotic effects
- Increased healing of wounds and burns

Antidepressant Activity

Among the different biological hypotheses for depression, the biogenic amine hypothesis is the most widely accepted. This hypothesis suggests that depression is the result of a deficiency in function of the biogenic amines (e.g., serotonin, catecholamines, dopamine). These neurotransmitters are stored in granules within neurons. After stimulation of the neurons, these neurotransmitters are released into the synaptic cleft via exocytosis. After binding to postsynaptic receptors, the neurotransmitters are either taken up again and restored in the vesicles or they are catabolized by the enzymes MAO or catechol-O-methyltransferase (COMT). Most antidepressant drugs increase the availability of these amines, particularly serotonin, by either inhibiting the reuptake or blocking MAO.

As stated earlier, initial studies indicated that St. John's wort extract's antidepressant action was based on the ability of crude hypericin preparations to inhibit both types A and B MAO.[8,9] As a result of this inhibition, there is an increase in the level of neurotransmitters within the brain that maintain normal mood and emotional stability, including serotonin, catecholamines, and dopamine. These preliminary results identified hypericin as the supposed active constituent. However, later chemical analysis of these crude hypericin preparations identified the active content as being as much as 20% of St. John's wort's other constituents, with flavonoids being the most important.[1] In other words, it is unknown to what extent hypericin or the flavonoids individually contribute to any MAO inhibition.

A study was conducted to better understand the influence of hypericin, hypericum total extract, and hypericum fractions on the activity of MAO and COMT.[10] An inhibition of MAO was shown using the following concentrations:

- Hypericin to 10^{-3} mol/L
- Hypericum total extract to 10^{-4} mol/L
- One extract fraction up to 10^{-5} mol/L

A COMT inhibition could not be shown for hypericin, with hypericum extract to 10^{-4} mol/L and with two extract fractions also up to 10^{-4} mol/L. The MAO inhibiting fraction contained hypericins, as well as flavonols, the COMT-inhibition fraction being mainly flavonols and xanthones. The key result from this study, as well as in another in vitro/ex vivo study, was the

demonstration that the concentrations of inhibition shown, particularly with regard to the inhibition of MAO activity, were likely insufficient to explain the clinically proven antidepressive effect of St. John's wort extract.[10,11] Therefore, additional mechanisms are likely responsible for these clinical benefits.

At least three other mechanisms have been proposed: modulation of interleukin-6 (IL-6) activity, inhibition of the reuptake of serotonin, and agonist action of σ-receptors. The modulating effect of St. John's wort extract on IL-6 is the most interesting, as it proposes a mechanism by which St. John's wort interacts with the link between the immune system and mood. The immune system and the nervous system share many common biochemical features and regulatory interactions. The cytokine, IL-6, is heavily involved in the communication between cells within and outside the immune system. With regard to the nervous system, IL-6 is known to modulate hypothalamic-pituitary-end organ axes, especially the hypothalamic-pituitary-adrenal axis. The hypothesis is that an elevation in IL-6 results in activation of the hypothalamic-pituitary-adrenal axis, leading to elevations in corticotropin-releasing hormone and other adrenal regulatory hormones—hallmark features in depression. St. John's wort extract showed an ability to reduce IL-6 levels; therefore, this action may explain the clinical effectiveness of St. John's wort extract.[12]

Animal studies comparing the effects of hypericum in mice who produce normal IL-6 levels versus IL-6 knockout mice (those with no IL-6 expression), found higher levels of serotonin produced in the former group.[13] An in vitro study demonstrating reduction of IL-6 levels involved taking blood samples from five healthy volunteers and four depressive patients.[12] The release of IL-6, IL-1β, and tumor necrosis factor-α was measured quantitatively after an incubation time of 24 hours on microtiter plates. A massive suppression of IL-6 release was found for phytohemagglutinin-stimulated St. John's wort extract. If these effects can be duplicated in vivo, it would provide a mechanism by which St. John's wort extract modulates release of corticotropin-releasing hormone and, subsequently, mood.

St. John's wort extract was also shown to inhibit the reuptake of serotonin in a similar fashion to drugs like fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft). The study that demonstrated a 50% serotonin reuptake inhibition used the 0.3% hypericin content standardized extract at a concentration of 6.2 mg/mL and did not attempt to identify the active inhibitors.[14] The authors of the study concluded that "the antidepressant activity of hypericum extract is due to inhibition of serotonin uptake by postsynaptic receptors." However, results were conflicting with regard to the effect of acute doses of St. John's wort extracts on the serotonergic system in rodents.[15] A marked increase of both serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) was reported in rat brain cortex. Other researchers reported high 5-HIAA and serotonin levels in the mouse hypothalamus and hippocampus, but not in the cerebral cortex, where only 5-HIAA increased. However, other research found no significant changes in either serotonin or 5-HIAA after a schedule of treatment during the forced swimming test. One study of the rat locus coeruleus showed that systemic hyperforin induced a lasting and marked (100% to 200%) increase in the extracellular concentrations of serotonin, but not 5-HIAA.[16]

There is gathering information that St. John's wort may affect function via σ-receptors. Sigma$_1$-receptors were shown to play an important role in antidepressive effects because selective σ_1-receptor agonists, as well as typical antidepressants, reduced the immobility time in the forced swimming and tail suspension tests.[17] Research demonstrated that the pretreatment of rats with St. John's wort extracts or hyperforin trimethoxybenzoate could block other ligand binding to σ-receptors. The antidepressant-like activity of hyperforin trimethoxybenzoate was completely antagonized by pretreating rats with BD 1047, a selective σ_1 antagonist. These results, together with the previous observation that agonists at σ_1 receptors are active in antidepressant models in rats, suggest that St. John's wort's antidepressant effects might be mediated in part by an indirect action on σ-receptors.[15]

A fascinating study evaluated the effect of both St. John's wort and imipramine on gene transcription in the rat hypothalamus.[6] The depressed patient's hypothalamus is known to manifest changes associated with food intake, decreased libido, and abnormal circadian rhythms. This research found a significant correlation of six genes directly modulated by both these test compounds. The probability of this occurring by chance was 1.14×10^{-23}. The functions of these specific genes include protein synthesis and degradation, cellular scaffolding and intracellular transport, mitochondrial and glycolytic energy metabolism, and cellular signaling through modulation of calcium-binding proteins. Although the implication of this research is not totally clear, the authors postulated that these modulated gene functions might be related to immune and inflammatory downregulation with neuronal protection from cellular injury.

Amentoflavone, one of the many flavone contents in St. John's wort, was shown to cross the blood–brain barrier by passive diffusion.[18] This might account for the ability of this botanical to travel into the brain and affect CNS gene transcription. Nevertheless, one point regarding the probable synergistic effects of the St. John's wort constituents should be underscored: given the multitude of active components in this botanical medicine, it is likely that synergistic sites of action outside the CNS, in accordance with CNS effects, account for the complete and effective global actions of St. John's wort.

Extracts of St. John's wort were tested in various animal models designed to study its antidepressant effects. In these studies, St. John's wort extract was found to enhance the exploratory activity of mice in a foreign environment, extend the narcotic sleeping time in a dose-dependent fashion, antagonize the effects of reserpine, and decrease aggressive behavior in socially isolated male mice.[1,19] These activities are consistent with the expected effects of antidepressant compounds and appear to be the result of increased monoamine activity.

Antiviral Activity

In vitro studies showed that hypericin and pseudohypericin exhibit strong antiviral activity against herpes simplex virus I and II, as well as influenza types A and B, and vesicular stomatitis virus.[20] These compounds also demonstrated remarkable antiviral activity against Epstein-Barr virus.[21]

Researchers from New York University Medical Center and the Weizmann Institute of Science in Israel generated a tremendous amount of excitement when they demonstrated the antiretroviral activity of hypericin and pseudohypericin.[22] This preliminary study examined the effect of these compounds on two animal retroviruses, Friend leukemia virus and radiation leukemia virus, both in vitro and in vivo (in mice). The researchers found the effective dose of hypericin in mice to be 1.5 to 2 mg/mL. The researchers concluded the following:

> *Hypericin and pseudohypericin display an extremely effective antiviral activity when administered to mice after retroviral infection. The antiviral activity is remarkable both in its mechanism of action and in the potency of one administration of a relatively*

small dose of the compounds. Availability and the relatively convenient and inexpensive procedure for the extraction and purification of hypericin and pseudohypericin further enhance the potential of these compounds.

Later, two possible mechanisms were described to explain the antiviral activity of both hypericin and pseudohypericin.[23] First was inhibition of assembly or processing of intact virions from infected cells—released virions contain no detectable activity of reverse transcriptase. Second, these compounds also directly inactivate mature and properly assembled retroviruses.

The antiviral activity of hypericin against human immunodeficiency virus (HIV) appears to require interaction with light to activate the hypericin.[24,25] Another requirement is sufficient concentrations, as entry of hypericin into infected cells depends on the concentration of hypericin in the blood. At sufficient concentrations, hypericin incubated with HIV-infected whole blood decreases culturable HIV, indicating significant antiviral activity.[26]

Antibacterial Activity

St. John's wort extracts have broad-spectrum antimicrobial activity against both gram-negative and gram-positive bacteria.[27] The organisms studied included *Staphylococcus aureus*, *Streptococcus mutans*, *Proteus vulgaris*, *Escherichia coli*, and *Pseudomonas aeruginosa*.

Pharmacokinetic Studies

Pharmacokinetic studies indicate that hyperforin, as well as hypericin and pseudohypericin, absorbed to produce serum levels that correspond to the levels showing benefit in in vitro studies.[28] However, hyperforin is the only ingredient of *H. perforatum* that could be determined in the brains of rodents after oral administration of alcoholic extracts. This result and others seem to indicate that it may be the chief constituent responsible for the antidepressant effects of *H. perforatum*.

CLINICAL APPLICATIONS

The primary use of St. John's wort is in the treatment of depression. It may also be of benefit in the treatment of chronic viral infections and, topically, in various skin products.

Depression

Extracts of St. John's wort standardized for hypericin content (most studies used the 0.3% hypericin content extract) have significant support in the treatment of mild to moderate depression.[1,29,30,31] The official German Commission E monograph for St. John's wort lists psychovegetative disturbances, depressive states, fear, and nervous disturbances as clinical indications for St. John's wort.

In initial studies,[1,29,30,32] St. John's wort extract improved many psychological symptoms, including the following:

- Depression
- Anxiety
- Apathy
- Sleep disturbances
- Insomnia
- Anorexia
- Feelings of worthlessness

Even more impressive is that St. John's wort extract was able to achieve these benefits without producing significant side effects.

The history of meta-analyzing hypericum studies has been full of tumult and contradiction. One meta-analysis in 1996 of 23 randomized trials included 1757 outpatients with mainly mild or moderately severe depressive symptoms. It showed that hypericum extracts were significantly superior to placebo and as effective as standard antidepressants. This analysis revealed 0.8% drop outs for side effects with hypericum and 3.0% with standard antidepressant drugs. In this research, side effects occurred in 19.8% patients on hypericum and 52.8% patients on standard antidepressants.[33]

However, there were two well-publicized clinical studies claiming that hypericum was ineffective in treating depression.[34] One 8-week trial employed suboptimal doses of hypericum, using 900 mg/day for patients with severe depression. If there was no response, doses were increased to only 1200 mg/day. In a previous severe depression study, patients improved significantly on hypericum, compared with placebo and the antidepressant drug imipramine, on a dose of 1800 mg/day.[35,36] Given that the trial was funded by a company who manufactures antidepressant medications, and in light of a strong history of positive hypericum trials, it is doubtful that this accurately reflects the clinical ability of such a well-studied botanical.

A second 8-week study from 2002 made a similar suboptimal dosing error, and subsequently deemed hypericum to be ineffective. A valuable note in this study was that the comparison drug, sertraline (with a much stronger side-effect profile than hypericum), was not any more effective than hypericum or the placebo.[37]

A third meta-analysis in 2008 included only trials from 1995 to 2006 that were randomized and double-blinded, involving patients with major depression. Extracts of hypericum were compared with placebo or standard antidepressants, including fluoxetine, sertraline, imipramine, citalopram, paroxetine, and amitriptyline. In all, 29 studies involving 5489 patients were analyzed. Hypericum extracts tested in the trials were superior to placebo and equally effective as standard antidepressants. Patients given hypericum extracts dropped out of trials less frequently because of adverse effects than those given standard antidepressants. It was concluded that the results "imply that an attempt of treating mild to moderate major depression with one of the hypericum preparations positively tested in clinical trials is clearly justified," but added that evidence was "still insufficient to draw conclusions about the efficacy of hypericum for treating severe major depression." The authors cited that the mild physical side effects associated with hypericum might be enhancing the placebo effect. A second concern was that hypericum was popular in Germany, so the more robust effects in the studies from German-speaking countries might be attributable to an "allegiance" effect. A third concern was that, although positive, the larger-scale trials used in the analysis produced overall smaller effects.[38]

Hypericum was compared to leading antidepressant medications.[38-40] In a randomized, controlled, double-blind trial, 70 patients with mild to moderate depression received one tablet of either hypericum extract or fluoxetine twice a day for 6 weeks. As evaluated by the 17-item Hamilton Rating Scale for Depression (HAMD), the von Zerssen depression scale (DS), and patients' response, there were significant decreases (P <0.001) in symptoms in the St. John's wort group (50%) and in the fluoxetine group (58%) on their HAMD scores. The hypericum extract achieved 83% of the efficacy of fluoxetine on the HAMD and 78% on the DS. Assessments by physicians and patients indicated considerable improvement with no between-treatment differences.[39] The authors concluded that the hypericum tested in this study was therapeutically equivalent to fluoxetine and that it was a reasonable alternative to synthetic antidepressants.

Hypericum extract was similarly tested and proven at least as effective as sertraline in the treatment of mild to moderate depression in a small group of outpatients.[40] Efficacy and tolerability of hypericum extract was also compared with imipramine, and was found equivalent to the drug in treating mild to moderate depression. In addition, as expected, patients tolerated the hypericum better.[41]

Although preliminary, St. John's wort may be a safe recommendation during pregnancy and postpartum depression (see "Pregnancy" and "Nursing" for more information). St. John's wort has also been studied in children. Three open-label trials in depressed children found benefit with minimal side effects. The first study of 101 children, less than 12 years of age, were administered 300 to 1800 mg/day at a standardized dose of 900 mcg hypericin.[42] A second, 8-week open-label trial in 33 youths from 6 to 16 years of age used a dose of 150 to 900 mg/day, and enjoyed an 80% response rate.[43] A third trial of 26 adolescents given 300 mg three times a day had an 82% response rate in the 11 patients who completed the study. However, in this study, 15 patients withdrew due to either noncompliance or worsening of symptomology.[44,45]

Seasonal Affective Disorder

Seasonal affective disorder (SAD) represents a subgroup of major depression with a regular occurrence of symptoms in autumn/winter and full remission in spring/summer. Light therapy has become the standard treatment for this type of depression. Apart from this, pharmacotherapy with antidepressants also seems to provide an improvement of SAD symptoms. The aim of a controlled, single-blind study was to evaluate if St. John's wort could be beneficial in treating SAD patients and whether the combination with light therapy would be additionally advantageous.[46] Patients who fulfilled *Diagnostic & Statistical Manual of Mental Disorders, 3rd Edition Revised* criteria for major depression with a seasonal pattern were randomized in a 4-week treatment study with 900 mg/day of St. John's wort extract (0.3% hypericin content) combined with either bright (3000 lux; n = 10) or dim light (less than 300 lux therapy). The significant reduction in the Hamilton Depression Scale in both groups (72% and 60%, respectively) indicated that St. John's wort extract might benefit patients with SAD as a sole therapeutic agent, as well as in combination with light therapy.

Insomnia

St. John's wort was shown to improve sleep quality and well-being in healthy elderly subjects.[47] With antidepressant drugs, particularly tricyclic antidepressants and MAO inhibitors, rapid eye movement sleep is reduced. St. John's wort did not interfere with rapid eye movement sleep like other antidepressants and was shown to increase the intensity of deep sleep during the total sleeping period as demonstrated by brainwave studies. Although St. John's wort improved sleep quality, it did not act as a sedative (i.e., it did not reduce sleep onset), nor did it change total sleep duration.

Mental Function

One of the most interesting comparative studies was a double-blind study in which St. John's wort extract (0.3% hypericin content) was compared with maprotiline in 24 healthy volunteers by measuring resting brainwave (electroencephalography) tracings and mental activity (visual and acoustic evoked potentials).[48] Interpretation of the differences in reactions indicated that, unlike maprotiline, which interferes with mental function, St. John's wort actually improved memory and other mental activities. Long-term administration of St. John's wort in rats improved learning and spatial memory with significant changes in the content of monoamines in several brain regions.[49]

Acquired Immunodeficiency Syndrome and Other Viral Infections

Research suggests that St. John's wort may be a useful adjunctive treatment for herpes simplex, mononucleosis, and influenza, although further human studies are necessary to establish the optimal dosage of the standardized extract. Combined with its antidepressant activity, St. John's wort also appears to be a promising treatment for chronic fatigue syndrome.

The greatest promise of St. John's wort, however, may be in the treatment of acquired immunodeficiency syndrome (AIDS). In response to in vitro and animal studies, many AIDS patients began self-administering St. John's wort. Although most patients reported feeling better with a more positive outlook, more energy, and less fatigue, it was not known to what degree this was due to a placebo effect.[50,51] In vitro studies reported St. John's wort's ability to inhibit light-induced activation of HIV gene expression.[52]

To better determine the benefits, a number of trials evaluated the efficacy of standardized extracts of St. John's wort in the treatment of HIV-infected individuals.

In one study, St. John's wort extracts, providing approximately 1 mg/day of hypericin, were studied in 31 patients.[53] Baseline and 4-monthly measurements including physical examination, T-cell subsets, and other laboratory parameters were performed. Concomitant use of azidothymidine (AZT) and other treatments was permitted. The results of the study were encouraging. In the subgroup of 10 patients who took no AZT either before or during the study ("AZT virgins"; none had AIDS), the mean helper T-cell count increased 13% from baseline after 1 month on St. John's wort; this increase was maintained for 4 months. Although these increases were not statistically significant, in contrast, T-helper cell counts of the 10 patients using AZT throughout the study fell significantly after an initial mild rise. Side effects were limited to reversible liver enzyme elevations in five patients, with all levels returning to baseline after 1 month without St. John's wort extract.

In another open pilot study, 18 HIV patients (3 with the Centers for Disease Control classification CDC II, 8 with CDC III, 4 with CDC IV B, and 3 with CDC IV C1 classification) were treated solely with standardized St. John's wort extract (weekly intravenous injection and daily oral intake), providing a daily intake of 2 mg of hypericin.[54] The 16 of 18 patients with good compliance showed stable or even increasing counts of absolute T-helper cells over the 40 months of observation. Also, the helper/suppressor T-cell ratio showed an improvement in the majority of these patients. Clinically, it was noteworthy that only 2 of these 16 patients encountered an opportunistic infection during the 40 months of observation. The other 14 of 16 patients remained clinically stable and active in work and life. This steady-state situation of the HIV infection also correlated with stable values of hemoglobin, leukocytes, and platelets. Furthermore, none of the otherwise known viral complications due to cytomegalovirus, herpes, or Epstein-Barr virus were encountered in these 16 patients.

Despite these good preliminary results, the trials proved disappointing, as significant blood levels of hypericin were not achieved using the extract either orally or intravenously. Use of the standardized extract for the treatment of HIV infection has since been replaced by the use of intravenously administered

synthetic hypericin. Preliminary studies are again producing some encouraging results with good safety, although photosensitivity may occur (see later discussion on "Toxicity"), and long-term controlled evaluation is necessary (for further discussion, see Chapter 173).[55,56]

Topical Application

St. John's wort has a historical use as an aid in wound healing. Research demonstrated antibacterial and wound healing activity.[3] St. John's wort preparations have also been used in burns, as a sunscreen, and in the treatment of muscular pain.[3] Oil-based preparations are preferred for topical applications.

DOSAGE

The dosages of St. John's wort preparations are based on their hypericin content. The overwhelming majority of the studies in depression used St. John's wort extract standardized to contain 0.3% hypericin and 3% to 5% hyperforin. This extract is produced via an extraction with 80% methanol (which is subsequently removed). Although hypericin and hyperforin are key components, this extract is composed of a wide range of compounds constituting the remaining 95% of the extract. Manufacturers of these standardized extracts employ high-performance liquid chromatography techniques to identify not only the hypericin, pseudohypericin, and hyperforin, but also related compounds, flavonoid components, xanthones, cinnamic acid, and several other key components. The point is that although the dosage is based on hypericin levels, assuring appropriate levels of these other constituents is also vitally important.

To achieve the benefits noted in the clinical trials, it is difficult to recommend any other forms beyond standardized extracts. Nonetheless, here are dosage recommendations for various forms of St. John's wort:

- Dried flowers: 2 to 4 g three times a day
- Tincture (1:5): 3 to 6 mL three times a day
- Fluid extract (1:1): 1 to 2 mL three times a day
- Standardized solid (dry-powdered) extract (0.3% hypericin and 3% to 5% hyperforin): 900 to 1800 mg a day

TOXICITY

The side-effect profile of hypericum extract is minor, especially compared with the well-known side-effects of antidepressant medications.[57] Symptoms matching excessive levels of serotonin should also be monitored when using hypericum with selective serotonin reuptake inhibitors, tryptophan, or 5-hydroxytryptophan. According to the U.S. Food and Drug Administration, symptoms of "serotonin syndrome" may include mental status changes (e.g., agitation, hallucinations, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, and hyperthermia), neuromuscular aberrations (e.g., hyperreflexia and incoordination), and/or gastrointestinal tract symptoms (e.g., nausea, vomiting, and diarrhea). Severe cases can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. An example of this was reported in a study of four elderly patients who ostensibly developed serotonin syndrome as a result of an interaction between tramadol and mirtazapine.[58] Although polypharmacy of antidepressants caused this syndrome, no reports of natural substances causing this syndrome have been reported to date. Because its action on serotonin is minor, it is unlikely that hypericum would cause this syndrome, but monitoring is prudent.

Photosensitivity

Although hypericum was demonstrated to induce photosensitivity in some patients (less than 1% of people taking 900 mg once a day or more), this is not likely with standard dosages. Cases of photosensitivity occurred mainly in HIV patients using higher than normal quantities for an antiviral effect.[59] It has been suggested that tincture or extract can be substituted for capsules if photosensitivity occurs.[60] Because of the possibility of photosensitivity, avoidance of exposure to strong sunlight and other sources of ultraviolet light when using St. John's wort is often recommended to individuals, especially those with fair skin. However, although this recommendation may be appropriate, it must be pointed out that the therapeutic dosage of 2.7 mg/day of hypericin is about 30 to 50 times below the level required to produce phototoxicity.[61]

Pregnancy

Despite the ample research on St. John's wort, relatively little research has focused on safety in pregnancy and breast feeding. Animal pregnancy toxicology studies showed no change in maternal weight gain or gestational length[62] and no change in offspring anomaly rates.[63,64] These negative animal studies can be reassuring because they suggest a lack of structural or functional deficits attributable to hypericum exposure during gestation.[65] However, we must always keep in mind that rodents and humans do have varying detoxification abilities.

Human studies are few. In 1998, there were reports on two women who took hypericum during their pregnancies to avoid using conventional synthetic medications. Both cases seemed to reveal no concerns. One of these cases was of a 38-year-old woman who started hypericum at 24 weeks' gestation. The pregnancy was unremarkable, with the exception of late onset of thrombocytopenia (which the author did not attribute to hypericum). The offspring was born healthy, had a normal birth weight, normal APGAR scores, and physical examination and laboratory results were normal. Infant behavioral assessment at 4 and 23 days was normal.[66]

One 2006 review by naturopathic physicians looked at the evidence on the use, safety, and pharmacology of hypericum. This review searched seven databases, including the Cochrane bases, MedLine, Natural Database, and Natural Standard. Some unpublished research and bibliographies were also included. Data were compiled according to grade of evidence. The researchers found varying levels of scientific evidence. They concluded that there was in vitro evidence from animal studies that hypericum during pregnancy does not affect cognitive development nor cause long-term behavioral defects, but found some evidence of lower offspring birth weight. It is important to remember that rodents have very different detoxification abilities, and extrapolation to humans may not be prudent. This review also pointed to weak scientific evidence that hypericum induced CYP450 enzymes, which may lower serum medication levels below therapeutic range, which would be of concern when administering medications during pregnancy. The authors concluded that caution is warranted with the use of hypericum during pregnancy until further high quality human research is conducted to determine its safety.[67]

The first study of hypericum, which aimed to determine whether exposure could be associated with major malformations, prospectively followed 54 subjects using hypericum and compared them with a matched group of 108 pregnant women taking other pharmacologic therapy for depression, as well as a third group of healthy women, who were not exposed to any known teratogens. The study showed that malformation rates were similar across the three groups, with 5%, 4%, and 0% in hypericum, pharmaceutical subjects, and healthy groups, respectively ($P = 0.26$). This was not different than the 3% to 5% risk expected in the general population. Live birth and prematurity rates were also not different among the three groups. The authors suggested that this first study on the effects of hypericum in human pregnancy did provide some evidence of fetal safety.[68]

Nursing

Albeit in its own infancy, studies using hypericum during breast-feeding are starting to support its use and safety for depressed mood in mothers while breast-feeding. Animal studies using doses up to 25 times the equivalent recommended human dose throughout lactation were unable to show any neurobehavioral or developmental effects on offspring.[69] One study evaluating the safety of St. John's wort while nursing studied 33 breast-feeding women over a 2-year period. Compared with 101 disease-matched and 33 age-matched controls, there were no statistically significant differences found in maternal or infant demographics or maternal adverse events. No significant difference was observed in the frequency of maternal report of decreased milk production among the groups, nor was a difference found in infant weight over the first year of life.[70] A review of multiple databases also suggested that hypericum consumption during lactation did not affect maternal milk production or infant weight, but could cause colic, drowsiness, or lethargy. The authors of this review concluded that hypericum use during lactation appeared to be of minimal risk, but could cause some side effects.[71] St. John's wort may be a choice if other natural recommendations are not sufficient for the lactating female, although more data would be welcome to confirm safety.

DRUG INTERACTIONS

Historically, those taking St. John's wort have been advised to avoid foods and medications that are known to negatively interact with MAO-inhibiting drugs, such as tyramine-containing foods (e.g., cheeses, beer, wine, pickled herring, yeast). Drugs such as L-dopa and serotonin should be avoided. However, given recent research demonstrating the lack of in vivo MAO inhibition, this recommendation is no longer justified.

Strong evidence warrants precaution when combining St. John's wort with pharmaceutic therapies. St. John's wort was found to decrease the plasma concentrations of alprazolam, amitriptyline, digoxin, cyclosporine, indinavir, irinotecan, methadone, nevirapine, simvastatin, tacrolimus, theophylline, warfarin, phenprocoumon, and oral contraceptives. In the case of cyclosporine, the interaction resulted in some transplantation graft rejections. Hypericum was also shown to decrease the bioavailability of the R and S forms of verapamil.[72,73]

When combined with serotonin reuptake inhibitors, antidepressants (e.g., sertraline, paroxetine, nefazodone), or buspirone, hypericum can theoretically contribute to "serotonergic syndrome,"[73] a syndrome caused by excess serotonin levels. This syndrome has been iatrogenically induced by psychotropic and nonpsychotropic pharmaceutic coadministration and may include symptoms such as agitation, confusion, severe shivering, diaphoresis, myoclonus, hyperreflexia, mydriasis, tachycardia, and fever.[74]

Women on oral contraception should also be informed regarding the possible decrease in birth control efficacy with hypericum. St. John's wort causes an induction of ethinyl estradiol and norethindrone metabolism consistent with increased CYP3A activity and can contribute to intracyclic bleeding.[75] One study evaluated the use of St. John's wort and oral contraception. St. John's wort appeared to contribute to breakthrough bleeding in 7 of 12 women (vs 2 of 12 women in the oral contraception alone group). When taking oral contraceptive pills with St. John's wort, women may experience breakthrough bleeding and should consider adding a barrier method of contraception.[76]

Hypericum is also starting to be studied for its positive effects on medication outcomes. A study using the platelet inhibitor clopidogrel found that 2 of 10 patients using clopidogrel were poor responders, but 300 mg of hypericum for 2 weeks in these patients resulted in an increase in platelet inhibition of 20%. A previous study using 300 mg three times daily demonstrated an increase of 36%. Furthermore, no negative changes were seen in patients on statin medications.[77] Hypericum may be a good choice in poor responders, or to help lower the dose necessary in normal responders experiencing side effects.

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CHAPTER 100

Lobelia inflata (Indian Tobacco)

Michael T. Murray, ND

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Lobelia inflata (family: Campanulaceae)
Common names: Indian tobacco, pukeweed, asthma weed, gagroot, vomitwort

GENERAL DESCRIPTION

Lobelia is an indigenous North American annual or biennial plant with an erect, angular, hairy stem that contains a milky sap and grows from 6 inches to 3 ft in height. Numerous small, two-lipped, blue flowers grow in spike-like racemes from July to November.

CHEMICAL COMPOSITION

Lobelia contains about 0.48% pyridine (piperidine) alkaloids composed mainly of lobeline (Figure 100-1), with lesser amounts of lobelanine, lobelanidine, and other alkaloids.[1] Other constituents include resin, gum, lipids, and chelidonic acid.[2]

HISTORY AND FOLK USE

Lobelia was named after Matthias de Lobel (1570 to 1616), a famous French botanist and physician to the court of King James I. After chewing the plant, early settlers noted that the taste was similar to tobacco and produced effects like that of nicotine, the principal alkaloid in domestic tobacco, *Nicotiana tobaccum*. Native Americans also smoked the dried leaves to obtain the central nervous system effects of the alkaloids in the plant. Thus, lobelia was commonly referred to as "Indian tobacco."

Lobelia became one of the most commonly used herbs by Thomsonians, who used it as an emetic, diaphoretic, expectorant, sedative, antispasmodic, and antiasthmatic. It has been used for the following conditions:

- Asthma
- Whooping cough
- Bruises
- Sprains
- Ringworm
- Insect bites
- Poison ivy symptoms

Thomson stated: "There is no vegetable which the earth produces more harmless in its effect on the human system, and none more powerful in removing disease and promoting health than lobelia."[3]

PHARMACOLOGY

Lobeline possesses many of the same pharmacologic actions as nicotine, only less potent. However, its complex actions cannot be explained simply as being a weaker version of nicotine. Detailed pharmacologic investigation comparing the effects of lobeline with nicotine indicate that lobeline possesses novel effects on nicotinic receptors.[4,5]

Respiratory Effects

One of the earliest known uses of lobeline was as a safe, short-acting respiratory stimulant. This respiratory stimulation was shown to be due to direct stimulation of the carotid body chemoreceptors. The powerful respiratory stimulant action of

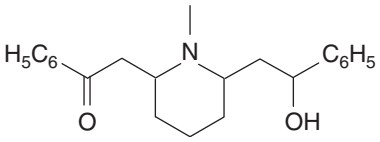


FIGURE 100-1 Lobeline.

lobeline has been used for stimulation of respiration in fever cases, cases of paralysis of respiratory centers due to narcotic poisoning, alcohol, soporifics, morphine, narcosis, or spinal anesthesia. Lobeline has also been used to treat accident victims who have been buried, nearly drowned, hit by lightning or electrically shocked, and poisoned by asphyxiating gases.

Gastrointestinal Effects

The emetic action of lobeline is mediated by its stimulation of the emetic chemoreceptor trigger zone in the area postrema of the medulla oblongata (outside the blood–brain barrier) and activation of the vagal and spinal afferent nerves that form the sensory input of the reflex pathways involved in vomiting.[6]

Central Nervous System Effects

One of the more promising lines of research with lobeline is that it appears to disrupt the fundamental mechanisms of dopamine storage and release. This action may help in antagonizing the neurochemical and behavioral effects of the psychostimulants amphetamine and methamphetamine. Lobeline was found to inhibit the amphetamine-induced release of dopamine in vitro and amphetamine-induced hyperactivity, drug discrimination, and self-administration in animal experiments.[7,8] Because lobeline is not addictive itself, it may reduce the abuse liability of these psychostimulants.

CLINICAL APPLICATIONS

Lobelia is primarily used as an expectorant in such conditions as pneumonia, asthma, and bronchitis. It appears that some of its actions may be mediated by the adrenal cortex.[9] Experimentally induced lung edema in rats was responsive to lobeline in many models that were unresponsive to any other medication. Furthermore, although lobeline causes bronchoconstriction in dogs and rats, in guinea pigs and (presumably) humans, the opposite—bronchodilation—occurs.[10]

Although effective when used alone in the treatment of asthma, it has traditionally been used in combination with other botanical agents, including *Capsicum frutescens* and *Symphlocarpus factida*.

Lobelia has also been used as an aid in stopping smoking with equivocal results from clinical trials.[11]

DOSAGE

- Dried herb: 0.2 to 0.6 g three times a day
- Tincture: 15 to 30 drops three times a day
- Fluid extract: 8 to 10 drops three times a day

TOXICOLOGY

Although lobelia has a reputation for being toxic, a thorough review of the medical literature was unable to find any well-documented case of serious problems or death due to lobelia.[12] The main reason may be that lobelia causes nausea and vomiting when the amount used is too high, thereby avoiding absorption of toxic amounts. In general, a dosage of more than 1 mL of tincture one time is enough to produce significant nausea and possibly vomiting. Lobelia should not be used for more than 1 month consecutively and should be avoided during pregnancy and breastfeeding.

Like nicotine poisoning, toxic symptoms of lobelia include the following:

- Nausea
- Salivation
- Diarrhea
- Disturbed hearing and vision
- Mental confusion
- Marked weakness

Faintness and prostration ensue; blood pressure falls; the pulse becomes weak, rapid, and irregular; breathing is difficult; and collapse occurs, followed by convulsions. Death may conceivably result from respiratory failure. The antidote in acute poisoning is 2 mg of atropine, which is given subcutaneously.

DRUG INTERACTIONS

There are no known drug interactions with lobelia.

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CHAPTER 101

Medicinal Mushrooms

Terry Willard, CIH, PhD

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INTRODUCTION

Medicinal mushrooms have a very long history of use in Asia, Europe, and Russia, but have only become an important category of natural medicine in North America over the last decade or so. Worldwide, mushrooms are one of the fastest growing categories of medicinal supplements, with 1.2 million tons of medicinal mushrooms produced in 1981, 7 million tons in 1999, and 9.9 million tons in 2004. However, the U.S. market is only a small fraction of this volume.[1] There have been several journals, books, and reviews written about mushrooms over the last decade in the United States.

GENERAL DESCRIPTION

Mushroom is not a taxonomic category, but a commonly used name. The definition of mushroom is: "a macrofungus with a distinctive fruiting body, which can be either hypogeous (below ground) or epigeous (above ground), large enough to be seen with the naked eye and to be picked by hand."[2] Taxonomically, mushrooms are mainly basidiomycetes with several species of ascomycetes. Mushrooms are neither plants nor animals, but are in a separate fungi kingdom. There are 14,000 to 22,000 known species of mushrooms, with an estimated 140,000 species worldwide. This shows that they are potentially a very large untapped resource, with an estimated 7000 species that have benefitted mankind.[3] Even among the known species, there are a very small number of thoroughly investigated mushrooms. The fact that there is a large amount of documented ethnomedicinal uses and strong bioactivity of researched species gives us the impression that we should expect many more natural medicinal substances from mushrooms in the future.

CHEMICAL COMPOSITION

There are several constituents of interest in medicinal mushrooms, with approximately 400 substances isolated from *Ganoderma* (Reishi) alone. The most studied constituents are polysaccharides, triterpenoids, nucleosides, ergosterol, fatty acids, protein/peptides, and trace elements. Of these, the most studied are various branched polysaccharides and triterpenoids. Most likely because of the large array of activity found from a variety of constituents, many health care practitioners consider medicinal mushrooms to be multiple medicinal supplements, akin to multiple vitamins and minerals.

Polysaccharides

Polysaccharides (in particular β-D-glucans) and polysaccharide protein complexes have immunomodulating effects on the body. Not new to the realms of natural healing, polysaccharides have been shown to stimulate nonspecific immune system function as well as exert antitumor activity through the stimulation of the host's defense mechanism.[4-6] These β-glucans have been termed "biological response modifiers," due to the large array of functions attributed to them. Although the mechanisms behind the various polysaccharides have been only partially worked out, there are many theories with no complete consensus.

Both clinical and animal studies have shown that the β-glucans can activate certain aspects of the immune system. The β-glucans found in medicinal mushrooms

have the ability to stimulate macrophages,[7] natural killer cells,[8] T cells,[9] and the production of immune system cytokines. Mushroom polysaccharides may also be able to increase dendritic cell function.[10] There is evidence that β-glucans function by binding to membrane complement receptor type 3 (CR3, α-Mβ2 integrin, or CD11b/CD18) on immune effector cells. The intercellular events that occur after glucan-receptor binds have not been fully worked out. The shape, size, degree of branching, and association with protein or peptide groups significantly affect the biological activity observed.

Much of the theoretical research is done in vitro, with no clear understanding of how these extremely large molecules are absorbed into the bloodstream and arrive at the receptor sites. The concept of pinocytosis, or "cell drinking" has been suggested as a mechanism of absorption that leaves whole or partial molecules intact.

Some subscribe to an alternative theory of signals being generated by the various polysaccharides and protein complexes from their location in the intestinal tract. It is thought that these signals are what really activate the receptor sites in the immune system.

Triterpenoids

Triterpenoids contain a lanostane skeleton often with steroidal-like shapes. The smaller molecular weights have shown biological activity, such as antitumor, immunomodulating, hepatoprotective, antiviral, and antioxidant effects.[11] There are many varieties of triterpenoids, with Reishi having over 120 alone.[12,13]

Vitamin D_2

Mushrooms are the only nonanimal source of vitamin D. When exposed to ultra violet light, mushrooms were shown to convert ergosterol into vitamin D_2. The amount of vitamin D found in these mushrooms is high enough to support vegans through the winter months. High vitamin D_2 mushrooms are now available in United States, but shelf life studies and more research are still needed in this area.[14-16]

Pharmacology

Listed below is only a small portion of the research, as the field is very large, and similar activities can be seen in multiple mushrooms.

Antioxidant Activity

Many of the medicinal mushrooms contain antioxidants such as ascorbic acid, carotenoids, ergothioneine, phenolic compound, superoxide dismutases, and tocopherols.[17] Medicinal mushrooms with antioxidant effects include: *Agaricus blazei*,[18] Chaga[19-21] *Flammulina velutipes*,[22] Maitake,[23] Reishi,[24,25] and Shiitake.[26,27]

Antibacterial and Antifungal Activity

Because of the natural environment of most mushrooms, it is not surprising that they have strong activity against bacteria and fungi. It is interesting that only compounds from microscopic fungi have been marketed as antibiotics, when there is a large array of compounds from most medicinal mushrooms. Several constituents have shown broad-spectrum activity. Some, including sesquiterpenoid hydroquinones from *Ganoderma sp*. have shown activity against multiresistant bacterial strains such as methicillin-resistant *Staphylococcus aureus*.[28-30] Oxalic acid as found in Shiitake, as well as ethanolic mycelial extract, have shown antimicrobial action.[31,32] A review summary of Aphyllophorales is provided by Zjawiony.[33]

Antiviral Activity

In contrast to bacterial and fungal infection, allopathic medicine has little for viral infections. There is great promise from both whole extracts of mushrooms, as well as from isolated compounds. This can be observed with direct contact of the viruses and indirect antiviral effect resulting from immunologic activity of the polysaccharides and other compounds.[34] Several triterpenes of Reishi and water extract of Chaga have activity against HIV-1.[35,36] Extract of Chaga also shows antiviral action against influenza A and B.[37] Ergosterol found in several mushrooms also has an antiviral action.[38] Many other mushrooms, including water extract Shiitake mycelium and protein-bound polysaccharides (polysaccharide-K [PSK] and polysaccharide-peptide [PSP]) from Coriolus and D-fraction from Maitake, show multiple antiviral function.[39-44]

Antitumor Activity

Some mushrooms have long folklore associated with their use on cancer, including Chaga, which was used in the sixteenth and seventeenth century in Eastern Europe to treat cancer,[45] and Reishi (Ling Zhi), which was used in China over 2000 years ago. Several extracts of whole mushrooms, as well as isolated compounds including triterpenes, ergosterol, and polysaccharides, have shown well-documented antitumor action. Most of the medicinal mushrooms reviewed here have shown various actions in this area.

Immunosuppressive and Antiallergic Activity

Although several of the mushrooms can stimulate the immune system, some can suppress immune function. Interestingly, sometimes both stimulatory and inhibitory functions can be found in the same mushroom. Reishi was shown to inhibit histamine release.[46,47] Isolates of Chaga, including ergosterol, hispolon, and hispidin, have been found in many mushrooms to have antiallergic action.[48,49,49a]

Antiatherogenic Activity

Several mushrooms have strong action of regulating cholesterol. Reishi[50,51] and *Agaricus blazei*[52,53] were shown to decrease cholesterol levels. Shiitake mushroom contains an anticholesterol compound called eritadenine.[54] Oyster mushroom has a naturally occurring statin drug known as lovastatin (brand name: Mevacor, Altoprev).[55] Many studies have shown that consumption of several of these mushrooms can control cholesterol.[30,56]

Hypoglycemic Activity

With the increase of both type 1 and type 2 diabetes around the world, more effective treatments are needed. Several medicinal mushrooms can lower elevated blood sugars. Polysaccharide from Maitake,[57-59] Ganoderan A and B from Reishi,[59-62] glucan-protein complex from Coriolus,[63] as well as whole extract and constituents from Chaga,[64] *A. blazei,*[65-67] and Cordyceps[68-70] all have blood sugar regulating effects. The mechanism has not been worked out for most mushrooms, but Maitake action was shown to be an α-glucosidase inhibitor.[71]

Antiinflammatory Activity

Several ganoderic acids from Reishi have been shown to have stronger antiinflammatory action than acetylsalicylic acid.[72] The ergosterol found in many mushrooms was shown to inhibit cyclooxygenase 1 and 2 activity.[23]

Hepatoprotective Activity

Ganoderic acids, some glucans, and other compounds from Reishi showed liver protection both in vitro and vivo.[73-75] Reishi was also

shown to have activity against hepatitis B.[76] Other mushrooms, especially Coriolus, showed strong protective action for the liver.

Neurologic System Activity

Lion's Mane showed possible antidementia activity, while demonstrating ability to stimulate nerve cell growth.[77,78,79] Lion's Mane also showed ability to stimulate myelination.[80] Several mushrooms were studied as a functional pain reliever with opioid-like action.[81-84]

INDIVIDUAL MEDICINAL MUSHROOMS

Only a few of the most prominent medicinal mushrooms are listed here due to space. As suggested, many of the models that fit one mushroom are similar to models in other mushrooms.

Reishi (*Ganoderma lucidum* and *G. applanatum*, *G. tsugae*, Lingzhi 灵芝, 영지)

Used as a medicine in China for over two thousand years, Reishi is described in the *Shen Nong's* Classic and *Pen T'sao Kang Mu*. Reishi was so important for the upper class of China that it was a major symbol of health and longevity for the Emperor in the Forbidden City. Having hundreds of β-glucans and triterpenes, Reishi has a wide range of uses. Research showed that it can be used therapeutically for cancer,[85,86] immune system issues,[87,88] cardiovascular system and respiratory problems, as well as urinary tract symptoms. It is antibacterial,[89] antiviral,[90,91] antifungal,[92] an angiotensin-converting enzyme inhibitor,[93] inhibits blood platelet aggregation, is protective to the liver,[94,95] and protects the body from radiation.[96] Reishi lowers blood cholesterol and other blood lipids,[51] reduces allergies and asthma, while reducing autoimmune issues. It is antioxidant, hypoglycemic, antifibrotic, and increases the body's vitality. Reishi calms the mind, reduces circular arguments, and aids in insomnia.

Cordyceps (*Cordyceps sinensis*, dong chong xia cao 冬虫夏草)

Cordyceps is a parasitic fungus that grows out of insects. It has a long history of use in China and Tibet, but has also been used by indigenous peoples around the world.[97] Cordyceps is specific for the respiratory tract, working as a bronchial dilator. Heavily used by athletes, Cordyceps aids in both getting more oxygen into the cells and increasing endurance.[98] Cordyceps is used mostly for relief from bronchial inflammation and as an expectorant. It is well known to relieve exhaustion, night sweats, sexual impotency, and acts as a sedative. It benefits the kidneys, lungs, and gonadal function. It is specific for uterine fibroids. Cordyceps will stimulate immune function (due to CS-1) by activating T cells and B cells, while increasing interleukin-1 (but not 2) and γ-interferon. It has also been shown to increase erythroid progenitor cells and erythroid colony forming units in bone marrow. Sedative and even hypnotic activity can be attributed to the amino acid content. Reduction of cholesterol and plasma triglycerides has been observed, as well as increased spermatogenesis. Improvement in arrhythmia, in chronic kidney problems, liver function after hepatitis B, and good success with treating tinnitus, have all been observed.[99] It has been used against cancer,[100,101] as an antidepressant,[102] to promote cellular health,[103,104] to regulate blood lipids,[105-107] for the inhibition of infection and reverse transcriptase activity of HIV,[108,108a] to increase both male and female fertility, and as an aphrodisiac.[109]

Coriolus versicolor (*Trametes versicolor*; Turkey tail, Kawaratake, Yun-Zhi, 云芝)

This mushroom and its isolates are some of the most studied of all medicinal mushrooms. In particular, the glucan-protein complex of PSK (Kresin, PSP) is used in cancer therapy to counteract the immune depressing action of common chemotherapy. Approved in 1980 by the Japanese equivalent to the U.S. Food and Drug Administration for concurrent use with chemotherapy, it is covered by all health care plans in Japan.[110] Both the isolate and the mushroom were shown to increase survival time of cancer patients.[111] In large studies, it was also shown to be useful in stomach cancer, colorectal cancer,[112] small cell carcinoma,[111] and non-small cell lung carcinoma.[113] PSK was shown to enhance activity of the chemotherapeutic drugs doxorubicin and etoposide.[114,115] U.S. cancer doctors have acknowledged that both PSK and whole mushroom extract show promise for chemoprevention due to multiple effects on the malignant process and reducing side effects of oral dosage.[116] These studies, published in *Lancet*, found the results to be significant.[117-119] The sales for these unique all-natural compounds have reached several hundred million dollars a year in Japan and China, making them the most widely used products in those countries by people facing serious immune challenges.[120]

There has been great interest in Coriolus' ability to work as an antiviral in treating HIV, human papilloma virus, hepatitis, and many other viruses.[43,121]

Chaga Mushroom (*Inonotus obliquus*, Kabanoanatake)

This mushroom has been used for at least several hundred years in Russia and Eastern Europe and is well known and used extensively by indigenous people of northern Canada, Europe, and Siberia. In Russia, an extract of Chaga is known as befungin and is an approved medicine.[122] Known for its anticancer properties and immunomodulating qualities, it has been heavily researched.[123,124] It is known to increase survival rates of test animals.[125] Growing mostly on birch trees, it contains betulin and inotodiol, which showed promise in leukemia models.[126,127] It is starting to get quite a reputation as an antioxidant.[128,129] Chaga can be used as an antiinflammatory, reducing pain sensation.[130] Blood sugar regulating properties were also noticed in this mushroom.[64]

Maitake (*Grifola frondosa;* Hen of the Wood)

This edible mushroom has been extensively researched as an adaptogen and for its effect against cancer.[131,132] The primary polysaccharide, β-D-glucan, is well absorbed when taken orally, and is currently under review for the prevention and treatment of cancer and as a supportive tool for HIV infection. It was shown to stimulate the immune system. Animal studies suggested Maitake might lower fat levels in the blood and lower blood pressure.[133-137] Maitake was shown to inhibit angiogenesis.[138] The blood sugar lowering effect of Maitake is well researched; it has a naturally occurring α-glucosidase inhibitor.[59,71,139,140] Maitake's antioxidant effect may be due to it partially inhibiting cyclooxygenase.[23]

Agaricus blazei (*Agaricus subrufescens*; Kawarihiratake, Himematsutake, 姬松茸)

This very popular mushroom is used extensively in the Orient, although it was initially discovered in South America. Agaricus is used to stimulate the immune system and against a large range of cancers.[141] With over 500,000 people using this mushroom, it is

considered one of the more popular alternative remedies in the Orient.[142] It was shown to inhibit angiogenesis,[143] as well as having a wide ranging effect against viruses and other pathogenic factors.[144-146] There is ongoing research on its effect on lowering cholesterol[52] and blood sugar levels.[65,66]

Oyster Mushroom (*Pleurotus ostreatus,* Hiratake, píng gū, 平菇)

Oyster mushroom was shown to lower cholesterol, because of a naturally occurring statin drug, lovastatin, contained within it. Both in vivo and in vitro studies showed effects against breast and colon cancers due to β-glucans.[147-149]

Shiitake *(Lentinula edodes;* 椎茸, 香菇, 표고*)*

An edible mushroom, Shiitake has been used extensively as a folk remedy in the Orient. It was shown to stimulate the immune system[150] and possess antibacterial[151-153] and antiviral properties.[154-156] Shiitake was shown to reduce platelet aggregation[157] and lower cholesterol.[54] The mushroom and, more importantly, the mycelium extract lentinan showed activity against many strains of cancer, especially gastric cancer.[158-162]

Lion's Mane (*Hericium erinaceus*; Yamabushitake, 山伏茸, 猴头菇)

Lion's Mane works mostly on the nervous system; it has been used to combat dementia and to stimulate nerve cellular growth,[77,78] while stimulating myelination[80] and improving cognitive ability.[163]

Enokitake (*Flammulina velutipes;* えのき茸, 팽이버섯)

Enokitake is an edible mushroom, which through epidemiologic studies, was shown to have antitumor activity.[164] One of the isolated compounds (proflamin) was shown to produce an 85% longer survival rate in mice with cancer.[165] Enokitake also has an antioxidant effect.[166]

TOXICOLOGY

Many of these medicinal mushrooms are also consumed as food in various parts of the world and are considered safe even when consumed in large quantities on a regular basis. One should be aware though, that because some of these mushrooms can chelate heavy metals from their substrate, growing conditions must always be considered. It is strongly suggested that medicinal mushrooms be obtained from dependable, certified organic sources.

Although mild side effects were reported in the literature, as with most natural health products, a practitioner will rarely run into these problems.

There were two reported cases of hepatic toxicity linked to the long-term use of Reishi.[167,168] There was also a case of chronic diarrhea in a 49-year-old man with non-Hodgkin lymphoma after prolonged consumption of Reishi extract.[169]

Prolonged consumption of Shiitake was linked to a few cases of dermatitis and photosensitivity.[170,171] Eosinophilia and gastrointestinal upsets were observed with the use of Shiitake.[172]

DOSAGE

The dosage range varies considerably depending on the mushroom, the application, and the concentration of the product. Because some of the mushrooms, such as Oyster mushroom, are also used as food, the therapeutic range is around 20 g/day or more.

DRUG INTERACTIONS

A short list of drug interactions with medicinal mushrooms was found when reviewing the literature, but most of these were theoretical and not proven. The average practitioner will likely never run into these interactions.

The most common category of these drug interactions is one of "theoretical accumulation." Many of these mushrooms work on blood sugar, blood pressure, and blood lipid issues–the type of concerns for which patients are often already prescribed pharmaceuticals. Frequently after consuming mushroom preparations together with the drugs for a month or so, the patient will require less or no pharmaceuticals for these conditions moving forward. This effect becomes less about drug–mushroom interactions and more about the mushroom preparation exerting its effects. Using mushroom preparation in diabetic or hypertensive patients requires close monitoring during the first few months of treatment as the pharmaceutical dosage may require adjustment.

The mushroom that has been highlighted the most in this area is Reishi, because of its large range of therapeutic uses and the large number of people consuming it. Although anticoagulant, antiplatelet, immunosuppressant, and cytochrome p450 interaction concerns can be found in the literature, it is difficult to find research on actual cases of these problems. Again, concerns seem to lie more in the realms of theory and caution than actual cases.

SUMMARY

As can be seen, there has been a lot of research done in the area of medicinal mushrooms, but the surface has barely been scratched. We can find many fungi with strong therapeutic uses. The bioactivity can often be found in the polysaccharide and the triterpenes, but many other mechanisms can also be found. Some of the various mushrooms have activity in many areas and thus have been used by health care practitioners as multimedicinal substances. There needs to be much more research in this area, with strong incentives for pharmaceutical prospecting.

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CHAPTER 102

Melaleuca alternifolia (Tea Tree)

Michael T. Murray, ND

CHAPTER CONTENTS

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Melaleuca alternifolia (family: Myrtaceae)
Common name: tea tree

GENERAL DESCRIPTION

Tea tree *(Melaleuca alternifolia)* is a small tree native to only one area of the world: the northeast coastal region of New South Wales, Australia. The leaves, the portion of the plant that is used medicinally, are the source of a valuable therapeutic oil. Although there are more than 50 members of the Melaleuca family, the oil from the leaf of *M. alternifolia* has received the most research attention.

CHEMICAL COMPOSITION

Tea tree leaves contain about 1.8% of oil obtained via steam distillation.[1] This oil contains more than 48 compounds, but is chiefly composed of the following[2]:

- 1-terpinen-4-ol
- 1,8-cineol
- Gamma-terpinene (see Figure 102-1)
- *p*-cymene
- Other terpenes

The Australian standard (AS 2782-1985) for "Oil of Melaleuca (Terpinen-4-ol type)" sets a minimum content of terpinen-4-ol at 30% and a maximum 1,8-cineol content of 15%.[1]

HISTORY AND FOLK USE

The medicinal properties of crushed tea tree leaves were known to the Bundjalung Aborigines of northern New South Wales, Australia. The waters of a lagoon where tea tree leaves had fallen and decayed for hundreds of years were viewed as having tremendous healing properties.[1]

The popular name of tea tree was first reported in 1777, in Captain Cook's account of his second voyage, entitled *A Voyage to the South Pole*. The leaves of *M. alternifolia* were also used by the early settlers of Australia to make tea; hence, the further use of the popular name "tea tree."[1]

The first report of tea tree's medicinal use appeared in the *Medical Journal of Australia* in 1930.[3] A surgeon in Sydney reported impressive results using a solution of tea tree oil to clean surgical wounds. According to this report[3]:

> *The results obtained in a variety of conditions when it (tea tree oil) was first tried were most encouraging, a striking feature being that it dissolved pus and left the surface of infected wounds clean so that its germicidal action became more effective without any apparent damage to the tissues. This was something new, as most efficient germicides destroy tissue as well as bacteria.*

During World War II, tea tree oil was issued to soldiers to use as a disinfectant. The Australian Army went so far as to commandeer supplies of the oil and exempt leaf cutters from national service to maintain production. The production of tea tree oil during World War II was regarded as an "essential" industry.[1]

After World War II, the tea tree oil industry stagnated for more than 30 years. There were a number of reasons for this, including the general trend away from natural medicines and toward synthetic medical drugs. However, during the late 1970s and early 1980s, the Australian tea tree oil industry was reborn as successful plantations growing *M. alternifolia* were established.[1]

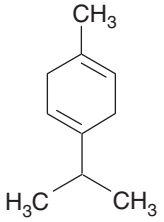


FIGURE 102-1 Gamma-terpinene.

Tea tree oil has been used in the treatment of the following conditions[1]:

- Acne
- Aphthous stomatitis
- Boils
- Burns
- Carbuncles
- Corns
- Gingivitis
- Herpes
- Impetigo
- Infections of the nail bed
- Insect bites
- Lice
- Mouth ulcers
- Pharyngitis
- Psoriasis
- Ringworm
- Root canal treatment
- Sinus infections
- Skin and vaginal infections
- Thrush
- Tinea pedis (athlete's foot)
- Tonsillitis

A variety of tea tree oil–based cosmetic products exist in the marketplace, including toothpastes, shampoos and conditioners, creams, hand and body lotions, soaps, gels, liniments, and nail polish removers.

PHARMACOLOGY

Tea tree oil possesses significant antiseptic properties and is regarded by many as the ideal skin disinfectant. This claim is supported by its efficacy against a wide range of organisms, its good penetration, and its lack of skin irritation.[1] The therapeutic uses of tea tree oil are based largely on its antiseptic and antifungal properties. Bacteria and fungal organisms inhibited by tea tree oil are listed in Tables 102-1 and 102-2.[1,4-6]

CLINICAL APPLICATIONS

The historical uses of tea tree oil demonstrate its wide range of applications as an antiseptic. Three of the more popular and documented uses are in the treatment of skin infections, vaginal infections, and common foot complaints.

Skin Infections

Tea tree oil is useful in a broad range of dermal infections, not only because of its broad-spectrum antiseptic properties, but also because of its capacity to mix with sebaceous secretions and penetrate the epidermis.

A clinical trial in patients with furuncles demonstrated that tea tree oil encouraged more rapid healing without scarring than was seen in matched control subjects.[7] Presumably, the positive clinical effects were due to the oil's germicidal activity against *Staphylococcus aureus*. Tea tree oil efficiently kills *S. aureus* in the stationary growth phase and within biofilms, making it a promising tool for *S. aureus* eradication.[8] In the clinical trial, the method of application consisted of cleaning the site followed by painting the surface of the furuncle freely with tea tree oil two or three times a day.

For most skin infections, the most effective treatment appears to be direct application of full-strength, undiluted oil at the site of infection. If irritation occurs, diluted preparations may be tried.

Lice Infestations

Pediculosis capitis (head lice infestation) treatment typically involves application of topical insecticides such as a pyrethrin or permethrin. An in vitro study showed that tea tree oil exerted the greatest effect of essential oils tested against head lice.[9] A clinical study compared the efficacy and safety of three topical pediculicides. A pediculicide containing tea tree and lavender oil was compared with a product containing pyrethrins and piperonyl butoxide; the percentage of subjects who were louse-free one day after the last treatment with the tea tree oil and lavender product was 97.6% (41 of 42 patients) compared with 25% (10 of 40 patients) of those using the product containing pyrethrins and piperonyl butoxide.[10] These clinical results, along with in vitro studies, indicate that products containing tea tree oil are effective alternatives to pyrethrin-based products.

Oral Infections

Tea tree oil was shown to exert significant activity against oral pathogens, both bacterial and fungal, and was suggested to be a suitable alternative to chlorhexidine.[11] From a clinical perspective, these effects may best be utilized in the treatment of oral candidiasis (thrush). In one open study, 27 patients with acquired immunodeficiency syndrome (AIDS) and oral candidiasis that was clinically refractory to fluconazole were randomly assigned to receive either an alcohol-based or an alcohol-free melaleuca oral solution four times daily for 2 to 4 weeks. Overall, 60% of patients demonstrated a clinical response to the melaleuca oral solution (seven cases were cured and eight cases clinically improved) at 4-week evaluation.[12]

Tea tree oil appears to be quite useful in oral candidiasis in cancer patients. Often these yeasts are resistant to azole antifungal drugs. In one study, 301 yeasts isolated from the mouths of 199 patients with advanced cancer were shown to be susceptible to tea tree oil, including 41 yeasts that were known to be resistant to both fluconazole and itraconazole.[13]

Dandruff

There is evidence that dandruff appears to be related to the yeast *Pityrosporum ovale*. Because tea tree oil has antifungal activity against *P. ovale*, a 4-week study was designed to investigate the efficacy and tolerability of 5% tea tree oil shampoo versus a placebo in 126 male and female patients, aged 14 years and older, with moderate dandruff. The 5% tea tree oil shampoo group showed a 41% improvement in the quadrant-area-severity score, compared with an 11% improvement in the placebo group. Statistically significant improvements were also observed in the total area of involvement score, the total severity score, and the itchiness

TABLE 102-1 **Bacteria Inhibited by *Melaleuca alternifolia* Oil**

	% (vol/vol)	
BACTERIAL SPECIES	**MIC**	**MBC**
Acinetobacter baumannii	1	1
Actinomyces viscosus	0.6	>0.6
Actinomyces spp.	1	1
Bacillus cereus	0.3	
Bacteroides spp.	0.06-0.5	0.06-0.12
Corynebacterium spp.	0.2-2	2
Enterococcus faecalis	0.5->8	>8
E. faecium (vancomycin resistant)	0.5-1	0.5-1
Escherichia coli	0.08-2	0.25-4
Fusobacterium nucleatum	0.6->0.6	0.25
Klebsiella pneumoniae	0.25-0.3	0.25
Lactobacillus spp.	1-2	2
Micrococcus luteus	0.06-0.5	0.25-6
Peptostreptococcus anaerobius	0.2-0.25	0.03->0.6
Porphyromonas endodontalis	0.025-0.1	0.025-0.1
P. gingivalis	0.11-0.25	0.13->0.6
Prevotella spp.	0.03-0.25	0.03
Prevotella intermedia	0.003-0.1	0.003-0.1
Propionibacterium acnes	0.05-0.63	0.5
Proteus vulgaris	0.08-2	4
Pseudomonas aeruginosa	1-8	2->8
Staphylococcus aureus	0.5-1.25	1-2
S. aureus (methicillin resistant)	0.04-0.35	0.5
S. epidermidis	0.45-1.25	4
S. hominis	0.5	4
Streptococcus pyogenes	0.12-2	0.25-4
Veillonella spp.	0.016-1	0.03-1

MBC, minimal bactericidal concentration; MIC, minimum inhibitory concentration.
Data from Carson CF, Hammer KA, Riley TV. *Melaleuca alternifolia* (tea tree) oil: a review of antimicrobial and other medicinal properties. Clin Microbiol Rev. 2006;19:50-62.

TABLE 102-2 **Fungi Inhibited by *Melaleuca alternifolia* Oil**

	% (vol/vol)	
FUNGAL SPECIES	**MIC**	**MFC**
Alternaria spp.	0.016-0.12	0.06-2
Aspergillus flavus	0.31-0.7	2-4
A. fumigatus	0.06->2	1-2
A. niger	0.016-0.4	2-8
Blastoschizomyces capitatus	0.25	
Candida albicans	0.06-8	0.12-1
C. glabrata	0.03-8	0.12-0.5
C. parapsilosis	0.03-0.5	0.12-0.5
C. tropicalis	0.12-2	0.25-0.5
Cladosporium spp.	0.008-0.12	0.12-4
Cryptococcus neoformans	0.015-0.06	
Epidermophyton flocossum	0.008-0.7	0.12-0.25
Fusarium spp.	0.008-0.25	0.25-2
Malassezia furfur	0.03-0.12	0.5-1.0
M. sympodialis	0.016-0.12	0.06-0.12
Microsporum canis	0.03-0.5	0.25-0.5
M. gypseum	0.016-0.25	0.25-0.5
Penicillium spp.	0.03-0.06	0.5-2
Rhodotorula rubra	0.06	0.5
Saccharomyces cerevisiae	0.25	0.5
Trichophyton mentagrophytes	0.11-0.44	0.25-0.5
T. rubrum	0.03-0.6	0.25-1
T. tonsurans	0.004-0.016	0.12-0.5
Trichosporon spp.	0.12-0.22	0.12

MBC, minimal bactericidal concentration; MIC, minimum inhibitory concentration.
Data from Carson CF, Hammer KA, Riley TV. *Melaleuca alternifolia* (tea tree) oil: a review of antimicrobial and other medicinal properties. Clin Microbiol Rev. 2006;19:50-62.

and greasiness components of the patients' self-assessments. The scaliness component of patient self-assessment improved but was not statistically significant. There were no adverse effects.[14]

Acne

Topical application of tea tree oil is a suitable alternative to benzoyl peroxide preparations. In one study, 124 patients with mild to moderate acne randomly received either a 5% gel of tea tree oil or 5% benzoyl peroxide lotion to be applied topically every day. After 3 months, both treatments produced a significant improvement in the mean number of both noninflamed and inflamed lesions, although with noninflamed lesions, benzoyl peroxide was found to be more effective. An important finding was that there were fewer reports of side effects (dryness, pruritus, stinging, burning, and skin redness) with tea tree oil (44% vs 79%).[15]

Common Foot Problems

Tea tree oil, in emollient form (8% tea tree oil) or in solution (40%), can be massaged into the feet daily for the treatment of tinea pedis, foot irritation, and bromhidrosis (severely foul-smelling feet).

One researcher concluded, after 6 years of using different concentrations and preparations, that tea tree oil eradicated or improved the symptoms of tinea pedis when used daily by patients at home.[4] He also reported that even undiluted forms had little effect on onychomycosis (discussed further in "Fungal Nail Infection"). Diluted tea tree oil in solution was found to reduce foot irritation and promote wound healing with surgical incision in cases of corns, calluses, bunions, and hammer toes, and was extremely effective in diminishing bromhidrosis.

In tinea pedis, one double-blind study found that 10% tea tree oil cream compared quite favorably with the antifungal tolnaftate in relieving symptoms, but was less effective in eliminating the fungi from cultures.[5] Specifically, both the tea tree group (24 of 37 patients) and the tolnaftate group (19 of 33 patients) showed significant improvement in the four clinical parameters of scaling, inflammation, itching, and burning, but only 30% of the subjects who applied tea tree oil cream tested culture negative, compared with 85% in the tolnaftate group.

In another double-blind trial, 158 patients with tinea pedis were randomly assigned to receive either placebo or 25% or 50% tea tree oil solution.[16] Patients applied the solution twice daily to affected areas for 4 weeks and were assessed after 2 and 4 weeks of treatment. A marked clinical response was seen in 68% of the 50% tea tree oil group and in 72% of the 25% tea tree oil group, compared with 39% in the placebo group. Mycologic cure was assessed by

culture of skin scrapings taken at baseline and after 4 weeks of treatment. The mycologic cure rate was 64% in the 50% tea tree oil group compared with 31% in the placebo group. Four (3.8%) patients applying tea tree oil experienced moderate to severe dermatitis that improved quickly upon cessation of the study medication.

Fungal Nail Infection

Fungal nail infections (onychomycosis) are the most common cause of nail disease, affecting approximately 2% to 13% of the population. Standard medical treatments include débridement, topical antifungals, and systemic antifungals. All current therapies have high recurrence rates. Oral therapy has the added disadvantages of high cost and potentially serious adverse effects.

One study compared the efficacy and tolerability of the topical application of 1% clotrimazole (CL) solution with that of 100% tea tree oil for the treatment of toenail onychomycosis.[17] The 117 patients received twice daily applications of either 1% CL solution or 100% tea tree oil for 6 months. Débridement and clinical assessment were performed at 0, 1, 3, and 6 months. Culture specimens were obtained at 0 and 6 months. Each patient's subjective assessment was also obtained 3 months after the conclusion of therapy. After 6 months of therapy, the two treatment groups were comparable on the basis of culture cure (CL = 11%, tea tree = 18%) and clinical assessment documenting partial or full resolution (CL = 61%, tea tree = 60%). Three months later, about half of each group reported continued improvement or resolution (CL = 55%, tea tree = 56%). These results indicate that topical therapy with tea tree oil, in conjunction with débridement, provides excellent improvement in nail appearance and symptomatology.

Vaginal Infections

Tea tree oil demonstrates germicidal activity against a number of common vaginal pathogens and opportunistic organisms, including *Trichomonas vaginalis* and *Candida albicans*.[18]

A 40% solution of tea tree oil emulsified with isopropyl alcohol and water was found in a clinical study to be highly effective for the treatment of cervicitis, chronic endocervicitis, trichomonal vaginitis, and vaginal candidiasis.[18] Weekly in-office treatment (usually four to six were necessary) involved thorough washing of the perineum, labia, and vagina with a suitable scrub (the commercial product pHisoHex was used in the study). After drying, the affected areas were washed with a 1% tea tree oil solution. This was followed by insertion of a tampon (three 4 × 4–inch sponges) saturated with the 40% tea tree oil solution. Patients were instructed to remove the tampon after 24 hours.

For infectious processes—trichomonas and candidiasis—daily vaginal douches containing 1 quart of water with a 0.4% concentration of the oil were prescribed. No irritation, burning, or other side effects were reported or observed with either the office applications or the douches.

DOSAGE

A number of commercial products contain tea tree oil. Tea tree oil can be used as a topical antiseptic for reducing microbial counts in wounds, surgical incisions, and skin and vaginal infections. In addition, tea tree leaves can be used to make teas that may be of benefit in cases of sore throat, tonsillitis, sinus infections, and colitis.

TOXICITY

Tea tree oil appears to be extremely safe for use as a topical antiseptic.[19] However, it may cause allergic contact dermatitis in some individuals. During a 3-year period, seven patients were seen in an outpatient dermatology clinic in Kona, Hawaii, for contact dermatitis due to the use of commercially available product containing 100% tea tree oil.[20] The patients were treating preexisting skin conditions, which included foot fungus, dog scratches, insect bites, and rashes. All patients presented with an eczematous dermatitis. Patch tests indicated that all patients were sensitive to a 1% solution of tea tree oil. It is recommended that individuals apply the oil to a small area of skin before using tea tree oil for the first time so as to avoid the bother of experiencing contact dermatitis over a larger area.

The oral ingestion of tea tree oil cannot be recommended because it could lead to a toxic reaction. However, folk use suggests that oral ingestion of tea from the leaves is reasonably safe.

DRUG INTERACTIONS

Tea tree oil may produce a synergistic effect with other topical antimicrobials. In an in vitro study, tea tree oil and tobramycin in combination produced significantly lower minimal inhibitory concentrations against *Escherichia coli* and *Staphylococcus aureus*.[21] A similar synergism was demonstrated between tea tree oil and the antifungal compound amphotericin in inhibiting Candida species.[22]

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CHAPTER 103

Melatonin

Ronald G. Reichert, BA, ND

INTRODUCTION

Melatonin (*N*-acetyl-5-methoxytryptamine) is a neurohormone synthesized in reply to neuronal signals arriving from the suprachiasmatic nucleus (SCN) of the anterior hypothalamus.[1,2] Its action in promoting sleep and the associated sleep/wake cycle is primarily the result of two G protein-coupled receptors within the SCN called MT1 and MT2.[3] Both receptors modulate neuronal activity within the SCN and influence circadian rhythm activation.[4] Biochemically, melatonin is synthesized as follows: L-tryptophan to 5-hydroxytryptophan to serotonin. The biogenic amine serotonin is then converted to *N*-acetylserotonin and ultimately into melatonin with the rate-limiting steps for melatonin production catalyzed by two enzymes, arylalkylamine *N*-acetyl transferase and hydroxyindole-*O*-methyltransferase.[5] Melatonin is secreted by the pineal gland in response to darkness. This latter action has been elegantly described as the "opening of the sleep gate."[6]

PHARMACOKINETICS

Peak plasma concentrations of endogenous melatonin in adults reach a high of 60 to 70 pg/mL and typically occur between 2:00 and 4:00 AM.[5] Supplementary exogenous melatonin, according to the result of one human study, has a 15% absolute bioavailability at the 2- and 4-mg oral doses.[7] In another study using 250 mcg of daytime melatonin in healthy volunteers, it was noted that melatonin had a rapid absorption, with a mean time to reach maximal concentration (T_{max}) of 23 minutes. The mean terminal half-lives of melatonin were 36 ± 6 minutes and 45 ± 14 minutes, in men and women, respectively.[8] Sustained-release melatonin (2 mg), in contrast, has a T_{max} of 3 hours, which is delayed in the presence of food (T_{max} 0.75 hours). Terminal half-life is 3.5 to 4 hours.[9]

CLINICAL APPLICATIONS

Jet Lag

Melatonin for the treatment of jet lag has been extensively studied in controlled studies and proven to be remarkably successful in reducing jet lag symptoms.[10] In one early double-blind, placebo-controlled study, 20 healthy volunteers (8 women, 12 men; 28 to 68 years) engaging in long-haul air flights across five time zones were invited to participate to explore the effects of melatonin on their jet lag symptoms. Subjects were randomly assigned to 5 mg of melatonin or placebo for three days before their outward flight (London to New Zealand) and during the flight between 10:00 AM and 12:00 PM local time, as well as for three days after their arrival between 10:00 PM and 12:00 AM. According to the results of visual analogue scale (VAS) testing, those using the melatonin had less overall jet lag symptoms at day 10 (mean score 2.15) versus placebo (3.40; P <0.01). Moreover, the melatonin group experienced a better adaptation pattern in terms of sleep pattern, daytime tiredness, and normal energy levels than the placebo group (P <0.05).[11] Although this latter study suggested an optimal time pattern for melatonin use in an eastbound flight, another author noted that bedtime may not be an ideal time to employ melatonin on a westbound flight that crosses less than six to eight time zones. He suggested employing a lower dose of melatonin (0.5 mg) on the westbound flight later in the evening as "melatonin has the least phase shifting effects when it overlaps with endogenous secretion."[12]

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Acute Sleep

It is estimated that 50 to 70 million American adults have difficulty sleeping.[13] This issue of poor sleep quality can have profound consequences for the individual and society at large, including an increased risk of accidents and mood and behavioral changes, as well as a reduction in work productivity.[14] One of the numerous options available to help improve overall sleep is melatonin, both in healthy adults as an acute remedy for insomnia and in the elderly dealing with issues of chronic insomnia.

The acute use of melatonin in healthy adults without insomnia at doses of 0.3 to 1 mg at 8:00 or 9:00 PM significantly reduces sleep-onset latency and latency to stage 2 sleep compared with the placebo (P <0.001). Moreover, melatonin does not produce any "sleep hangover" symptoms (according to the Profile of Mood States and Four Choice Reaction Time Test) commonly associated with benzodiazepine-type drug use.[15]

Insomnia in the Elderly

Most elderly individuals report sleeping an average of 7 hours a night. Although the total amount of sleep time does not change as we age, alterations in sleep architecture are common.[16] This includes a decrease in both deep sleep (stages 3 and 4 slow wave sleep) and rapid eye movement (REM) sleep, as well as an increase in stage 1 (light) sleep.[17] Older individuals also have a reduction in endogenous melatonin production (likely due to a deterioration in the neuronal functioning of the SCN), which in turn disrupts the normal wake/sleep cycle.[18]

In a controlled clinical trial, 30 men and women over 50 years of age with both chronic insomnia and normal sleep patterns were randomized to receive capsules with either 0.1, 0.3, or 3 mg of melatonin or placebo 30 minutes before bedtime for 7 days. Treatments were separated by a 1 week washout period. Using polysomnography, the researchers concluded that although melatonin did not improve sleep efficiency in normal subjects, those with chronic insomnia had significant improvements in sleep efficiency at all three melatonin doses used, with the 0.3 mg dose triggering the strongest effect (P <0.0001). The physiologic dose acted primarily in the middle portion of the night and raised plasma melatonin levels to normal. The authors noted that 3 mg of melatonin significantly raised plasma levels throughout a portion of the day and triggered reductions in core body temperature after ingestion of the hormone.[6]

Prolonged Release Melatonin in the Elderly

After a 2-week single blind run-in period, 354 elderly men and women (55 to 80 years of age) with primary insomnia were randomized to receive 2 mg of a prolonged release (PR) melatonin or placebo 2 hours before bedtime, for 3 weeks. Subjects enrolled in the study were asked to complete a sleep diary measuring quality of day and night, plus a battery of sleep questionnaires including the Pittsburg Sleep Quality Index (PSQI), Leeds Sleep Evaluation Questionnaire (LSEQ), as well as quality of life (World Health Organization-5 [WHO-5] Well Being Index) and clinician Clinical Global Impression (CGI) scores. At the conclusion of the trial, those who took the melatonin had improved (26%) quality of sleep and morning alertness as recorded by the LSEQ in contrast to placebo (15%) (P = 0.014). Sleep latency, as noted by the PSQI results, improved in subjects employing the PR melatonin by 24.3 minutes compared with 12.9 minutes for the placebo group (P = 0.028). Quality of life as recorded by the WHO-5 Index was also improved in the active group (P = 0.034).[19] A similar study supported the latter conclusion with a positive effect found on the restorative value of sleep in elderly patients using 2 mg of PR melatonin. Moreover, melatonin users did not experience any rebound insomnia or withdrawal symptoms at the conclusion of the controlled study. The authors noted that plasma cortisol increased in middle-aged adults, and this phenomenon might impair sleep. Administration of PR melatonin in older adults with primary insomnia may delay the production of nighttime cortisol, with subsequent improvements in both sleep quality and morning alertness.[20]

Magnesium, Melatonin, and Zinc on Primary Insomnia and the Elderly

Magnesium, along with zinc, is crucial for the endogenous synthesis of melatonin according to the results of one study. Elderly men and women (n = 43; average age 78.3 years) living in a long-term care facility were invited to participate in a double-blind, placebo-controlled study of 60 days' duration on melatonin, zinc, and magnesium on primary insomnia. Each volunteer was randomized to receive a 100 g pear pulp food supplement with 5 mg melatonin, 225 mg of magnesium, and 11.25 mg of zinc, or placebo 1 hour before bedtime for 2 months. At the conclusion of the trial, those employing the active supplement experienced an improvement in their overall PSQI scores compared with placebo (P < 0.001). Moreover, the LSEQ results confirmed that those employing the food mixture not only had better quality of sleep but had greater ease getting to sleep (P <0.001). Quality of life was measured by the Medical Outcomes Study Short-Form 36 scale, which noted that the active group had better physical and mental functioning after 8 weeks of treatment (P = 0.006). Adverse effects were minimal, with only two participants in the treatment group complaining of headache, whereas one volunteer in the placebo group complained of epigastric pain.[21]

Insomnia in Perimenopausal Women

In a case series of reports, 11 perimenopausal women (45 to 52 years) with insomnia were treated with 7.5 to 15 mg of mirtazapine for 2 to 4 weeks. Two milligrams of melatonin were then added to the treatment regimen, along with a concomitant reduction and discontinuation of mirtazapine for 30 to 90 days. Global PSQI scores decreased from 17.45 at baseline to 8.55 at the second visit (mirtazapine and PR melatonin) to 6 by the third visit (PR melatonin) (P <0.01). These latter changes were paralleled by a similar drop in PSQI sleep latency scores, with 52.73, 21.36, and 18.64 minutes at baseline, visit 2, and visit 3, respectively (P <0.01). Volunteers also noted that their quality of life as measured by the WHO-5 score improved significantly by 89% from baseline (P <0.01).[22]

Chronic Sleep Onset Insomnia in Children

Pediatric insomnia is estimated to affect 1% to 6% of children, but can be significantly elevated to 50% to 75% if there are other associated psychiatric or neurodevelopmental issues such as attention deficit hyperactivity disorder (ADHD), autistic spectrum disorders (ASDs), and epilepsy.[23]

A group of children (49 boys, 13 girls; aged 6 to 12 years) with chronic sleep-onset insomnia of more than 12 months' duration were randomized to receive 5 mg melatonin or placebo at 7 PM for

30 days. Using several questionnaires measuring overall health status (RAND General Health Rating Index and Functional Status II), children who used the melatonin had better outcomes in terms of eating, sleeping, response to attention, fatigue, illness, and overall health than those who received the placebo (P <0.05). In addition, melatonin users had an advancement in their sleep onset by 57 minutes (P = 0.003), a reduction in sleep latency by 17 minutes (P = 0.048), and a decrease in their dim light melatonin onset (DLMO) by 82 minutes (P <0.001).[24]

Fibromyalgia

Fibromyalgia (FM) is a challenging condition with characteristic symptoms that include widespread and variable chronic pain, as well as fatigue, stiffness, cognitive disturbances, depression, and insomnia.[25] Although alterations in the secretion of melatonin have been observed in FM patients, whether or not this latter phenomenon contributes to the pathophysiology of this disease remains controversial.[26] Several studies suggested, however, that melatonin is of value in treating this chronic musculoskeletal condition.

Twenty-one female patients (average age 51 years) who met the American College of Rheumatology (ACR) criteria for primary FM for at least 6 months before their participation in a uncontrolled pilot study were invited to help evaluate the effects of a 3 mg capsule of melatonin 30 minutes before bedtime for 1 month. Of the 21 patients who completed the study, 19 were found to have a significant reduction from baseline in musculoskeletal tender point count (–28.6%), severity of pain (–33.4%), and sleep disturbances (–67.2%) as measured by VAS (P <0.05). Although fatigue, depression, and anxiety did not show statistical improvement on VAS, the overall physician and patient VAS global treatment assessment scores of FM disease status (with 10 representing the worst score) improved from 7.6 to 5.7 and 7 to 4.7, respectively. Four patients experienced mild and transient side effects during the trial, including tremor, heartburn, anxiety, and somnolence.[27]

In another randomized, double-blind placebo-controlled trial, 101 patients (6 men, 95 women; 18 to 65 years) with ACR confirmed primary FM were randomized to one of four treatment groups: (A) 20 mg/day fluoxetine and placebo; (B) 5 mg/day melatonin and placebo; (C) 20 mg/day fluoxetine with 3 mg/day melatonin; and (D) 20 mg/day fluoxetine and 5 mg/day melatonin for 2 months. Using the Fibromyalgia Impact Questionnaire (FIQ) to evaluate the clinical outcomes, the researchers determined that compared with baseline, both fluoxetine and melatonin as single therapies significantly reduced within-group symptom scores by 21.5% and 18.9%, respectively (P <0.05). However, those volunteers combining fluoxetine and melatonin at both 3 and 5 mg doses experienced nearly comparable (28.8% vs 28.9%) and highly significant reductions in their FIQ scores (P <0.001). Although all treatments reduced FIQ pain scores, it was interesting to note that the reduction in fatigue scores in groups B, C, and D by 23.7%, 20.3%, and 34.7%, respectively, compared with only 9.9% in the fluoxetine only treatment group. Fluoxetine as a single agent did not alter the rest/sleep score compared with the significant improvements seen in groups B, C, and D.[28]

Chronic Fatigue Syndrome

Much like FM, chronic fatigue syndrome (CFS) is associated with a number of symptoms, including intense and disabling fatigue that does not improve with rest.[29] One of the factors contributing to fatigue and sleep disturbances in CFS is disruption in the hypothalamic-pituitary-adrenal axis.[30] However, under research scrutiny, both adults and adolescents with CFS have increased levels of melatonin, suggesting the hormone has no role to play in this disorder.[30] Research on DLMO concluded that a certain subset of CFS patients may respond to the therapeutic use of melatonin. DLMO is a naturally occurring event that may account for delayed sleep phase syndrome in 10% of chronic insomniacs.[31]

Twenty-nine patients (24 women, 5 men; average age 33.2 years) with CFS were asked to take 5 mg of melatonin at bedtime for 3 months. Using the checklist individual strength (CIS) questionnaire to measure several variables, the authors determined that the total score (P = 0.006), as well as the sub-scores of fatigue (P = 0.017), concentration (P = 0.031), motivation (P = 0.010), and activity (P = 0.008), improved significantly after 90 days of melatonin use. Moreover, those patients with late DLMO (>21.30 hours) overall CIS and its subscores were better than in those CFS patients with early DLMO.[32]

Children with Epilepsy

Seizure-free epileptic children (n = 31; 3 to 12 years of age) with a history of either partial or generalized seizures and utilizing 10 mg/kg per day of sodium valproate participated in a double-blind, placebo-controlled study of 8 weeks' duration. The children were randomized to receive either melatonin tablets (6 mg for those less than 9 years of age and less than 30 kg body weight or 9 mg for those more than 9 years of age and more than 30 kg body weight, to be taken in the evening) or comparable placebo 1 hour before bedtime. The primary end point of the study was evaluated using the parental Sleep Behavior Questionnaire. By the conclusion of the controlled trial, those children using the additional melatonin had a significantly greater average percentage reduction in their total sleep scores (24.4%) compared with placebo (14.4%) (P <0.05). Moreover, the median reduction in the parasomnia scores significantly favored those who took melatonin (60%) relative to the placebo (36.4%) (P <0.05). No adverse effects were noted during the trial.[33]

Autism/Fragile X Syndrome

In a recent review and meta-analysis, the authors noted that children with ASDs not only have a higher incidence of sleep-associated problems, but that melatonin use led to significant improvements in sleep duration and sleep-onset latency compared with placebo (P <0.01). This poor sleep pattern in turn can lead to a worsening of overall autistic behavior symptoms.[23]

In one double-blind, placebo-controlled, crossover trial, 18 subjects (16 boys, 2 girls; mean age 6 years) with ASD or fragile X syndrome, or both, and insomnia were randomized to receive 3 mg melatonin or placebo 30 minutes before bedtime for 14 days. After 2 weeks, subjects were crossed over, such that the active group received placebo and vice versa. Children were evaluated using actigraphy and parentally recorded sleep diaries. After 4 weeks and in 12 of 18 children who had complete data sets, the authors noted that those using the melatonin had an improvement in the total night's average sleep duration (+21 minutes longer than placebo; P = 0.02), a reduction in sleep latency time (28 minutes vs placebo; P = 0.0001), and a 42-minute earlier sleep-onset time in contrast to the placebo group (P = 0.02).[24a]

Children with Insomnia and Attention Deficit Hyperactivity Disorder

Twenty-seven children (6 to 14 years of age) diagnosed with ADHD and insomnia and employing stimulant medications (i.e., methylphenidate, dextroamphetamine), participated in a controlled trial. Those subjects who did not respond to a 10-day sleep hygiene regimen were randomized to receive 5 mg of melatonin or placebo 20 minutes before bedtime for 1 month. Compared with the placebo, children who took melatonin had a significant reduction in sleep-onset latency as measured by somnolog (46.4 minutes vs 62.1 minutes placebo) and actigraphy (P <0.01) at the conclusion of the trial. Adverse events were considered mild by the investigators. Melatonin treatment and the subsequent improvement in sleep did not, however, improve ADHD symptoms as noted by Conner's Attention Deficit Scale, Parent version scores.[34]

One hundred and five medication-free children (aged 6 to 12 years) with ADHD were randomized to receive 3 mg of melatonin or 6 mg of melatonin if body weight was less than 30 kg or greater than 30 kg, respectively, or placebo at 7:00 PM for 30 days. Those subjects who used melatonin had advancements in sleep onset as measured by actigraphy, (26.9 ± 47.8 minutes) compared with a delay (10.5 ± 37.4 minutes) in the placebo group (P <0.0001). Additionally, there was a significant increase in total sleep time (19.8 ± 61.9 minutes) versus a reduction (13.6 ± 50.6) seen in the placebo group (P = 0.01). Children treated with the active compound showed an advance in DLMO of 44.4 ± 67.9 minutes compared with a delay in children who received the placebo (P <0.001). No changes were noted in behavior and cognition. Adverse events did not differ between active groups and placebo.[35] A long-term 3.7-year follow-up using the same group of children (93% response rate) verified that melatonin use was not associated with any serious side effects, but also did not provide a permanent cure for insomnia in ADHD children.[36]

Children with Migraine/Tension-Type Headaches

Headaches and migraines are two of the more likely reasons that will cause children to complain of pain. Annual prevalence for migraine and tension-type headaches can vary with between a 3% to 11% and a 10% to 24% occurrence, respectively.[37]

In an uncontrolled pilot study, 22 children (10 boys and 12 girls; age range 6 to 16 years) with various types of long-standing (average 40.05 ± 30.2 months) headache-type discomfort (13 recurrent migraines/no aura; 8 chronic tension-type headaches; 1 migraine with aura) participated in a 12-week study on the effects of oral melatonin. After a 1 one-month washout period in which all preventive therapy was discontinued, the children were asked to take 3 mg of melatonin at bedtime for 90 days. At the conclusion of the study and according to the results of a structured daily headache diary, the frequency (i.e., the number of attacks per month) and the duration of attacks (hours) decreased from 12.3 to 5.7 and 13.5 to 9.7, respectively (P <0.001). Pragmatically, and as the authors noted, 14 of the 21 subjects (one child stopped the melatonin due to excessive somnolence) had a greater than 50% reduction in headache attacks. Notably, four of the children had complete resolution of their headaches.[38]

Functional Dyspepsia

Postprandial fullness and early satiation, along with epigastric pain and burning without evidence of upper gastrointestinal structural pathology on endoscopy are the hallmark of Rome III diagnostic criteria for functional dyspepsia.[39] One group of researchers suggested that melatonin use stimulates enterocytes to produce bicarbonate, which in turn may help neutralize gastric hydrogen chloride and, therefore, reduce symptoms as evidenced by the following study.[40] Sixty patients (18 men, 42 women; ages 19 to 39 years) with a 3 to 12-year history of nonulcer dyspeptic symptoms (i.e., chronic or recurrent epigastric pain) were randomized to receive 5 mg of melatonin or placebo in the evening for 3 months. After 12 weeks of treatment and using a 10-point scale (0 = no symptoms; 10 = maximum symptoms) for therapeutic evaluation, 17 of 30 (56.6%) patients using the melatonin had their condition resolve completely, such that they did not require further treatment, whereas an additional 9 of 30 (30%) patients experienced a partial improvement in symptoms (i.e., reduction in nighttime gastric pain) (P <0.01). Although four patients in the active treatment group noted no change in symptoms, a larger percentage of subjects (93.3%) using placebo noted no change in their condition. The authors noted that those who had a previous infection with *Helicobacter pylori* were less likely to respond to melatonin treatment.[40]

Irritable Bowel Syndrome

It is estimated that 7% to 15% of the U.S. population has irritable bowel syndrome (IBS), a painful abdominal condition that is primarily associated with diarrhea and/or constipation, along with a number of other symptoms, including gas and bloating.[41] Research recent showed that the excretion of the urinary metabolite of melatonin (6-sulphatoxymelatonin) was significantly lower in subjects with IBS than controls (P = 0.0004), suggesting that melatonin is involved in the pathogenesis of IBS by acting on the enterochromaffin cells in the gastrointestinal tract.[42]

In a double-blind, placebo-controlled study, 18 patients (12 men, 6 women; ages 18 to 65 years) with IBS were randomized to receive 3 mg of melatonin at bedtime or a matching placebo for 2 months. By the conclusion of the trial, those subjects taking melatonin had a 45% improvement in their overall IBS symptom scores (i.e., pain severity and frequency, bloating) compared with 16.7% in those taking placebo (P <0.05). Moreover, the extracolonic symptom scores, including headache, backache, body aches, thigh pain, and lethargy, were significantly lower in the melatonin group compared with pretreatment values (P <0.001) and the placebo group (P <0.05). Overall, those subjects taking the melatonin experienced an improved quality of life score (43.63%) in contrast to those taking placebo (14.64%) (P <0.05). Three subjects experienced side effects, including decreased libido and drowsiness.[43]

Gastroesophageal Reflux Disease

In 2004, it was estimated that 20% of the American population has gastroesophageal reflux disease (GERD), which is responsible for 64.6 million prescriptions annually.[44] According to several studies, melatonin is of therapeutic value with or without omeprazole.

In this study, 36 individuals with GERD were selected and equally placed into four groups: control; 3 mg melatonin at bedtime; 20 mg of omeprazole twice daily; and 3 mg of melatonin and 20 mg of omeprazole twice daily for 2 months. After 8 weeks, those using the melatonin alone had a significant reduction in GERD symptoms, increase in lower esophageal sphincter (LES) pressure (better LES tone), increase in serum gastrin, a reduction in gastric basal acid output, and an increase in serum melatonin

levels (P <0.05). In contrast, although omeprazole was also effective in reducing GERD symptoms (P <0.05), it did not alter LES tone in a significant fashion. The combination of melatonin and omeprazole had similar results in the single melatonin group, but had a better reduction in basal acid output and an increase in serum gastrin (P <0.05).[45]

Individuals (141 men, 210 women; mean age 44 years) with at least one episode of moderate to severe heartburn within the previous week before the onset of treatment within a clinical trial were randomized to receive 6 mg melatonin plus vitamin B_6 (25 mg), vitamin B_{12} (50 mcg), folic acid (10 mg), tryptophan (100 mg), methionine (100 mg), and betaine (100 mg) or 1 capsule (20 mg) omeprazole per day in the evening for 40 days. After 40 days, individuals using the natural product combination had 100% reduction in symptoms as measured by a five-point severity scale, compared with the reduction in symptoms seen (65.7%) in the omeprazole group (P <0.05). As an observation, those 34.3% of the subjects who experienced a persistence of their GERD symptoms with the use of omeprazole had complete resolution of their symptoms after 40 days with the natural combination of vitamins, melatonin, and amino acids.[46]

The authors suggested that the efficacy for their combination medication was due to several factors. Melatonin may block the production of nitric oxide synthase, which may help lower the degree of LES relaxation. Melatonin also stimulates the production of bicarbonate, which protects against the action of gastric acid production. Moreover, the combination of vitamin B_6, tryptophan, and vitamin B_{12} may decrease acute gastrointestinal pain due to serotonin inhibiting the nociceptive system. Methionine and betaine may induce S-adenosyl methionine production, which has both antiinflammatory and analgesic properties.[46,47]

Cancer

According to the results of a systemic review, melatonin decreased the risk of death from solid tumors at the 1-year mark.[48] This was supported by several independently published articles, primarily by one of the premier researchers on melatonin use and cancer, Professor Paolo Lissoni.

Non-Small Cell Metastatic Lung Cancer

One hundred patients (59 men, 41 women; average age 39 to 81 years) with metastatic non-small cell lung cancer were randomized to receive chemotherapy (cisplatin and etoposide) every 21 days for four cycles or chemotherapy plus 20 mg of melatonin in the evening. Patients in the melatonin group continued to use melatonin after chemotherapy cessation. Reviewing the clinical response after 60 to 72 months of follow-up, the authors determined that those using the melatonin and chemotherapy combination had a significantly better complete and partial response (35%; 17 of 49 patients) to treatment versus the chemotherapy group (18%; 9 of 51 patients) (P <0.05). Moreover, a progressive disease state was seen in 20 of 51 patients in the chemotherapy group in contrast to 6 of 49 patients in the chemotherapy/melatonin group (P <0.01). Side effects of chemotherapy, including neurotoxicity, thrombocytopenia, weight loss of more than 10%, and asthenia were notably reduced in the melatonin group. Overall 5-year survival rate was significantly longer in those concomitantly treated with melatonin (P <0.001). Three of the 49 patients were still alive 5 years from the date of therapy onset in the combination group compared with no patients in the chemotherapy alone section.[49]

Metastatic Solid Tumors: Gastric, Colorectal, and Non-Small Cell Lung Cancer

Three hundred seventy patients with metastatic non-small cell lung cancer, colorectal cancer, or gastric cancer were randomized and treated with the appropriate chemotherapy alone or chemotherapy plus melatonin 20 mg/day in the evening. After 24 months, the overall response rate (complete and partial remission) was higher in the melatonin and chemotherapy group (68 of 167 patients; 36%) versus chemotherapy alone (37 of 183 patients; 20%) (P <0.001). In addition, the 2-year survival rate in those using melatonin adjunctively was better (47 of 187 patients; 25%) versus those employing chemotherapy as a sole treatment (24 of 183 patients; 13%) (P <0.05).[50]

Metastatic Breast Cancer

Melatonin may enhance the effects of the drug tamoxifen according to the results of one preliminary study. Fourteen women (age 42 to 80 years) with metastatic breast cancer, whose breast cancer did not respond to tamoxifen therapy (n = 3) or who had progressed after their disorder had stabilized (n = 11) on tamoxifen, participated in this Phase II trial. After a 1-month washout of tamoxifen, patients were given melatonin 20 mg in the evening, 1 week before starting tamoxifen and 20 mg midday for at least 12 months. Although no complete response to the combination therapy was noted in any of the patients, 28.5% (4 of 14 patients) did achieve a partial response. Moreover, 10 of 14 patients were still alive after 1 year. Serum levels of insulin-like growth factor (IGF-1) were reduced in response to the treatment at both 1 (P <0.05) and 3 months (P <0.01). Prolactin levels were also reduced from 25 ± 3 ng/mL^1 to 13 ± 2 ng/mL^{-1} after 12 weeks (P <0.05). No toxicity was noted.[51]

Metastatic Prostate Cancer

Fourteen men (mean age of 71.5 years) with metastatic prostate cancer (tumor grades G2 [n = 9] and G3 [n = 5], whose prostate-specific antigen [PSA] scores had worsened using a combination of triptorelin [3.75 mg intramuscular every 28 days] and flutamide [750 mg/day by mouth for 1 month only]) participated in this open clinical trial. After a 30-day washout period in which no triptorelin was given, patients were asked to begin melatonin 20 mg at night 7 days before starting their monthly injections of luteinizing hormone-releasing hormone (LHRH) analogue drug. After 90 days, 8 of 14 patients had a greater than 50% reduction in their PSA scores compared with pretreatment values. In addition, average PSA serum concentrations were reduced from a pretreatment value of 421 ± 118 ng/mL to 108 ng/mL (P <0.05) after 3 months of melatonin and triptorelin. IGF-1 and prolactin serum values were significantly reduced in patients using the combination of the two drugs (P <0.05).[52]

Taxane-Related Neuropathy

Although the two types of taxanes (paclitaxel and docetaxel) are widely utilized in oncology, they have several side effects, including neuropathy.[53] A recent study suggested that melatonin might help with this issue. In this open-label Phase II pilot study, 22 women with breast cancer (33 to 68 years of age) who underwent chemotherapy with taxanes were instructed to take 21 mg of melatonin at bedtime for up to 6 months. Using the National Cancer Institute-Cancer Treatment Center's scale for neuropathy, the authors noted that, "in our trial, patients receiving melatonin during taxane chemotherapy had a reduced incidence of all grade neuropathy (46%) compared to historical controls (around 60%)." Fifty-five percent of the patients (n = 11) reported

no neuropathy (grade zero). Adverse events included nausea, vomiting, and fatigue. None of the patients reported any incidence of daytime sedation.[54]

Cachexia

Progressive weight loss, anorexia, and reduction in the body's cell mass are hallmarks of cancer-related cachexia.[55] The cytokine tumor necrosis factor-alpha (TNF-α) plays a role in cancer cachexia according to the conclusions of one trial. Patients (56 men, 30 women; 39 to 76 years) with untreatable solid tumors (i.e., breast, colorectal, gastric, non-small cell lung cancer, etc.) and metastasis to various sites were stratified according to tumor type and randomized to either standard care (nonsteroidal antiinflammatory drugs and opioids for pain) or standard care plus melatonin (20 mg in the evening) for at least 3 months. The authors noted that at the end of 16 weeks, weight loss of greater than 10% occurred in 32% of the patients treated with conventional care versus only 4% of the patients treated with melatonin and conventional care (P <0.01). Concomitantly with the lower reduction in weight loss, serum values of TNF-α were also significantly lower in patients using the standard care and melatonin compared with the standard care group alone (P <0.01).[56]

Fertility

It is estimated that about 6.1 million women in the United States between the ages of 15 to 44 years have difficulty with either becoming pregnant or staying pregnant. Because the success rate with in vitro fertilizations (IVFs) and subsequent pregnancies can vary,[57] researchers have considered other options, including melatonin. One hundred fifteen women (24 to 45 years) who had not become pregnant using in vitro fertilization were divided into two groups and given 3 mg of melatonin at 10:00 PM from the fifth day of the previous menstrual cycle until the day of oocyte retrieval. Those using the melatonin in conjunction with the second IVF had a higher fertilization rate (50.0 ± 38.0%; P <0.01) compared with the first IVF trial (20.2 ± 19.0%), with a higher number of pregnancies (19.6%; 11 of 56 patients) being reported. In contrast, the non-melatonin users had no improvement in their fertilization rates (20.9 ± 16.5% first IVF versus 22.8 ± 19.0% second IVF), resulting in a lower number of successful pregnancies (10.2%; 6 of 59 patients) during the second IVF-ET trial. The difference between the two groups' pregnancy rates was not statistically significant. In an additional analysis of 54 infertile women, it was determined by the authors that 3 mg of melatonin at 10:00 PM or 200 mg of vitamin E (given from the fifth day of the previous menstrual cycle until oocyte retrieval) three times a day significantly decreased the intrafollicular oxidative stress by decreasing the 8-OHdG concentrations compared with the first IVF cycle (P <0.05).[58]

Forty-six infertile women (38 to 42 years of age) who had not conceived previously using IVF were recruited to receive 2 g of myoinositol plus 200 mg of folic acid in the morning and the latter combination in the evening plus 3 mg of melatonin daily for 90 days. After 3 months of using the treatment, a second cycle of IVF was instituted, resulting in a significant improvement in the number of embryos (0.48 ± 0.51 vs 0.80 ± 0.69; P = 0.01) and the quality of the embryos transferred (0.13 ± 0.48 vs 0.35 ± 0.48; P = 0.01). The implantation rate during the second IVF cycle was 22.8% compared with 0% in the initial IVF cycle, resulting in 13 pregnancies. Four of the thirteen pregnancies were not successful and spontaneously aborted.[59]

Depression

Although 6 mg of melatonin for 4 weeks did not show significant improvement in major depressive disorder symptoms, some individuals may benefit from melatonin use such as those with depression and delayed sleep phase syndrome and women during perimenopause or menopause.[60]

Depression and Delayed Sleep Phase Syndrome

In a double-blind, placebo-controlled crossover trial, 13 men (age 35.6 ± 14 years) and 7 women (aged 30.8 ± 12.4 years) with established delayed sleep phase syndrome were divided into groups: those with (group I; n = 8; three men and five women) or without depression (group II; n = 12; four women and eight men) based on a clinical assessment and the results of the Center for Epidemiological Studies Depression Scale (CES-D) and the Hamilton Depression Rating Scale (HDRS). Patients were randomly assigned to either 5 mg of melatonin or placebo and asked to consume the medication between 7:00 PM and 9:00 PM for 4 weeks followed by a 1-week washout before treatment crossover for another 4 weeks. Those in group I had a significant reduction in their HDRS and CES-D scores in comparison to placebo (P <0.05). Moreover, according to polysomnographic results, sleep-onset latency was reduced in both groups I and II compared with both placebo and baseline measures (P = 0.03).[61]

Depression in Menopause/Perimenopause

Women with either perimenopause (n = 36), premenopause (n = 25), and postmenopause (n = 18), ranging in age from 42 to 62 years, were divided into two age groups (42 to 49 years and 50 to 62 years) and given either 3 mg of synthetic melatonin or placebo at bedtime between 10:00 PM and 11:00 PM for 6 months. Subjects were evaluated for salivary melatonin and serum levels of several hormones, including thyroid-stimulating hormone (TSH), T3, T4, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, estrone, estradiol, and progesterone at time 0, 3, and 6 months. After 6 months of treatment, melatonin use significantly increased T3 and T4 (P <0.0001) compared with time 0. The placebo group also had increases in T3 after 3 months (P <0.05) but not at 6 months. TSH was not affected by either treatment group. Melatonin use also reduced plasma LH levels in the younger group of women (28.6%), but not in the older group (P <0.05). FSH levels were also significantly reduced, especially in women with low basal melatonin levels (P <0.05). In contrast to placebo, women who took melatonin had an improvement in their mood state, with only 6.7% of the active group reporting morning depression compared with 21% of the placebo users (P <0.05).[62]

Alzheimer's Disease

Alzheimer's dementia (AD) is a growing concern both in the United States and throughout the global community. It is estimated that there were 24.3 million people worldwide with dementia in 2001, and that this figure would rise to 81.1 million by the year 2040.[63] Similarly in America, AD is expected to increase to an estimated 13 million by the year 2050.[64] In addition to a deterioration in memory and day-to-day functioning, sundowning syndrome or nocturnal delirium is a common behavior found in 2.4% to 25% of those diagnosed with AD.[65] Sundowning can occur typically between 3:00 PM and 7:00 PM and is associated with a heightened degree of agitation, irritation, and confusion.[66] Since this problem can cause great distress for both caregivers and

health care professionals, several researchers noted that sundowning is a form of circadian rhythm disturbance and that the associated delirium would respond well to melatonin.[67]

Sundowning Phenomenon in Alzheimer's Disease

In a retrospective study, 14 patients (8 women, 6 men; average age 72 years) diagnosed with AD received 9 mg melatonin daily at bedtime for 22 to 35 months. The researchers concluded that although melatonin use significantly improved their sleep quality ($P = 0.001$), none of the other neuropsychiatric test parameters (i.e., Functional Assessment Staging [FAST] or Alzheimer's Disease Assessment Scale [ADAS]) showed any difference between initial and final assessment. However, the condition of sundowning was no longer clinically detectable in 12 of 14 patients. Moreover, the melatonin users did not exhibit the typical cognitive and behavioral deterioration normally seen in these patients over a 1- to 3-year evolution of dementia. No side effects were noted.[68]

Moreover, in a preliminary pilot study, 11 nursing home participants (8 women, 3 men; 79 to 82 years) with dementia received one 3 mg tablet of melatonin in the evening for 3 weeks. Using the Nurses Ratings of Sleep Patterns Questionnaire as an assessment tool, sleepiness during the daytime hours (how long and how often the residents napped) was significantly reduced ($P = 0.0245$ and $P = 0.0105$), but no changes were noted in the evening or nighttime hours. Frequency of agitation, as recorded by the Cohen-Mansfield Agitation Inventory, was significantly reduced in five subjects ($P = 0.05$), especially during the evening hours when sundowning is most prevalent.[69]

Alzheimer's Dementia

In this randomized controlled trial, 20 patients with confirmed AD (3 men, 17 women; 67 to 90 years of age) were randomized to receive either 3 mg of melatonin or placebo at 8:30 PM daily for 1 month. In those utilizing the melatonin, actigraphic data demonstrated that the melatonin users had an increase in the amount of mean evening sleep time (33.2 ± 37.6%) compared with a reduction in placebo users (0.2 ± 13.7%) ($P = 0.017$). Similarly, there was a reduction in the night time activity counts in the active group (−44.9 ± 21.9%) compared with the increase (29.8 ± 77%) seen with placebo use ($P = 0.014$). There was no change in daytime sleep or activity between the two groups. Those utilizing the melatonin also had a significantly improved ADAS cognition and non-cognition scores (−4.3 ± 3.6 and −4.1 ± 2.2) versus placebo (−0.3 ± 3.7 and −0.8 ± 1.0), respectively ($P = 0.017$ and $P = 0.002$).[70]

Headache

Migraine

Individuals with chronic migraines have decreased levels of urinary 6-sulphatoxymelatonin levels, supporting melatonin's role in the pathophysiology of migraine. In an open study, 34 patients (29 men, 5 women) with episodic migraines were given 3 mg of melatonin 30 minutes before bedtime for 3 months. Compared with baseline and after 12 weeks of therapy, melatonin use decreased headache frequency, intensity, and duration ($P < 0.001$). Complete resolution of the migraine was seen in 25% of the patients. The use of medication (i.e., analgesics and triptan) for the treatment of migraine was also reduced ($P < 0.001$).[71]

Cluster Headache

Twenty cluster headache (2 chronic; 18 episodic) patients (15 men, 5 women; 30 to 40 years) who met the International Headache Society (IHS) criteria were invited to participate in this trial. After a 1-week washout period in which prophylactic treatment was stopped, patients were randomized to receive 10 mg of melatonin in the evening or placebo for 14 days. Those employing the melatonin had a significant reduction in daily attacks, from 3.31 to 1.51, by the end of week 2 ($P < 0.03$). There was also an observed decrease in daily analgesic use by the melatonin group, but this was not statistically significant ($P < 0.06$). Additionally, and in contrast to placebo, headache frequency was reduced in both the first ($P < 0.03$) and second week of melatonin treatment ($P = 0.01$). However, the two chronic cluster headache patients did not respond to melatonin use. The authors speculated that melatonin could act by modulating 5HT2 receptors, inhibit the synthesis of prostaglandin E_2, or increase the activation threshold level of aminobutyric acid pain pathways.[72]

Tinnitus

A perception of a ringing or roaring or a humming sound within the ears without any acoustic stimulation is known as tinnitus.[73] It was speculated by researchers that melatonin could assist in the reduction of tinnitus symptoms by reducing labyrinth pressure.[74] Based on case reports in which melatonin use symptomatically improved tinnitus patients, one group of medical investigators embarked on a double-blind, placebo-controlled crossover study in 30 patients (15 men, 8 women; average age 64.4 years) with this condition. Patients were randomized to either 3 mg of melatonin 1 to 2 hours before bedtime or placebo for 30 days. After a 7-day washout, patients were crossed over for another 30 days. Of the 23 patients who completed the study, there was no statistical difference between active and placebo groups in terms of Tinnitus Handicap Inventory (THI) scores. However, those melatonin users (n = 9) with an initial pretreatment THI score of 47.6 and who reported an overall improvement in their symptoms had significantly higher than the average pretreatment scores (25.1) compared with melatonin users (n = 14) who did not respond to therapy ($P = 0.02$). This suggests that patients with higher initial THI scores are more likely to respond to melatonin use. In addition, 7 of 15 patients who reported difficulty in falling asleep secondary to tinnitus symptoms were able to fall asleep more readily in contrast to only 3 of 15 patients in the placebo group ($P = 0.04$). Bad dreams were noted as a side effect in 17% of both the active and placebo users.[75]

A more recent controlled trial employing 102 subjects with tinnitus determined that only the combination of 3 mg melatonin in the evening with a sulodexide (250 mg twice daily for 40 days; then 250 mg/day for another 40 days) significantly improved their symptoms as measured by THI scores and acufenometry evaluation compared with melatonin alone.[76]

Nicotine Withdrawal

Despite the fact smoking is strongly associated with increased cardiovascular disease risk, many individuals continue to smoke.[77] One of the factors contributing to engaging in smoking cessation is the symptoms associated with acute nicotine withdrawal. In one study, 12 subjects (19 to 53 years) who had smoked on an average for 3 to 27 years were given 0.3 mg of melatonin or placebo at 11:30 PM on the second night of the experiment, 3.5 hours after nicotine withdrawal. Those using the melatonin had significant reductions in VAS self-rating scores for anxiety ($P < 0.01$), irritability ($P = 0.001$), anger ($P < 0.05$), and craving for cigarettes ($P < 0.005$) compared with placebo.[78]

DOSAGE

Melatonin has been used at a variety of different dosages as described in the Clinical Applications section. For its most popular use to enhance sleep quality the typical dosage is 3 mg thirty to forty-five minutes before bedtime. Dosage ranges for the clinical applications are given in Table 103-1. In general, utilize the same dosage level used in the positive clinical studies for the specific application.

Side Effects and Contraindications

Common side effects of high dosage melatonin use include headaches, dizziness, nausea, and drowsiness.[79] One author notes that "…despite the well-recognized role of melatonin in the regulation of reproduction in photoperiodic species, it seems unlikely that chronic ingestion of moderate melatonin doses will have a profound impact on reproductive function in humans."[80] However, without further clinical evidence of safety, melatonin should not be employed in pregnancy and lactation. One study in women noted that high dose melatonin (300 mg/day for 4 months) could significantly reduce mean LH levels in contrast to nonmedicated controls (P <0.001) (see Table 103-1).[81]

DRUG INTERACTIONS

Although melatonin overall has an excellent safety record, clinicians should be cognizant of several drug interactions, especially zolpidem and melatonin.

Zolpidem

In a controlled study, 16 healthy subjects (12 men, 4 women; average age 59.4 years) were randomized to receive placebo, 2 mg prolonged release melatonin, 10 mg zolpidem, or both active medications for 2 days in the evenings (8:00 PM) with a 2- to 10-day washout period between treatments. Psychomotor functions (i.e., reaction time, vigilance), memory, dexterity, sedation, and simulated car driving were evaluated at 1 to 4 hours, the next morning after drug administration. The results demonstrated that compared with placebo, PR melatonin on its own did not impair any of the variables tested. However, the use of zolpidem and zolpidem with PR melatonin significantly impaired memory and psychomotor performance 1 to 4 hours after administration. In a simulated driving task, the number of collisions significantly increased at the 1 to 4 hour mark by 1.4 and 2.8 in the zolpidem (P <0.05) and zolpidem-PR melatonin (P <0.001) groups compared with placebo, respectively. No changes were noted by the investigators the following morning, except that the decline in memory recall was still evident with zolpidem.[82]

Fluvoxamine

The bioavailability of melatonin is increased by the co-administration of the selective serotonin reuptake inhibitor fluvoxamine. When 50 mg of fluvoxamine was used in concert with 5 mg of melatonin, on average, there was a seventeen-fold increase (P <0.05) in the area under concentration-time curve (AUC) and a twelve-fold higher (P <0.01) serum peak concentration (C_{max}) of melatonin. The terminal elimination half-life was not significantly affected.[83]

Fluoxetine

Melatonin was employed in concert with fluoxetine to reduce the incidence of dyskinesia. In a case report, one 23-year-old male with obsessive-compulsive disorder and major depression developed shoulder and neck dyskinesia after taking 60 mg fluoxetine for 4 months. Because the patient and the doctors did not want to stop the medication, which had proven clinically helpful, they added 6 mg of melatonin twice a day. Within 2 weeks the dyskinesia resolved. Secondary to experiencing daytime drowsiness, the patient discontinued the melatonin with a reappearance and worsening of the dyskinesia. Resumption of the melatonin 6 mg at nighttime again resolved the problem within 2 weeks of onset. The authors noted that the antioxidant effects of melatonin might help scavenge the toxic free radicals that may trigger dyskinesia.[84]

Caffeine

Caffeine intake can affect the bioavailability of melatonin, which is likely due to the inhibition of CYP1A2 activity. In 12 healthy volunteers, when 600 mg of caffeine was co-administered with 6 mg of melatonin, the C_{max} and AUC of melatonin were increased on average by 142% (P = 0.001) and 120% (P <0.001), respectively. The inhibitory effect of caffeine was more pronounced in nonsmokers and in individuals with the *1F/*1F genotype.[85]

CYP1A

As melatonin is metabolized by CYP1A in vitro, there are a number of potential drug interactions that could occur, including coadministration of acetaminophen, omeprazole, theophylline, warfarin, and estradiol. Caution should be exercised by clinicians when administering melatonin and prescription medications metabolized by CYP1A.[86]

Progesterone

In women, 300 mg melatonin and 75 mg of melatonin combined with 0.3 mg of the synthetic progestin norethisterone caused a significant decrease in LH, estradiol, and progesterone levels compared with a non-medicated control group in the first and fourth months of the investigation (P <0.05). This strongly suggests that melatonin and progesterone have an additive effect and should not be used by women taking progesterone.[87]

TABLE 103-1 **Dose Ranges**

CONDITION	DOSE
Alzheimer's dementia (+ sundowning symptoms)	3-9 mg in the evening
Acute insomnia	0.3-1 mg at bedtime
Cancer (solid tumors: breast, lung, prostate)	20 mg in the evening
Cachexia	20 mg in the evening
Taxane-related neuropathy	21 mg at bedtime
CFS and insomnia	5 mg at bedtime
Chronic insomnia	0.3-3 mg 30 minutes before bedtime
Children and insomnia	5 mg at 7 PM
Depression	
Delayed Sleep Phase Syndrome	5 mg at 7 to 9 PM
Perimenopausal/Menopausal	3 mg at 10 to 11 PM
Epilepsy and insomnia	6 mg for those less than 9 years of age and less than 30 kg in the evening; 9 mg for those greater than 9 years of age and greater than 30 kg
ASD and insomnia	3 mg before bedtime
ADHD and insomnia	3 mg for those less than 30 kg and 6 mg for those greater than 30 kg at 7 PM
Fibromyalgia	3 mg 30 minutes before bedtime
Functional dyspepsia	5 mg in the evening
GERD	3 to 6 mg in the evening
Headache	
Children: migraine prevention	3 mg at bedtime
Adults: migraine	3 mg at bedtime
Adults: cluster headache	10 mg at bedtime
IBS	3 mg in the evening
Infertility in women with IVF	3 mg in the evening
Jet lag	
Eastbound	5 mg 3 times daily, 3 days before and 3 days after, in the evening local time
Westbound	0.5 mg in the evening
Nicotine withdrawal symptoms	0.3 mg in the evening
Tinnitus	3 mg in the evening

ADHD, attention deficit hyperactivity disorder; ASD, autistic spectrum disorder; CFS, chronic fatigue syndrome; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; IVF, in vitro fertilization; TID, three times daily.

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CHAPTER 104

Melissa officinalis (Lemon Balm)

Eric L. Yarnell, ND, RH(AHG), and Kathy Abascal, BS, JD, RH(AHG)

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Melissa officinalis (family: Lamiaceae)
Common names: lemon balm, balm, melissa, balm mint

GENERAL DESCRIPTION

Melissa officinalis, a mint, has square stems and opposite leaves. The leaves are used medicinally and exude a lemony odor when brushed or crushed. Lemon balm is native to southern Eurasia. The word balm is derived from the term "balsam," referring to the delightful odor of the plant. The genus name *Melissa* is derived from a Greek word for bees, which are strongly attracted to this plant.

CHEMICAL COMPOSITION

Lemon balm leaves contain volatile oil, giving the plant its scent of lemon. Two major classes of terpenoids are found in this oil—hydrocarbon terpenes, particularly citrals a and b, and sesquiterpenes, particularly β-caryophyllene.[1] Lemon balm is also a rich source of flavonoid glycosides.[2,3] More than 3% of the dry weight of lemon balm is composed of rosmarinic acid, a phenylpropanoid derivative[4] (Figure 104-1).

HISTORY AND FOLK USE

Lemon balm has been used for millennia in Europe, primarily for dyspepsia and nervousness.[5] The ancient Greeks also used it for wound healing and insect bites.[6] The seventeenth century herbalist Nicholas Culpeper lauded the benefits of lemon balm in enhancing digestion, relieving melancholy, and "opening the brain."[7]

The Basque people used lemon balm as a digestive for nervous stomachs and as a sedative for insomnia, hysteria, and depression, as well as for heart palpitations caused by nerves. They also used it for neuralgias and to regulate menses, and combined it with cloves as a topical for toothaches.[8]

The Eclectic physicians in North America used lemon balm as a moderate stimulant, diaphoretic, and antispasmodic.[9] The standard infusion was often combined with lemon juice to treat fevers and painful menstruation. The Cherokee used the plant similarly, and the Costanoan tribe used the decoction for infant's colic and stomachaches.[10]

PHARMACOLOGY

The pharmacodynamics of lemon balm are complex because of the large number of active and secondary constituents present in the plant. The volatile oil fraction appears to have antimicrobial, antiviral, and antiparasitic activity, and contributes to the anxiolytic and relaxing effects of lemon balm. The flavonoids and rosmarinic acid are antioxidant, anxiolytic, sedative, and antiviral, and they inhibit both complement and protein synthesis. Various extracts of these constituents show similar properties as well as antithyroid effects.

Sedative Effects

Animal studies confirmed that lemon balm has a calming effect. For instance, a tincture of lemon balm was sedative, analgesic, and hypnotic in mice and potentiated phenobarbital.[11] In vitro studies on human neurons with ethanolic extracts of lemon balm showed that it has cholinergic activity.[12]

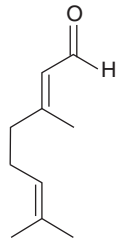


FIGURE 104-1 Citral.

Antiviral Effects

Lemon balm consistently showed antiviral and antiretroviral effects in vitro, particularly against herpes simplex virus but also against HIV-1.[13-16] The volatile oil of lemon balm was active against *Trypanosoma brucei,* but had minimal activity against *Leishmania major*.[17]

Thyroid Effects

Lemon balm has diverse effects on the thyroid gland and thyroid hormones. It inhibits rat iodothyronine deiodinase and prevents bovine thyroid-stimulating hormone (TSH) from stimulating human thyroid membranes in vitro.[18,19] The latter effect was due to adduct formation between polyphenols and TSH, thereby preventing TSH receptor binding. Adducts also formed with immunoglobulin-G antibodies formed in patients with Graves' disease, which mimicked TSH, blocking their binding to the TSH receptor in vitro.[20]

Other Effects

Preliminary investigations suggest a wealth of other miscellaneous effects: rosmarinic acid inhibited C3 and C5 convertases, suggesting an antiinflammatory effect.[21,22] Lemon balm flavonoids show potent antiperoxidant activity.[23] Lemon balm was antiulcerogenic in rats in one trial, both alone and in combination with various other herbs.[24]

CLINICAL APPLICATIONS

Herpes Simplex Virus

Two clinical trials investigated the effect of lemon balm on herpes labialis lesions. In one double-blind trial, 116 patients with an acute outbreak of herpes were randomly assigned to receive treatment with a cream containing a 70:1 extract of lemon balm or placebo.[25] Redness was reduced more in the lemon balm group, but other symptoms were not significantly different from the placebo group. No major adverse effects occurred in either group.

In a second double-blind trial, 66 patients were randomly assigned to apply either a lemon balm cream or placebo.[26] Average daily symptomatic relief was significantly better in those given lemon balm. Other measures of efficacy were not significantly different between the groups, although there was a consistent trend in favor of lemon balm.

Anxiety, Agitation, Insomnia

Lemon balm was studied in people with mild anxiety and as a relaxant in healthy people. In a double-blind study, 102 individuals with mild anxiety were randomly assigned to receive either a lemon balm combination product or placebo for 8 weeks.[27] Those taking the lemon balm product had significantly less overall anxiety, nervousness, excitability, and emotional lability than subjects taking the placebo. In a study of 24 healthy individuals, a mixture of lemon balm and *Valeriana officinalis* (valerian) had a dose-dependent anxiolytic effect.[28]

Another randomized, double-blind crossover trial administered varying doses of lemon balm extract to 20 healthy individuals.[29] At lower doses, lemon balm had a calming effect, and at moderate doses, it increased alertness, an effect lost at the highest dose tested. In vitro investigations suggested that these results might have been mediated by the cholinergic effects of lemon balm constituents.

This mechanism of action led researchers to investigate the effects of lemon balm volatile oil applied as a lotion in a double-blind trial of patients with Alzheimer's disease.[30]

Lemon balm was also studied in patients with insomnia. A double-blind trial in 98 individuals with mild insomnia compared a combination of valerian root and lemon balm with placebo for 1 month.[31] The extract was significantly more effective than placebo in improving subjectively rated sleep quality, although recordings of sleep quality on a visual analog scale did not show any differences between the two groups. A similar combination product had a positive action in a study of 918 children with restlessness and dyssomnia.[32] Lemon balm was approved by the German Commission E for the treatment of nervous sleeping disorders.[33]

Dyspepsia and Irritable Bowel Syndrome

Lemon balm leaf was approved by the German Commission E for treatment of dyspepsia and possibly irritable bowel syndrome (IBS).[33] No clinical trials documenting the efficacy of lemon balm alone for digestive disorders could be found. All trials included lemon balm only as a component of herbal products. A systematic review of the formula Iberogast I (Iberogast, in addition to lemon balm, contains *Iberis amara* [bitter candytuft], *Matricaria recutita* [chamomile], *Mentha x piperita* [peppermint], *Carum carvi* [caraway], *Glycyrrhiza glabra* [licorice], *Angelica archangelica* [garden angelica], *Chelidonium majus* [greater celandine], and *Silybum marianum* [milk thistle]) found the formula efficacious in dyspepsia.[34] Another preliminary study of 32 patients with IBS found that a mixture of lemon balm, *Mentha spicata* (spearmint), and *Coriandrum sativum* (coriander) reduced abdominal pain and bloating.[35] In infants, a mixture of lemon balm, *Matricaria recutita* (chamomile), and *Foeniculum vulgare* (fennel) reduced colic symptoms.[36] Although these trials did not address the efficacy of lemon balm in isolation, they do support the historical use of lemon balm in patients with dyspepsia or IBS.

Radiation Protection

In a single open study, workers in a medical radiology department used lemon balm tea (1.5 g in 100 mL water twice per day) for 30 days.[36a] Plasma catalase, superoxide dismutase, and glutathione levels rose while DNA damage, myeloperoxidase, and lipid peroxidation product levels all fell significantly compared to baseline. Controlled trials are warranted in people exposed to chronic low-dose ionizing radiation.

DOSAGE

Lemon balm is traditionally employed as a tea or tincture. The dried leaf should still smell strongly of lemon and should be dark green; if not, it is of inferior quality. For a tea, 2 to 3 teaspoons of herb are steeped in 1 cup hot water for 10 to 15 minutes; three cups of this

are drunk daily.[37] The dose of a tincture, made preferably from fresh material and as concentrated as possible (1:2 to 1:3 weight/volume ratio), is taken 2 to 6 mL three times daily.[37]

There is no widely accepted standardization to ensure quality lemon balm extracts, although a minimum 0.05% volatile oil content is recommended by the German Commission E.[33] Pure volatile oil of lemon balm may also be utilized at a dose of 1 to 3 drops taken internally three times daily in adults, or by topical application to the skin in a cream, lotion, or fixed oil base. Because of the expense of extracting the oil from this plant, however, there are many adulterated products on the market that contain lemon scent, lemon grass, or other lemon-scented herbs and not lemon balm.

TOXICOLOGY

Lemon balm has no known toxic effects. Despite the theoretical concern that it might suppress thyroid function in euthyroid or hypothyroid patients, there are no published reports of this occurrence. Controlled trials in humans proved that lemon balm, combined with extracts of *V. officinalis* (valerian) root, does not interfere with the ability to drive or operate heavy machinery.[38]

DRUG INTERACTIONS

There are no documented drug interactions for lemon balm. It does not interact with alcohol.[38] Given its effects on thyroid function in vitro, there is a theoretical concern that the herb may have additive or synergistic effects with thyrosuppressive drugs and may interact in unpredictable ways with thyroid hormone replacement agents. Lemon balm should be combined with these classes of drugs only under careful supervision by an experienced health care professional.

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CHAPTER 105

Mentha piperita (Peppermint)

Michael T. Murray, ND

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Mentha piperita (family: Labitae)
Common name: peppermint

GENERAL DESCRIPTION

Peppermint is a natural hybrid of garden spearmint *(Mentha spicata)* and water mint *(Mentha aquatica)*. First described in England in 1696, peppermint now grows all over the world.[1] The two most popular varieties are white peppermint (*Mentha piperita* var. *officinalis*) and black peppermint (*M. piperita* var. *vulgaris*). Both are typical members of the mint family, that is, herbs with square stems, horizontal rhizomes, and lanceolated leaves with a serrated edge. Black peppermint has deep red stems with purplish-tinged dark green leaves, whereas white peppermint has green stems with lighter green leaves. Both varieties produce purple flowers during the summer months. For medicinal effects, the aerial portion of the plant is the most widely used.

CHEMICAL COMPOSITION

The major medicinal component of peppermint is its volatile oil, which can be found in concentrations of up to 1.5% in the herb, but is usually present in the range of 0.3% to 0.4%. The principal components of the oil are menthol (28% to 29%) (Figure 105-1), menthone (20% to 31%), and menthyl acetate (3% to 10%), although gas chromatographic analysis of peppermint oil typically shows more than 40 different peaks. Most of the volatile oil components are terpenoids.[1]

The composition of menthol and other volatile oil components is sensitive to climate and latitude as well as to the maturity of the plant. Pharmaceutic grade peppermint oil is produced by distilling the fresh aerial parts of the plant harvested at the very beginning of the flowering cycle. The oil is standardized to contain no less than 44% free menthol and a minimum of 5% esters calculated as menthyl acetate. The ketone component (calculated as menthone) usually ranges from 15% to 30%, with the remainder of the oil being composed of various terpenoids.[1] Menthol is also synthesized by hydrogenation of thymol.

Other components of peppermint herb that may contribute to its medicinal effects are polymerized polyphenols (19% of dry weight), flavonoids (12%), tocopherols, carotenes, betaine, and choline.[2]

HISTORY AND FOLK USE

Although peppermint was not officially recognized until the seventeenth century, mints have been used for their medicinal effects for thousands of years. Records from the ancient Egyptian, Greek, and Roman eras show that other members of the mint family, particularly spearmint *(M. spicata)*, were used.[1]

The most popular uses of peppermint for medicinal purposes were in the treatment of indigestion and intestinal colic, colds, fever, and headache.

PHARMACOLOGY

The pharmacology of peppermint is attributed almost entirely to its menthol components. The major categories of actions for peppermint and menthol are as follows:

- Carminative
- Antispasmodic

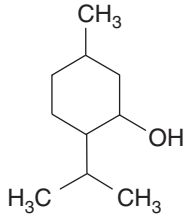


FIGURE 105-1 Menthol.

- Choleretic
- External analgesic
- Nasal decongestant

Carminative Effects

Carminatives promote the elimination of intestinal gas. Peppermint and peppermint oil are well-accepted carminatives. Although the exact mechanism of action has not been determined, one proposed mechanism is relaxation of the esophageal sphincter, which leads to the release of gas pressure in the stomach.[3]

Antispasmodic Effects

The mechanism behind peppermint oil's antispasmodic effects was determined. Researchers concluded that peppermint oil inhibits contractions of isolated smooth muscles by blocking the influx of calcium into the muscle cells.[4,5] Researchers hypothesized that the clinical effectiveness of peppermint oil in the treatment of irritable bowel syndrome (IBS) is a result of inhibition of the hypercontractility of intestinal smooth muscle, thereby returning the muscle to its proper tone.

Choleretic Effects

Choleretics stimulate the flow of bile. Menthol and related terpenes were shown to exert a choleretic effect as well as to improve the solubility of the bile.[6-10]

External Analgesic Effects

The external analgesic and counterirritant effects of menthol are well accepted. When applied to the skin, peppermint oil or menthol stimulates the nerves that perceive cold and simultaneously depresses those for pain. The initial cooling effect is followed by a period of warmth.

CLINICAL APPLICATIONS

Peppermint oil is the most extensively used of all the volatile oils. Pharmaceutic preparations often utilize peppermint oil or menthol for its therapeutic and flavoring properties. For example, it is used extensively in antacid products and irritant laxatives for both its flavor and its therapeutic effects. The same is true for its inclusion in mouthwash preparations and after dinner mints.

The pharmacologic effects of peppermint and peppermint oil are useful in a number of clinical situations. The most notable are as follows:

- IBS
- Intestinal colic
- Gallstones
- Musculoskeletal pain
- The common cold

Irritable Bowel Syndrome

Enteric-coated peppermint oil (ECPO) was shown to be quite helpful in improving gastrointestinal (GI) function in individuals with IBS, a common functional disorder of the large intestine characterized by some combination of: (1) abdominal pain; (2) altered bowel function, constipation, or diarrhea; (3) hypersecretion of colonic mucus; (4) dyspeptic symptoms (flatulence, nausea, anorexia); and (5) varying degrees of anxiety or depression.

Several double-blind studies showed ECPO to be effective in relieving all symptoms of IBS in approximately 70% to 85% of cases within 2 to 4 weeks.[11-15] In one trial, 42 children between 8 and 10 years old with IBS were given ECPO or placebo for 2 weeks. Dosage was one capsule three times daily for children weighing 30 to 45 kg and two capsules three times daily for children weighing more than 45 kg. After 2 weeks, 76% of the ECPO group reported significant improvements, compared with only 19% in the placebo group.[15]

In one double-blind study, 57 patients with IBS, with normal lactose and lactulose breath tests and negative antibody screening for celiac disease, were treated with peppermint oil (two enteric-coated capsules twice per day or placebo) for 4 weeks in a double-blind study. Results showed that 75% of the patients in the ECPO group showed a more than 50% reduction of basal total IBS symptoms score compared with 38% in the placebo group.[16]

In an 8-week randomized double-blind, placebo-controlled study on 90 outpatients with IBS, the number of subjects free from abdominal pain or discomfort changed from 0 at week 0 to 14 at week 8 in the ECPO group and from 0 to 6 in controls. The severity of abdominal pain was also reduced significantly in the ECPO group compared with controls.[17]

One of the central findings in IBS is a hypercontractility (excessive contraction) of intestinal smooth muscle. Peppermint oil, especially when combined with caraway oil, inhibits the hypercontractility of intestinal smooth muscle, making it useful in IBS as well as esophageal spasm and intestinal colic.[18] It may also impact gallbladder and small intestine function. A pharmacodynamic study of 90 mg peppermint oil and 50 mg caraway oil demonstrated that complete inhibition of gallbladder emptying was caused by both oils, and the transit time in the small intestine as well as the orocecal transit time was significantly prolonged by peppermint oil.[19]

Although effective on its own, ECPO is best used within a comprehensive treatment protocol for IBS (see Chapter 183).

Nonulcer Dyspepsia

In addition to its effects in IBS, ECPO has benefits in nonulcer dyspepsia (NUD), gastroesophageal reflux disorder (GERD), and intestinal overgrowth of *Candida albicans* (a common yeast implicated in many cases of IBS) and *Helicobacter pylori*.

NUD and GERD are basically catch-all terms that reflect a kind of wastebasket diagnosis that doctors use when they cannot find any real reason for a patient's upper GI dysfunction, just as IBS is used as a wastebasket diagnosis for lower GI dysfunction. Symptoms of NUD and GERD include heartburn as well as difficulty swallowing, feelings of pressure or heaviness after eating, sensations of bloating after eating, stomach or abdominal pains and cramps, and the symptoms of IBS. About 3 of every 10 patients with NUD and GERD also meet the criteria for IBS.

Several of the clinical studies in patients with IBS featured the combination of peppermint oil and caraway oil in an enteric-coated capsule (ECPCO). The results of these trials indicated that this

combination produced better results than peppermint oil alone for symptoms of IBS. Later studies also indicated that the combination of peppermint and caraway oils was quite helpful in improving NUD.[20,21] In one double-blind study, 120 patients with NUD were given either the ECPCO combination or cisapride (Propulsid) for 4 weeks.[21] The mean reduction of pain score was comparable in the two groups (4.62 for ECPCO; 4.6 for cisapride). Other symptoms of NUD also improved in a similar fashion. Positive results were also found in *H. pylori*–positive individuals.

Although the ECPCO combination is extremely safe at recommended levels, cisapride caused fatal heart rhythm problems. According to the U.S. Food and Drug Administration, at least 111 people died as a result of cisapride use, and nearly 400 experienced heart abnormalities. Cisapride (Propulsid) was subsequently taken off the market.

Cholelithiasis

Several studies showed that a formula containing menthol and related terpenes (menthone, pinene, borneol, cineol, and camphene) demonstrated efficacy in dissolving gallstones.[6-10] This approach to gallstone removal offers an effective alternative to surgery and was shown to be safe even when the formula was consumed for prolonged periods (up to 4 years). Terpenes, like menthol, help dissolve gallstones by reducing bile cholesterol levels while increasing bile acid and lecithin levels in the gallbladder. Because menthol was the major component of this formula, peppermint oil, especially if enteric-coated, may offer similar benefits.

External Analgesic

Menthol and related substances can be used as counterirritants in the treatment of arthritis, fibromyositis, tendonitis, and other inflammatory conditions involving the musculoskeletal system.

The Common Cold

Menthol and peppermint oils are often employed in the treatment of the common cold as components of topical nasal decongestants, cough and throat lozenges, ointments, salves, and inhalants. Whether the use of these products is of benefit has not been proven in clinical studies. However, their popularity appears to represent their ability to help make breathing easier during the common cold. The best method for using menthol or peppermint oil is to apply commercial preparations to the upper chest during periods of rest so that the vapors can be inhaled continuously.

Peppermint tea may also be of benefit during the common cold. Peppermint as well as other members of the mint family demonstrated significant antiviral activity as well as a mild diaphoretic effect.[22] The most active antiviral components, the polyphenols, are concentrated in the tea.[2] Peppermint oil also showed antiviral activity against Newcastle disease, herpes simplex, and vaccinia.

Headache

In a double-blind, placebo-controlled, randomized crossover trial, topical application of peppermint oil to the forehead and temples resulted in a statistically significant decrease in muscle tension as reported subjectively and measured objectively by electromyographic activity of the temporal muscle. In addition, the oil application decreased sensitivity to pain.[23]

DOSAGE

Peppermint is most widely used as a tea (infusion), on its own or in combination with other botanicals. The infusion is usually prepared with 1 to 2 teaspoons of the dried leaves per 8 oz of water.

The dosage of peppermint oil administered in an enteric-coated capsule for the treatment of the IBS is one to two capsules (0.2 mL per capsule) three times daily between meals. This dosage is also appropriate for the treatment of gallstones.

The dosage of menthol as an external analgesic is 1.26% to 16% applied to the affected area no more than three or four times daily.

TOXICOLOGY

Peppermint herb is generally regarded as safe when used as a tea; however, hypersensitivity reactions have been reported. Adverse reactions to ECPO capsules are rare but include hypersensitivity reactions (rash), heartburn, bradycardia, and muscle tremor.

When applied topically, peppermint oil or menthol can induce contact dermatitis and hypersensitivity reactions. The likelihood of development of such a reaction is enhanced when heating pads are used in conjunction with topically applied preparations containing menthol.[24]

In rats, the lethal dose for 50% of subjects of menthol is 3280 mg/kg. The fatal oral dose in humans is calculated at 1 g/kg. In one study, repeated high-dose feeding of rats for 28 days with peppermint oil produced signs of dose-related brain lesions, but the dosage (40 mg/kg) given to the rats far exceeded that used in humans.[1,25,26]

DRUG INTERACTIONS

Peppermint oil may enhance the oral bioavailability of certain drugs. Most notably, in a study in rats, peppermint oil (100 mg/kg) tripled the mean cyclosporine maximum concentration and increased the area under the concentration-versus-time curve.[27] This dosage does not reflect the dosage used in clinical studies; however, physicians should be aware that peppermint oil may raise serum levels of certain drugs when the agents are coadministered.

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CHAPTER 106

Microbial Enzyme Therapy: Clinical Applications of Fungal Enzymes

Corey Resnick, ND

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INTRODUCTION

Enzymes derived from fungal species such as *Aspergillus oryzae, A. niger,* and *Rhizopus* spp. have been shown to be safe and effective in the treatment of a variety of clinical disorders. In some cases, fungal enzymes may be more effective than animal-derived enzymes or other available therapies. Some fungal enzyme preparations are particularly well suited for clinical application because of their inherent ability to resist degradation by stomach acid and their ability to hydrolyze physiologically or pathologically important substrates over a wide pH range.

Clinically, fungal enzyme preparations are most often administered orally at mealtime to aid digestion by hydrolyzing dietary substrates such as fats, carbohydrates, and proteins. They have also been used intravenously for the treatment of vascular obstruction, thrombotic disorders, and ischemic disease. Controlled studies in humans and animals have demonstrated efficacy of various fungal enzyme preparations administered orally or parenterally in a wide range of conditions, including the following:

- Maldigestion and malabsorption
- Pancreatic insufficiency
- Steatorrhea
- Lactose intolerance
- Arterial obstruction
- Ischemic disease
- Thrombotic disease

This chapter reviews evidence of efficacy for fungal enzyme preparations in a number of the above conditions. It also presents indirect evidence that some portion of orally administered fungal enzymes may be absorbed intact in an enzymatically active form. To the extent that such absorption does occur, fungal enzyme supplements administered orally between meals may be of possible benefit as an adjunct in the treatment of systemic conditions, such as the following:

- Inflammatory conditions
- Food allergies

DIGESTIVE ENZYME DEFICIENCIES

Adequate digestion is a prerequisite for normal gastrointestinal function and overall health. Deficiencies in digestive enzymes and imbalances in gastrointestinal pH can lead to impaired digestion, which can cause or aggravate a number of conditions, including the following[1-6]:

- Pancreatic insufficiency
- Maldigestion and malabsorption
- Intestinal permeability defects
- Food intolerance
- Gastrointestinal discomfort
- Food allergy
- Autoimmune conditions
- Bacterial overgrowth

Oral administration of supplemental digestive enzymes can help to treat enzyme deficiencies and improve conditions that are related to impaired digestion such as these.

ACID-STABLE FUNGAL ENZYMES

Oral supplementation with acid-stable fungal enzymes, also known as plant enzymes or microbial enzymes, has been shown to be safe and effective in the treatment of a number of disorders in humans and animals. In individuals with gastrointestinal pH imbalances, these enzymes may offer advantages over conventional pancreatin and enteric-coated pancreatic enzyme preparations.[2,7-10]

Pancreatic enzymes have optimal activity in neutral to alkaline conditions around pH 7 and above. They are unstable in acidic conditions. As a result, exposure to gastric acid can destroy up to 90% of orally administered pancreatic lipase and 65% of pancreatic trypsin according to some studies.[10] Enteric-coated preparations are designed to protect pancreatic enzymes from gastric acidity; however, these do not work reliably in all cases.[2,10,11] This is because most patients with pancreatic insufficiency are not able to concentrate bicarbonate sufficiently to alkalinize the upper small intestine. As a result, enteric-coated tablets or capsules often fail to dissolve and deliver their enzymes in the duodenum or jejunum as intended. The resulting jejunal hyperacidity can also inhibit pancreatic enzyme activity even if enteric coatings do dissolve as intended.[2,7,10,12] Gastric hyperacidity can also lead to impaired fat digestion by causing acidic jejunal pH.[12] Although H2 receptor antagonists, such as cimetidine, are often used along with pancreatin to lessen intragastric inactivation, this approach is unsuccessful in improving lipid digestion in many patients and carries the possible risk of adverse side effects.[13]

Studies show that certain acid-stable fungal enzyme preparations are naturally stable and enzymatically active in both acid and alkaline pH conditions. For example, lipase preparations derived from both *A. oryzae* and *R. arrhizus* were shown to be active and stable in the broad range of pH 2 to pH 10.[7,8] As a result, such preparations do not require enteric coatings or coadministration of pH-altering drugs. They are effective even in patients with gastrointestinal pH imbalances, such as pancreatic insufficiency, jejunal hyperacidity, and gastric hyperacidity, which can limit the effectiveness of pancreatic enzymes.

Due to their broad pH range of activity, acid-stable fungal enzymes begin digesting food in the acid environment of the stomach and continue working in the alkaline pH of the small intestine.[2,10,14] As discussed in this chapter, the following fungal enzymes have been shown to aid digestion in humans when administered orally at the time of food consumption:

- Lipase
- Protease
- Amylase
- Lactase
- Phytase
- Cellulase

TREATMENT OF PANCREATIC INSUFFICIENCY AND OTHER DIGESTIVE DISORDERS

Studies compared the efficacy of pancreatic enzymes and acid-stable fungal lipase in the treatment of exocrine pancreatic insufficiency in humans and animals. Some studies showed that acid-stable fungal lipase is effective at a substantially lower dose of enzyme activity than that required for pancreatin to reduce pathologically elevated fecal fat levels, stool weight, and diarrhea.[7,8]

A controlled, crossover-design clinical trial in 17 patients with severe pancreatic insufficiency compared the effects of an acid-stable fungal enzyme preparation to conventional pancreatic enzymes and enteric-coated pancreatin. One group of nine patients with duodenopancreatectomy and bowel resection (Whipple procedure) were found to have pancreatic enzyme levels less than 10% of normal on stimulated secretion before the trial. A second group of eight nonsurgical patients had stimulated pancreatic enzyme levels less than 29% of normal. Both groups were placed on a diet containing 100 g/day of fat. Stools were collected for 72 hours before treatment beginning 5 days after discontinuing all medications and supplemental enzymes. Thereafter, all patients were placed on consecutive 2-week periods of treatment, beginning with enteric-coated pancreatin (100,000 International Pharmaceutical Federation [FIP] lipase units [LU]), followed by conventional pancreatin (360,000 FIP LU), and finally, acid-stable fungal lipase (75,000 FIP LU). The fungal enzyme preparation and both of the pancreatic enzyme preparations also contained protease and amylase activity. Stools were collected for the last 72 hours of each treatment period and analyzed for fecal fat content and stool weight. All three of the enzyme treatment protocols led to a significant reduction in fecal fat excretion in both groups (P <0.05), and all patients became virtually symptom-free with regard to diarrhea and abdominal discomfort. Of note, the enteric-coated pancreatin dosage was one third higher and the conventional pancreatin dosage was nearly five times higher than that required for fungal lipase to produce comparable clinical improvement.[8]

A similar randomized, placebo-control, crossover-design study in dogs compared the effectiveness of 4000 LU of acid-stable fungal lipase derived from *A. oryzae* to 60,000 LU of lipase from pancreatin in the treatment of surgically-induced pancreatic insufficiency and steatorrhea. Dogs in the placebo group had significant weight loss due to malabsorption as well as pathologically elevated fecal fat content and stool weight. Compared with placebo, dogs in both enzyme treatment groups experienced significant reductions in fecal fat and stool weight, with no significant weight loss. In this study, the enzyme dose of pancreatin was 15 times higher than that required for the acid-stable fungal lipase to produce comparable clinical results.[7]

One controlled clinical trial showed that an acid-stable fungal lipase derived from *R. arrhizus* was effective at reducing steatorrhea by 56.5% and stool weight by 45.2% compared with placebo in 7 patients with pancreatic insufficiency. The study also demonstrated that the fungal lipase retained greater than 80% of its enzyme activity under conditions of simulated gastric acidity at pH 3 for 1 hour.[15]

Another study in 100 outpatients evaluated the efficacy of a fungal enzyme preparation containing lipase derived from *R. arrhizus* and protease and amylase from *A. oryzae* in a range of gastrointestinal complaints, including epigastric pain and pressure, flatulence, heartburn, belching, and nausea. Investigators reported that 96% of patients experienced some relief of symptoms and rated treatment outcomes as good to very good in 65% of patients.[16]

Some clinical trials reported on the efficacy of enzyme preparations containing protease, amylase, cellulase, and hemicellulase derived from *A. oryzae* in combination with pancreatic enzymes in the treatment of a range of digestive disorders.[17,18] One double-blind, placebo-controlled, crossover design study in a group of 31 outpatients (ages 17 to 75 years) and 23 geriatric hospital inpatients (ages 70 to 90 years) found that this enzyme combination was significantly effective in the global improvement of diverse gastrointestinal symptoms (P <0.05) that included pain, nausea, heartburn, bloating, flatulence, constipation, and diarrhea.[17]

TREATMENT OF LACTOSE INTOLERANCE

Deficient secretion of intestinal lactase (β-galactosidase) can produce signs and symptoms of dietary lactose intolerance, including abdominal pain, diarrhea, bloating, flatulence, and an increase in breath hydrogen excretion. Studies indicate that lactase deficiency occurs in more than half of the adult human population.[19] Some degree of lactose maldigestion is also a common problem in children, occurring in 76% of apparently healthy children in one study and 56% in another controlled trial.[20] Maldigestion of lactose can result from genetic nonpersistence of intestinal lactase some time after weaning as well as from acquired lactase deficiencies. Deficient lactase production may or may not produce clinical symptoms of lactose intolerance.[3] A study of 232 children with intestinal biopsies found that lactase activity decreased significantly with age and correlated with degree of intestinal injury. Other studies also showed that intestinal secretion of lactase, sucrase, and maltase were decreased in conditions with intestinal mucosal injury and morphologic changes, including those seen in celiac disease and chronic diarrhea.[21-24]

A number of controlled human studies showed that fungal lactase administered orally at the time of milk consumption or added to milk at mealtime was each effective at preventing or treating signs and symptoms of intolerance in lactose-intolerant individuals.[3,20,25] One double-blind, placebo-controlled study showed that oral supplementation with fungal lactase taken at the time of lactose consumption was significantly effective at reducing breath hydrogen excretion and treating clinical symptoms in 18 children with lactose intolerance (ages 8 to 14 years). Test subjects were given tablets containing β-galactosidase derived from *A. oryzae* co-ingested with a lactose solution (3000 Food Chemicals Codex [FCC] lactase units [ALU]/5 g lactose) after a minimum fast of 8 hours. Breath hydrogen was measured every 30 minutes and clinical symptoms were monitored for the 120-minute test period. Lactase treatment successfully lowered breath hydrogen to below lactose malabsoprtion threshold levels in 89% of patients (P <0.001). In the placebo group, 89% experienced abdominal pain, 83% bloating, 61% diarrhea, and 44% experienced flatulence. In the lactase group, only 6% experienced abdominal pain, 6% had diarrhea, and none of the test subjects experienced bloating or flatulence.[3]

IMPROVING NUTRIENT ABSORPTION

Bioavailability of minerals can be considerably reduced by dietary phytate. Humans and monogastric animals produce little or no endogenous phytase in the gastrointestinal tract.[26] A controlled clinical trial in humans showed that dietary supplementation with an acid-stable fungal phytase from *A. niger* increased absorption of iron from the diet. The study also showed that the fungal phytase was stable and active across a broad range from pH 1.0 to 7.5, and that it initiated digestion of dietary phytate beginning in the stomach.[14] Animal studies showed that supplementation with fungal phytase helped to improve zinc, calcium, and phosphorus bioavailability, and increased bone strength in a dose-dependent manner.[27,28]

Studies showed that supplementation with fungal cellulase helped to increase nutritional value of dietary grains in animals. Cellulase significantly improved digestibility of dietary cell wall components and increased solubility of calcium, phosphorus, iron, zinc, and copper associated with cell walls.[29] Studies using multienzyme combinations, including fungal amylase, protease, invertase, phytase, and cellulase, showed increased digestibility of nutrients and improved growth in pigs and chickens.[30,31]

TREATMENT OF VASCULAR DISEASE

A number of placebo-controlled clinical studies confirmed the effectiveness of a proteolytic fungal enzyme in the treatment of chronic arterial obstruction in humans.[32-35] A single-blind, placebo-controlled, crossover study evaluated the effectiveness of protease from *A. oryzae* versus placebo in 18 patients (ages 63 to 75 years) with stable intermittent claudication.[32] Patients were divided into an experimental group and a placebo group of nine subjects each, and all patients were assessed before testing. Translumbar aortogram, Doppler ultrasound, and peripheral systolic blood pressure were used to assess the patency of eight different arterial segments in each patient (a total of 72 arterial segments in each group). Anticoagulant therapy with warfarin was introduced after assessment and continued throughout an observation period of 3 months and a subsequent trial period of 2 weeks. Patients were reassessed after the 3-month observation period. Thereafter, a series of six intravenous infusions of fungal protease or normal saline placebo was given to experimental and control groups, respectively, over the 2-week trial period. Assessment of peripheral circulation was repeated at the end of the trial period. No other form of therapy was given, except warfarin for anticoagulation. Before treatment, patients in the experimental group were found to have 27 obstructed segments (completely obstructed), 34 stenosed segments (partially obstructed), and only 11 patent arterial segments. Patients in the placebo group had 25 obstructed, 26 stenosed, and 21 patent arterial segments before treatment.

At the end of the 3-month observation period, no changes in Doppler ultrasound findings or peripheral blood pressure were found in either group. At the end of the 2-week trial period, three of the stenosed arterial segments in the placebo group had progressed to complete obstruction, and none of the obstructed segments had become patent (i.e., 4% worse). In the protease group, 16 of the 17 arterial segments that were completely obstructed became patent and 1 improved to stenosed status during the 2-week treatment period. Overall, treatment with the fungal protease infusion improved patency of 33 of 72 arterial segments, a 46% improvement (P <0.001).

Further analysis of results from this study suggested that an increase in the number and/or dosage of protease infusions might have resulted in even greater improvement in obstructed and stenosed arterial segments. Other studies showed intravenous administration of fungal protease to be effective in the treatment of arterial obstruction in patients with more advanced conditions, such as gangrene and other severe ischemic disease.[33,35]

PHARMACOLOGY OF FUNGAL PROTEASE

Fungal proteases have been used for many years in food production and medical applications. The most common fungal proteases used in medical and dietary supplement applications are derived from *A. oryzae* and *A. niger*. *A. oryzae*–derived protease preparations are used orally for the prevention and treatment of digestive disorders and are treated as drugs for this purpose in some countries.[17,18,36] *A. oryzae* produces three main proteases that are naturally acid-resistant and that exhibit aggregate proteolytic enzyme activity over a broad range from pH 3 to 9.[36,37] One of these three proteases, sometimes referred to in the literature as *A. oryzae* protease I, was used for treatment of vascular disease in the previously cited clinical trials.[32,33] Studies showed that the thrombolytic effects it exhibited were due to its fibrinolytic activity.[38,39] It also has hydrolytic enzyme activity

against fibrinogen. It does not affect the plasminogen–plasmin system nor does it interfere with normal blood clotting in therapeutic doses.[40]

A. oryzae protease I has a molecular weight of about 35 kDa.[39] It is carried in the blood bound to protease inhibitor proteins α_2-macroglobulin and α_1-antitrypsin.[32,39] These are the same plasma proteins that act as carriers for trypsin, chymotrypsin, and bromelain.[41-43] These protease inhibitors help to maintain a protective balance by modulating proteolytic activity in the blood while also maintaining the proteases they carry in an enzymatically active form.

As mentioned previously, acid-stable fungal protease has been used and studied clinically to aid digestion of dietary protein in the gastrointestinal tract on oral administration at mealtime.[17,18,36] Anecdotal reports suggested that some clinicians also administer fungal protease supplements orally between meals as an adjunct in the nutritional treatment of inflammatory conditions and food allergies. A possible mechanism of action for these applications is supported by indirect evidence that some portion of orally administered fungal enzymes is probably absorbed intact and retains enzymatic activity in the blood.

Absorption of Orally Administered Enzymes

Contrary to long-held theories that the healthy intestinal mucosa is an essentially impermeable barrier to intact proteins, including enzymes, there is compelling evidence that such macromolecules can and do pass intact from the human gut into the bloodstream under both normal and pathologic conditions.[1,44-47]

Numerous whole proteins, including animal and plant-derived enzymes, were shown in human and animal studies to be absorbed intact into the bloodstream after oral administration. Several human studies showed that exogenous pancreatic trypsin (molecular weight approximately 23 kDa) and chymotrypsin (25 kDa) were absorbed intact in an enzymatically active form after oral administration.[48-50] Studies showed that an enteropancreatic circulation normally exists, in which pancreatic enzymes are absorbed from the gut intact and while enzymatically active, travel in the circulation, are reabsorbed by the pancreas, and re-secreted back into the gut mixed with newly synthesized enzymes.[51,52]

Other examples of enzymes and other proteins that are absorbed intact on enteral administration include amylase (54 kDa), elastase, chymotrypsinogen, human albumin and lactalbumin, bovine albumin, ovalbumin, lactoglobulin, and other large molecules, such as ferritin (500 kDa) and botulism toxin (1,000 kDa).[44-47,50,53-55] Studies also demonstrated the intact absorption of orally administered plant enzymes, such as bromelain (24 kDa), papain (39 kDa), and peroxidase from horseradish (40 kDa).[41,50,56]

Some studies examined the quantitative significance of the absorption of orally administered enzymes. A randomized, double-blind, placebo-controlled trial measured the absorption of orally administered bromelain in 19 healthy men (ages 18 to 45 years). Enteric-coated bromelain was given to the test group in six daily doses, averaging 660 mg each over a 2-day period. Bromelain was found to be absorbed intact in an enzymtically active form and in time-dependent concentrations in the blood of all subjects in the test group. Individuals in the placebo group had no detectable bromelain levels. Total bromelain measured in the blood of test subjects over a 4-day monitoring period was equivalent to approximately 0.7% of the administered oral dose.[41]

Studies in animals looked at the percentage of total administered doses of pancreatic enzymes and papain that were absorbed intact after enteral administration. One study in rats found that approximately 27% of the total administered dose of trypsin, 14% of chymotrypsin, 8% of amylase, and 6% of the administered dose of papain were absorbed into the bloodstream as intact macromolecules in an enzymatically active form after enteral administration.[50]

Based on indirect evidence in humans and animals such as this, it appears likely that some portion of *A. oryzae*–derived protease and other fungal enzymes is absorbed intact after oral administration between meals. To the extent that such absorption does occur, orally administered fungal proteases may exhibit therapeutic properties in the systemic circulation and tissues. These properties include fibrinolytic acitvity that may be of potential benefit in the treatment of inflammatory conditions in various tissues throughout the body. They also include the ability to hydrolyze dietary proteins and polypeptides that may be of potential benefit in the treatment of food allergies.

FOOD ALLERGIES

Under healthy conditions, adequate protein digestion, normal intestinal permeability, and healthy immune function are important physiologic mechanisms that act together to limit the amount of undegraded dietary proteins and polypeptides that is absorbed into the general circulation. Under pathologic conditions, these food-derived macromolecules can act as antigens and contribute to food allergies.[1,47,57] Fungal protease administered orally at mealtime helps to hydrolyze dietary protein in the gut[17,18,36] and may therefore help to reduce the supply of foreign macromolecules available to leak into the bloodstream. In addition, it is possible that fungal protease administered orally between meals may be partially absorbed in an enzymatically active form and help to some extent to "digest" dietary protein-derived antigens in the blood. This could potentially reduce the quantity of circulating antigens and be of benefit in the treatment of food allergies or perhaps even food-linked autoimmune disorders. Further research is needed to evaluate these proposed mechanisms of action and confirm whether fungal enzyme supplementation may be a useful adjunct in the treatment of food allergies.

SUMMARY

Research has shown that certain enzymes derived from fungal species such as *A. oryzae, A. niger,* and *Rhizopus* spp. are safe and effective at increasing digestion and treating certain digestive disorders when administered orally at mealtime. These enzymes are inherently stable on exposure to stomach acid and exhibit digestive enzyme activity on a wide variety of dietary substrates over a broad pH range. Because of these properties, fungal enzymes may offer clinical advantages over pancreatic enzymes and pH-altering drugs in some conditions such as pancreatic insufficiency.

Indirect evidence suggests that fungal enzymes may be partially absorbed in an intact and enzymatically active form when administered orally between meals. To the extent that such absorption does occur, it is possible that orally administered *A. oryzae* protease may have potential benefit as an anti-inflammatory agent due to its known fibrinolytic activity; however, any efficacy in this application remains unproven. Further research is also needed to confirm a possible benefit for the use of fungal enzymes in the treatment of food allergies.

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CHAPTER 107

Natural Product Quality Control

Rick Liva, RPh, ND

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BACKGROUND

Dietary supplements (DSs) are obviously beneficial to promote health, restore balance, and treat disease. People take them for long periods of time, often for years and years. A sensible strategy for limiting contaminants in DSs, making sure that they are authentic and the potency they claim to be, is to require suppliers to prove that they routinely do thorough testing to verify and assure those quality parameters. DS prescribers and consumers need to ask for legitimate proof of quality from each manufacturer.

Before launching into the details and challenges of product quality control, the author and editors want to acknowledge and commend those nutritional supplement manufacturing companies that perform most, or all, of the processes necessary for quality verification. Unfortunately, too many in the industry—retail, mail order, professional, and online—fall short in providing legitimately verified quality DSs.

Abbreviations and Definitions

COA: Certificate of Analysis.

DS: Dietary supplement(s).

DS CGMPs: Dietary Supplement Current Good Manufacturing Practices. The "current" is included because they are subject to updating and changes, and DS manufacturers are responsible for staying current with the updates in the regulations.

DS manufacturer: A company that obtains raw materials from domestic or foreign suppliers and uses those materials to manufacture, label, and sell capsules, tablets, powders, liquids, etc.

EMA: Economically Motivated Adulteration.

FDA: Food and Drug Administration.

FP: Finished product.

HPLC: High performance liquid chromatography. An instrument used to analyze and check for the potency level(s) of botanical and nonbotanical raw materials and FPs.

HPTLC: High performance thin layer chromatography. An instrument used to analyze and check for the correct genus and species (identity) of botanical raw materials.

OOS: Out-of-specification (studies).

RM: Raw material, also know as a component or DS ingredient used to make the final DS.

Scientifically Valid Method: This is from the preamble section of the FDA CGMP final rule for Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements: "Consistent with the view that we expressed in the 2003 CGMP Proposal, we believe a scientifically valid method is one that is accurate, precise, and specific for its intended purpose. In other words, a scientifically valid test is one that consistently does what it is intended to do."

SOPs: Standard operating procedures.

Supplier: A domestic or foreign company that sells DS raw materials, as a distributor, broker, agent, or it may be the original direct manufacturer.

Verify: To prove the truth of, as by evidence; confirm; substantiate; to ascertain the truth or correctness of, as by examination; to act as ultimate proof or evidence of; serve to confirm.

STATE OF THE INDUSTRY

There are approximately 1500 DS manufacturing companies in the United States. In addition, there are a number of marketing companies that have their DSs made by a private label contract manufacturer and sell their brand nationally or worldwide. Many of these manufacturing companies historically have performed little or no testing on their raw materials (RM) or their finished DSs. They accept a certificate of analysis (COA) from their supplier. The COA is just a piece of paper that says the material is what it is supposed to be. When a DS manufacturer blindly accepts a COA as the "sole" proof of authenticity, potency, and purity, they relinquish their verification role. Why do they do this? Because it is quick, easy, cheap and saves money, hassle, delay, and personnel. In short, they take the easy way out. This practice is likely to continue until practitioners and consumers knowledgeably demand quality or the Food and Drug Administration (FDA) clamps down and puts noncompliant manufacturers out of business or makes them comply under the threat of constant scrutiny, steep fines, or shutting down their business. The chain of events needed to produce high-quality DSs is too long and complicated to "trust" it will happen with consistent integrity without comprehensive testing of raw materials and finished products (FPs).

Pharmaceutical drugs are all too frequently sold as DSs. Unscrupulous DS manufacturers or marketing companies will sell products for weight loss, erectile dysfunction, fatigue, athletic performance, etc. These products are advertised as DSs, but the active ingredient is a pharmaceutical drug. In addition, drug and disease claims are often used in the marketing of DSs. These two practices give the DS industry a bad name, tarnishing the legitimate manufacturers and leading the FDA to mistrust companies that produce DSs.

THE FOOD AND DRUG ADMINISTRATION

The FDA has had regulatory oversight of the DS industry for 15 years or longer. In 2007, they put into place Current Good Manufacturing Practice (CGMPs) regulations. The regulations are basically rules to follow when manufacturing DSs, much like a strict recipe that has to be followed to get the intended outcome. They are "the law," and every manufacturer has to follow them. It has been fairly recent (since late 2007) that the FDA has been conducting inspections of DS companies to see if they are complying with the new regulations. Word on the street is that many manufacturers are not complying. Maybe they will at some point in the future, but how will you know if a particular company is, or is not, complying with DS CGMPs?

Points regarding the FDA:

- The FDA's mission is to promote and protect the public health by helping safe and effective products reach the market in a timely way, and monitoring products for continued safety after they are in use.
- The FDA is probably underfunded and overburdened. At present, they probably do not have the capacity to strictly oversee the DS industry and enforce wide compliance in a short period of time.
- The DS CGMP regulations were written loosely so as to be flexible. This is a serious problem because it allows each manufacturer to apply "their own" interpretation of what it will take to comply with the regulations, possibly resulting in poor quality DSs in the marketplace.
- Because the regulations were written to be flexible, the FDA gives little to no guidance on the detailed specifics of "Expected Best Practices" to DS manufacturers. The lack of FDA specific guidance parameters keeps everybody guessing as to whether or not the way "they" interpret the regulations will be acceptable to the FDA.
- The FDA will strictly enforce the DS CGMPs. As they do, it is likely to bring significant positive change to the DS industry that will ultimately benefit the consumer.

If a DS manufacturer says that they are in compliance with FDA CGMPs, it does not mean they have done enough to adequately test and verify their raw materials and FPs and to ensure that the final product is authentic, potent, and has maximum freedom from contamination. In addition, it is important to know that the FDA has mandated by law that if a product has an expiration date or best used by date on the label, the DS manufacturer has to have data to support the expiration date time period.

What data does a DS manufacturer have to show? The FDA is silent on this point. The FDA CGMPs do not give any guidance to the industry as to what is acceptable to meet this requirement. This is a perfect example of the FDA providing no guidance on an important part of the DS CGMPs and leaving it to the DS manufacturer to guess and interpret what may be adequate.

Basics of Food and Drug Administration Current Good Manufacturing Practices

Companies that supply DS ingredients (domestic or foreign) to DS manufacturers do not have to follow the FDA DS CGMPs. According to the FDA, this means that the responsibility for the quality of raw material ingredients falls on the FP DS manufacturer and not on the supplier of the materials. This is unfortunate and a major deficiency in the DS CGMPs. Why? Because companies that supply ingredients to DS manufacturers can produce and sell poor quality or tainted ingredients and are not held accountable. If the supplier of the ingredients and the manufacturer that uses the ingredients had to follow the same regulations, there would be a synergy to bring quality ingredients to the marketplace.

The following information comes from the FDA's website (www.fda.gov), and it gives enough detail to see what DS manufacturers must do to comply with these legally required regulations. The FDA DS CGMPs are not voluntary, but must be followed because they are the law. All DS manufacturers are required to follow these rules as of June 2010.

CGMP Final Rule:

- The current good manufacturing practices (CGMPs) final rule will require that proper controls are in place for dietary supplements so that they are processed in a consistent manner, and meet quality standards.
- The CGMPs apply to all domestic and foreign companies that manufacture, package, label, or hold dietary supplements, including those involved with the activities of testing, quality control, packaging and labeling, and distributing them in the U.S.
- The rule establishes CGMPs for industry-wide use that are necessary to require that dietary supplements are manufactured consistently as to identity, purity, strength, and composition.
- The requirements include provisions related to:
 - the design and construction of physical plants that facilitate maintenance,
 - cleaning,
 - proper manufacturing operations,
 - quality control procedures,
 - testing final product or incoming and in-process materials,

- handling consumer complaints, and
- maintaining records.

Consumer Benefits:

- Consumers should have access to dietary supplements that meet quality standards and that are free from contamination and are accurately labeled.
- The rule will give consumers greater confidence that the dietary supplement they use has been manufactured to ensure its identity, purity, strength, and composition.
- The rule addresses the quality of manufacturing processes for dietary supplements and the accurate listing of supplement ingredients. It does not limit consumers' access to dietary supplements, or address the safety of their ingredients, or their effects on health when proper manufacturing techniques are used.

Manufacturers:

- Under the Dietary Supplement Health and Education Act (DSHEA), manufacturers have an essential responsibility to substantiate the safety of their products and for determining that any representations or claims made about their products are substantiated by adequate evidence to show that they are not false or misleading.
- The CGMPs will help to ensure manufacturers produce unadulterated and properly labeled dietary supplements.
- Under the CGMP rule, manufacturers are required to:
 - Employ qualified employees and supervisors;
 - Design and construct their physical plant in a manner to protect dietary ingredients and dietary supplements from becoming adulterated during manufacturing, packaging, labeling, and holding;
 - Use equipment and utensils that are of appropriate design, construction, and workmanship for the intended use;
 - Establish and use master manufacturing and batch production records;
 - Establish procedures for quality control operations;
 - Hold and distribute dietary supplements and materials used to manufacture dietary supplements under appropriate conditions of temperature, humidity, light, and sanitation so that the quality of the dietary supplement is not affected;
 - Keep a written record of each product complaint related to CGMPs; and
 - Retain records for 1 year past the shelf life date, if shelf life dating is used, or 2 years beyond the date of distribution of the last batch of dietary supplements associated with those records.
- Examples of product quality problems that the rule will help prevent are:
 - dietary supplements that contain ingredients in amounts that are greater than those listed on the label,
 - dietary supplements that contain ingredients in amounts that are less than those listed on the label,
 - wrong ingredient,
 - other contaminant (e.g., bacteria, pesticide, glass, lead),
 - foreign material in a dietary supplement container,
 - improper packaging, and
 - mislabeling

The regulations mandate that each DS manufacturer set, document, and meet quality specifications for raw material ingredients and FPs. Each manufacturer gets to set their own specifications based on what they feel and/or think is important and complies with the regulation to ensure the four buzz words: identity, purity, strength, and composition. Herein lies a major problem with the CGMPs. The FDA gives little if any guidance on setting specifications.

Purity is one of the buzzwords; one aspect of purity is contamination. Part 111.70 of the regulation states, "You must establish limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement to ensure the quality of the dietary supplement." No guidance is given as to the types of contamination to consider. In CGMP seminars conducted around the country in the past few years, the FDA mentioned some examples of contamination and ultimately stated that the DS manufacturer should know globally what contaminants to consider.

Here is an example to illustrate:

- DS manufacturer "A" sets a specification for testing for a wide panel of chemical solvent residues in each batch of received RMs, examines those results for acceptable limits, and approves or rejects materials based upon those limits.
- DS manufacturer "B" sets a specification for testing for chemical solvent residue only if they are listed on the suppliers' COA, examines those results for acceptable limits, and approves or rejects materials based upon those limits.
- DS manufacturer "C" sets a specification that does not include chemical solvent residue testing.

Each DS manufacturer set a specification per the CGMPs, but each was different. Are they all acceptable to the FDA? We do not know. Which manufacturer's products would you prefer to prescribe?

THE IMPORTANCE OF QUALITY CONTROL

The first reason quality control is very important is clinical effectiveness. In other words, will it have the intended physiologic effect on the body? Great quality does not always ensure significant clinical response, but most would agree that a low potency product or one that was not even what it claimed to be is not likely to help patients.

The second reason quality control is very important is that some sort of contamination may be present in the product. Long-term use of contaminated DSs may possibly cause harm. Depending upon whether it is botanical or nonbotanical, the contaminants present could be lead, mercury, cadmium, arsenic, an array of chemical solvents, aflatoxins (liver toxins from mold growth), herbicides and pesticides, harmful bacteria, and industrial chemicals.

Unfortunately, with RMs coming from all over the world, contamination is a risk that is unavoidable.

Food and Drug Administration Definition of Quality

The FDA DS CGMP regulation has specific definitions for quality and quality control.

- Quality means that the dietary supplement consistently meets the established specifications for identity, purity, strength, composition, and limits on contaminants, and has been manufactured, packaged, labeled, and held under conditions to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act.
- Quality control means a planned and systematic operation or procedure for ensuring the quality of a dietary supplement.

The only test specifically mandated by the FDA that must be performed is identity testing. The need for further testing is open to interpretation by the DS manufacturer.

A More Specific and Robust Definition of Quality

A DS is a quality product or not based upon three parameters.

Is it Real?

In other words, is the RM authentic, i.e., has it been properly identified via a test method that is widely accepted as scientifically valid? If no testing was performed to verify or identify the RM, and it was used in a FP anyway, its inclusion in the product could have resulted in not only decreased response, it may have actively caused harm.

Identifying and authenticating botanical products can be challenging especially if they are powdered extracts versus plant parts or powdered plant parts that have not been extracted. Plant parts (leaves, roots, stems) when whole or in pieces can be identified more easily by gross and microscopic examinations to ensure compliance with published criteria that are specific to the plant. Most powdered botanical extracts need to undergo some sort of chemical or technical testing to verify correct genus and species.

Vitamins, amino acids, and many other nonbotanical materials are somewhat easier to chemically identify than botanicals, and botanicals are much more prone to adulteration.

Mineral forms can also present a serious challenge to truly authenticate. For example, magnesium glycinate is thought to have some absorption advantage over magnesium oxide and other magnesium forms. Magnesium glycinate is supposed to be magnesium chemically bonded in a particular way to glycine. This is a true chelate, i.e., one molecule. Some mineral RM suppliers skip the bonding part either in part or completely and just mix magnesium carbonate or magnesium oxide with glycine and call it magnesium glycinate. In essence, it is a dry blend of two compounds with only partial or no bonding.

Is It the Potency It Claims to Be?

In most cases (there are some exceptions for skip lot testing if a RM supplier is properly qualified; more under "Supplier Certification and Skip Lot Testing") testing every lot of material received for potency helps ensure a consistently potent FP. If most lots are solely identified as authentic and not tested for potency, this does not document the potency of the FP.

Much of the potency issue has to do with label claims as well. Some examples:

Scenario 1: If a licorice extract product has a label stating licorice extract 12% 200 mg (i.e., the licorice extract contains 12% glycyrrhizin), one would have to verify the potency (by testing) of the RM going into the FP and would also have to verify by testing that there was 12% glycyrrhizin in the FP.

If a label has a potency claim, the DS manufacturer has to prove that the claim was met and the FP contained 100% of the labeled potency claim. Always meeting 100% of a potency claim is stipulated by current DS labeling law.

Scenario 2: Another option could be a licorice extract 200 mg with no glycyrrhizin claim. The label just says licorice extract 200 mg. The amount of glycyrrhizin does not have to be verified at the RM or the FP stage. The only thing that has to be verified is that 200 mg is in each capsule, and that it is really licorice. In this scenario, the potency of the product has not been verified, it could be high, low, or really low.

Scenario 3: The same label of licorice extract 200 mg product as in scenario 2. The label just says licorice extract 200 mg. The amount of glycyrrhizin does not have to be verified as RM or at FP stage, but the conscientious manufacturer tested anyway to ensure the potency of the material at the RM stage, i.e., how much glycyrrhizin is in the RM. To stay consistent, let us say the potency was 12% glycyrrhizin, because this is the level known to be clinically effective. No need to test at the FP stage because no label claim for a specific potency is made. The only need is to verify that 200 mg is in each capsule. In the end, the potency was verified by the RM testing.

The difference between scenarios 2 and 3 is the DS manufacturer in case 3 had full knowledge and verified the potency of the licorice extract RM, whereas in scenario 2, the DS manufacturer may not have had a clue as to how potent the FP licorice extract is (high or low) because no testing was performed on the RM or FP.

Clearly, no matter what the obligation is regarding potency testing per label claim, it is always best to know the strength of a botanical going into a FP. This can only be accomplished through potency testing the RM batch. A point of clarification must be made. Many botanical RM products do not have marker compounds to test, or there is no scientifically valid method that exists to perform the potency testing. In this case, no potency/strength testing is the only option.

Ideally, one should ask and know if a DS manufacturer is routinely conducting potency/strength testing on RMs and/or FPs.

Does the Product Contain Any Contaminants?

Another way of saying this is: does it have maximum freedom from contamination? Usually, contaminants can only be found through testing the RM. It is generally not possible to detect low level contamination by relying on physical inspection and no testing. A physical inspection may find plastic, metal, glass, bug parts, and other filth.

As noted before, the FDA CGMP regulations leave it up to the DS manufacturer to determine if contaminant testing will be done, and if so, to set the acceptable specification(s) for such testing. Some DS manufacturers perform comprehensive contaminant testing, some perform partial testing, and some perform none. As a prescriber of DSs, which contaminant testing profile makes you feel most comfortable and safe?

CONTAMINANT TESTING

Nonbotanical Raw Materials

Heavy Metal(s) Where Indicated

An example of heavy metal contamination is lead content in calcium and magnesium or products made from the shells of shellfish.

Solvent Residue

Many vitamins, minerals, amino acids, enzymes, and glandular products are manufactured using one or more chemicals or chemical solvents. Currently, the natural products industry has no limits on chemical or solvent residue allowed in natural products. One could use and comply with the allowable chemical and solvent limits for the pharmaceutical industry. Testing a panel of multiple solvents is recommended when trying to find residual solvent levels in botanicals or nonbotanicals. Why a panel? Most DS suppliers do not give adequate, accurate, or often any information regarding residual solvent levels on the COA for a RM under consideration for purchase. Often DS manufacturers in the industry will do no testing for any solvents if there are no solvents listed on the COA. This is a mistake, because when a wide net is cast looking for solvent residue, one or more solvents are frequently found.

Bacterial, Yeast, Mold

All batches of RMs and FPs should be tested for these microbiological parameters.

Miscellaneous Items to Consider Where Appropriate

For example, test for melamine levels in protein powders or foods.

Botanicals

Heavy Metal(s)

Every batch of RM should be tested for lead, mercury, cadmium, and arsenic.

Solvent Residue

A panel of multiple solvents is recommended when trying to find residual solvent levels in botanicals as previously explained.

Bacterial, Yeast, Mold

All batches of RMs and FPs should be tested for these microbiological parameters. Some forms of botanical materials are more prone to having higher levels of these items compared with nonbotanical materials.

Herbicide, Pesticide, and Fungicide Residue

Ideally, every batch of botanical product purchased should be tested for residual amounts of a variety of herbicides, pesticides, and fungicides. Certified organic botanical products can be exempted. There are a number of testing profiles to choose from: FDA, United States Pharmacopoeia (USP), European Pharmacopeia, or the California Department of Food and Agriculture. Testing broadly for organochlorines, organophosphates, organonitrogens, and carbamates is ideal and covers a wide spectrum. Every batch should be tested because plant medicines come from all over the world, and various countries have strict or lax rules on what is allowed or not allowed to be applied on crops. Despite rules and regulations in some third world countries, there could be a lack of enforcement, which creates a big wide hole for skirting the rules and even more of a reason to test comprehensively every batch received. For example, testing of a sample of kava extract from Indonesia could reveal residues of dichlorodiphenyltrichloroethane (DDT), which is banned in the United States and has been for years. The FDA has a zero tolerance limit for DDT and its metabolites.

Aflatoxin Residue

Aflatoxins are toxic metabolites produced by certain fungi that are in or on foods and plant materials. Four different aflatoxins, B1, B2, G1, and G2, have been identified, with B1 being the most toxic, carcinogenic, and prevalent. Aflatoxins are probably the best known and most intensively researched fungal toxins in the world. Aflatoxins have been associated with various diseases, such as aflatoxicosis in livestock, domestic animals, and humans throughout the world. Aflatoxins have received greater attention than any other fungal toxins because of their demonstrated potent carcinogenic effect in susceptible laboratory animals and their acute toxicologic effects in humans. Many countries have attempted to limit exposure to aflatoxins by imposing regulatory limits on food and feed for animals. The FDA has set a limit of less than 20 ppb for total aflatoxins in food and feed. The European Union has a much lower overall tolerance (10 ppb), and is more specific for limits on individual aflatoxins, especially B1 at 2 ppb or 5 ppb depending upon the food.

Contaminant Testing for Fish Oil and Vegetable Oil Products

Heavy Metal(s)

Every batch of RM should be tested for lead, mercury, cadmium, and arsenic.

Bacterial, Yeast, Mold

All batches of RM and FP should be tested for these microbiological parameters.

Dioxins and Dioxin-like Compounds

Testing every batch received is ideal because levels of these chemicals are present from batch to batch. The same can be said for polychlorinated biphenyls (PCBs), as explained in the following. Fish oil processing can remove many of these residues if the crude material is cleaned. Some portion of the crude fish oil sold worldwide and used to make capsules or liquid fish oil is not cleaned and may contain higher levels of these chemicals.

Dioxin is a generic term used to describe a family of 210 compounds. The most dangerous of this family are 17 members of this group characterized by the presence of chlorine atoms in the 2, 3, 7, and 8 positions. Each of those 2, 3, 7, 8-substituted congeners has been assigned a Toxic Equivalent Factor, which is used for the computation of the Toxic Equivalency Quotient. This scale is used in risk assessment studies to calculate the probability of causing cancer and other life-threatening diseases in humans. The European Union has set a fish oil for human consumption tolerance limit for dioxins.

Polychlorinated Biphenyls

PCBs are a mixture of individual chemicals that are no longer produced in the United States, but are still found in the environment. Health effects that are associated with exposure to PCBs include acne-like skin conditions in adults and neurobehavioral and immunologic changes in children. PCBs are known to cause cancer in animals. The Department of Health and Human Services concluded that PCBs may reasonably be anticipated to be carcinogens. The Environmental Protection Agency and the International Agency for Research on Cancer determined that PCBs are probably carcinogenic to humans.

Rancidity Testing

Oil products ideally should be tested for primary oxidation by-products (peroxide levels) and secondary oxidation by-products (anisidine levels). A high level of any of either is indicative of rancidity of long-chain fatty acids in the oil product. It is critical to test for both because peroxides are transitory and can drop to a low level as they transform into secondary oxidation by-products (anisidines). Once an oil has started down the path of rancidity, it usually proceeds to higher levels of rancidity.

FINISHED PRODUCT EXPIRATION DATE AND STABILITY TESTING

Many DS companies have no data to support their expiration date or "best if used by" claims. The following information is taken from the preamble portion of the FDA DS GMP regulations:

> *"Because the final rule does not require that you establish an expiration date, we (the FDA) decline to offer guidance on the type of data that are acceptable to support an expiration date, other than to repeat that any expiration date that you place on a product label (including a "best if used by" date) should be supported by data."*

Because the FDA gives no guidance on the matter, what should be asked of a DS manufacturer? Strength/potency testing is probably most important because the potency of the product over time might be critical to the product producing intended results.

Some questions to ask are:

1. Are you conducting any stability testing on your FPs?
2. If so, what testing? Strength/potency? Bacteria, yeast, mold testing?

3. If no testing is taking place, are you performing physical parameter inspections (appearance; weight; integrity of the capsule, tablet, or powder, etc.)?
4. If no testing is taking place, how do you verify the strength/potency of the product over the shelf life expiration dating period? What data do you have to support the expiration date period and stability of your product(s)?

ASSESSING QUALITY VIA COMPREHENSIVE TESTING

Start with the concept that "you only find what you look for." This can and should be applied to DS RM ingredients. When a DS manufacturer buys a RM (domestic or foreign), generally they cannot just tell that the material is of good quality. The measure of quality of a DS FP is a function of the quality of the ingredients that went into it. If a DS manufacturer looks at the quality of an ingredient in a cursory manner and only performs the most minimal of tests, some essential quality parameters may be missed, and the ingredient goes unverified overall. If comprehensive testing is performed for an array of quality parameters, the ingredient may be deemed verified as a quality ingredient if the test results are acceptable.

The definition of verification is repeated to make a point about the value of assessing quality via comprehensive testing. To verify means:

- To prove the truth of, as by evidence; confirm; substantiate
- To ascertain the truth or correctness of, as by examination
- To act as ultimate proof or evidence of; serve to confirm

Verification of quality via testing provides evidence, proof, substantiation, and confirmation of quality parameters. How else can it be achieved? Testing is king when it comes to confirming and assessing the quality parameters of DS ingredients and FPs.

If a DS manufacturer does extensive and comprehensive testing on all RM ingredients that go into the FP, the overall quality of the FP is mostly assured. To fully assure quality in this scenario, the only items left to test on the FP would be strength/potency (if potency claims are made) and microbiological profile to make sure it did not become contaminated with bacteria, yeast, or mold as it went through manufacturing. Ideally, the FP would also be run through a metal detector to rule out the possible introduction of metal pieces from the manufacturing process. Finally, if any of the active constituents could be damaged by the manufacturing process, such as a heat labile substance, its potency should be checked before quality control release.

SUPPLIER CERTIFICATION AND SKIP LOT TESTING

The FDA DS CGMPs allow for certifying a DS supplier. Once a DS supplier is certified, the DS manufacturer can perform reduced testing of RM batches, i.e., skip certain testing parameters because they have done enough due diligence to "trust" the DS supplier's quality.

The FDA CGMP regulation in Subpart E, §111.75 states:

A firm may rely upon a certificate of analysis (COA) from its supplier of a component (in other words not test), provided that certain criteria are met which include the following:

- The firm first qualifies the supplier by establishing the reliability of the supplier's COA through confirmation of the results of the supplier's tests or examinations;
- maintains documentation of how it qualified the supplier;
- periodically reconfirms the supplier's COA;
- quality control personnel review and approve the documentation setting forth the basis for qualification (and requalification) of any supplier.

Some questions remain regarding these guidelines. The FDA gives no acceptable criteria on establishing reliability of the supplier—does this need to happen once, twice, six times? How was this confirmed? How often is the COA from the supplier reconfirmed? Every year, 2, 3, or 5 years?

Officials from the FDA have said the following at numerous trade shows and conferences. Unfortunately, this provides no guidance for DS manufacturers. "We anticipate that Industry will be creative in qualifying the global supply chain." In addition, the FDA has told the DS industry that qualifying a supplier must include an onsite comprehensive audit of the supplier's facility (wherever it may be) and manufacturing and quality assurance processes for the ingredients in question.

LABORATORY TESTING AND LABORATORY QUALITY

DSs are tested by contract laboratories to ensure identity (assure authenticity without adulteration), purity (assess contamination levels), and strength (verify the claimed potency). Laboratories use "methods" to test DSs. Ideally, a validated method would be used for the specific item in the specific mix of ingredients. However, few laboratories have adequately validated methods to cover all situations.

The most pressing issue regarding laboratory quality assurance is, by far, the lack of available validated methods. Method validation shows that a method is suitable and fit for its purpose—demonstrating accuracy and reproducibility. It is easy to define and hard to implement because many different, time-consuming experiments need to be performed to accomplish it. Method validation is extremely important in the DS industry, especially because the FDA requires manufacturers to support their ingredient label claims.

Validating a method proves beyond a reasonable doubt that the results are accurate and reproducible. Method validation is absolutely necessary to ensure the highest degree of reliability. In addition, method validation is needed to settle variant results from laboratory to laboratory. If the laboratory has a variety of quality systems in place, then this may not be completely necessary within a single laboratory.

The quality systems of any laboratory are paramount to achieving the goal of consistently producing accurate, precise, and reproducible results. However, there is no systematic way to know that laboratories are producing accurate results. Many of them do not have the necessary systems or methods in place to ensure quality results. Some laboratories start out using a validated method, but later "modify" the method to suit their purposes. By doing this, they invalidate the validation because the method has been changed. This "method rigging" may introduce inaccuracies and unreliability in the results.

Quality systems every contract laboratory should employ include:

- Use of appropriate reference standards.
- Repeatability studies.
- Ensuring system suitability requirements are performed, such as:
 a. Determining if the instrument is calibrated properly and operating correctly.
 b. Following written standard operating procedures (SOPs).
 c. Performing out-of-specification (OOS) studies. An OOS study is triggered when a laboratory gets a test value that is either substantially lower or higher than the anticipated value. The OOS study verifies that the laboratory had everything correct (by rechecking all necessary parameters) when the analysis was run. Then the laboratory repeats the analysis to see if the same value is obtained or not.

d. Regularly performing recovery studies using pure compound for recovery to test extraction performance and equipment. A recovery study is when the analyst prepares a sample (extraction) with a known concentration of substance and runs it in the machine. The recovery of the result should be the concentration expected. If not, something is wrong with the equipment or sample preparation (extraction).
e. Ensuring the method used is based on good, valid science, and is applicable for the DS being tested.
f. Allowing independent audits of procedures, practices, and data.

If an officially approved validated method is not available, a scientifically valid analytic method is one that is based on scientific data or results published in, for example, scientific journals, references, textbooks, or proprietary research. These methods can yield good results if they are not changed to any significant degree and they are appropriate for the analysis. The author had a schisandra extract (*Schisandra chinensis* or *S. sphenanthe*) tested at one laboratory that yielded a 10% schisandrins result and at another laboratory that yielded a less than 2% result. The first laboratory was using a method that was designed to test material in blood or serum and not a botanical extract. Clearly, it was not a "good science" method because it was not appropriate for the intended purpose.

Validated methods are the gold standard for obtaining accurate laboratory results. Unfortunately, official (meaning recognized by the government) or unofficial validated methods do not exist for many dietary supplements. The bottom line: only trust the laboratories that follow and adhere to the quality systems outlined previously and strive to use scientifically valid methods when validated methods are not available.

ECONOMICALLY MOTIVATED ADULTERATION

Economically motivated adulteration (EMA) is the fraudulent, intentional substitution or addition of a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its production, i.e., for economic gain. EMA includes dilution of products with increased quantities of an already present substance (e.g., increasing inactive ingredients of a drug with a resulting reduction in strength of the FP, or watering down of juice) to the extent that such dilution poses a known or possible health risk to consumers, as well as the addition or substitution of substances to mask dilution.

Examples of Products That Are Prone to Economically Motivated Adulteration

- Ginkgo biloba extract: The most common method of adulterating ginkgo is to add an inexpensive flavonoid source that artificially inflates the total flavonoid level in the extract to meet the required 24%. Rutin, a flavonoid source extracted from buckwheat with a low cost, has been the most common additive used for this purpose. *Sophora japonica* (Japanese Pagodatree) is also used to artificially elevate the flavonoid level of ginkgo extract.
- Panax and American Ginseng extract: Ginseng root is widely considered the source of the herb's therapeutic activity; however, large quantities of the leaf can be added to surreptitiously and artificially increase levels of some ginsenosides.
- Goldenseal root extract: Goldenseal root naturally contains a compound called berberine at a concentration of approximately 4% to 8%. Goldenseal root extract can be spiked with added pure berberine or substituted with other berberine containing plants.
- Coptis chinensis extract: This can be spiked with berberine or substituted with other berberine containing plants.
- Bilberry extract 25% anthocyanosides: The anthocyanoside content can be manipulated by blending in cheaper berries, such as black currant and elderberries; reports showed even amaranth dye has been used to spike bilberry in an attempt to fool the testing and pass as a quality product.[1]
- Saw palmetto extract: This extract may be spiked with exhausted plant effluent (powder left over after the plant is extracted) or adulterated with palm oil. Addition of palm oil allows for the fatty acid content to meet the claim, but it throws off the natural balance of fatty acids in the extract, which can be detected with proper testing. In addition, unripe berries can be used versus the traditional use of ripe fruit.
- Grape seed extract: Addition of cheap flavonoids can allow a poor quality product to pass as high quality product.
- Black cohosh extract: Other cohosh species are used rather than *Cimicifuga racemosa.* The substituted species are not therapeutically active or have a different therapeutic activity.
- Pomegranate extract: Ellagic acid can be added to the pomegranate extract to fraudulently meet the guaranteed amount in the final extract without spending the money on expensive pomegranate dry material.
- Fish oil: This can be adulterated with vegetable oils. Proper analytic testing of the fatty acid profile and examination of fat ratios can usually detect if a fish oil product has had vegetable oil added.
- Protein powders: Addition of a plastic-like agent called melamine can artificially raise the apparent protein level. A test is available to detect the adulteration of protein powders with melamine. Melamine can cause serious health problems, including death.

RESIDUAL CHEMICAL SOLVENTS IN DIETARY SUPPLEMENTS

It is important to note that solvent residue testing is not mandated as part of the FDA guidelines for CGMPs in regard to DSs. It is up to the DS manufacturer themselves to determine if solvent residue testing is needed.

This is a big hole in the FDA CGMPs because many RM components used to manufacturer DSs have some level of chemical solvent residue. The question is how much chemical residue is present, and is the level acceptable, safe, and will not cause harm over a long period of ingestion? Hence, unacceptable residual solvent levels will be an ongoing quality challenge for many DS manufacturers and thus an ongoing quality concern.

A Solvent Primer

The issue of solvents is complex and involved. Official U.S. policy began in 1997 when a joint initiative involving both regulators and research-based industry members from numerous countries published the *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Impurities: Guideline for Residual Solvents*. This was then adopted by the FDA. Based on these guidelines, the USP revised Chapter 467, "Residual Solvents," in 2007. This then became official policy on July 1, 2008. Basically, there are 4 classes of solvents. The following is a simple primer based on the more current USP revisions.[2]

Note that these guidelines are for pharmaceutical products. There are no guidelines for DSs. So, in the absence of DS residual solvent

TABLE 107-1 **Class I Solvents (Solvents That Should be Avoided)**

SOLVENT	ACCEPTABLE LIMIT (ppm)	CONCERN
1,1,1 Trichloroethane	1500	Environmental hazard
1,1 Dichloroethene	8	Toxic
1,2 Dichloroethane	5	Toxic
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard

guidelines, it seems obvious to use the existing standard for pharmaceuticals rather than do nothing and completely ignore the issue.

Class I Solvents

These solvents should not be employed in the manufacture of drug substances, excipients, and drug products (and, hence, natural medicines, either) because of their unacceptable toxicity or their deleterious environmental effects. However, to produce a drug product (or natural medicine), if their use is unavoidable, then their levels should be restricted as shown in Table 107-1.

Class II Solvents

These solvents should be limited in use because of their inherent toxicity. There are 27 in this category, with acceptable limits from 50 to 4840 ppm. Some examples are chloroform, cyclohexane, hexane, methanol, and toluene.

Class III Solvents

These solvents are regarded as less toxic and of lower risk to human health. There are also 27 in this category, all with limits of 5000 ppm. Some examples are acetone, dimethyl sulfoxide, ethanol, ethyl acetate, and methyl acetate.

Class IV Solvents

These solvents may be of interest, but no toxicity data were found.

THE BUYING DECISION

Most consumers and practitioners do little or nothing to assess and verify product quality before they choose a supplier or make a buying decision. All too often our buying decisions are based on what other people, clinicians, educators, books, magazines, and DS company marketing materials have told us. We may like an ad, the packaging, the salesperson, believe the company's quality story, be influenced by their marketing claims, or recognize that the company has good clinical education that ties their products to the education piece. In essence, usually everything but evidence of quality verification drives our decision. It is critical to verify quality claims.

To verify is to prove the truth of something by presentation of evidence. People do not usually ask for that evidence to verify that a manufacturer is providing verified quality products. Why not? Probably because we are too busy, we assume companies are providing the quality we seek, we are not educated enough to know how to separate the marketing hype from the real evidence of quality verification, and lastly the average person may be too intimidated to call the company and ask very pointed quality questions.

This is a huge missing piece. Health care professionals would be wise to demand to see the evidence that supports the marketing claims of quality products. If we choose not to, we must realize that we could be prescribing subpotent, inauthentic, and/or contaminated products.

The author (and editors) has seen far too many examples of subpotency, lack of authenticity, contamination, and a general lack of quality assurance all across the supply chain that feeds the natural products industry. If we think that all the companies we purchase from have done all their quality assurance homework and have applied it, we need to think again. We do not know because most companies do not divulge what they do or, more importantly, what they do not do regarding the full story of the quality assurance they apply to their products.

The bottom line take home message is this: step out of your comfort zone and call companies you intend to purchase from and do your best to determine their quality practices by asking very pointed questions and requesting some proof to support their answers. You can read and become familiar with the questionnaire provided in this chapter to give you some idea of what to ask for. Asking for some level of accountability from the company you plan to buy from is better than blindly assuming they are performing adequate quality assurance to protect you and your patients.

Verifying the quality of a brand has to be done by asking the company if they have in place and consistently follow a comprehensive testing protocol to test RMs and FPs at release and conduct FP stability testing. You can use the questionnaire provided here to give you information and guidance on what questions to ask and the necessary information to gather.

DIETARY SUPPLEMENT PRICING AND QUALITY

A specific brand of DS may carry a high price. A high or low priced DS does not necessarily correlate with product quality. Two thoughts to consider regarding price and quality: First, a low or very low priced DS product is not likely to have been put through comprehensive quality testing. The cost of consistently performing comprehensive quality testing on DS products is very steep, and product pricing needs to reflect that financial investment. Second, full adherence with DS FDA CGMPs is very, very costly, as it requires financial investments in testing, personnel education and training, facility system changes, and experienced quality managers to run the quality department and comply with developing and maintaining the volumes of documentation dictated by FDA CGMPs. The days of cheap DSs are probably coming to an end.

CURRENT GOOD MANUFACTURING PRACTICE CERTIFIED PROGRAMS

In the United States and abroad, there are government and nongovernment agencies that conduct audits of DS manufacturers to assess their CGMP compliance with the standard set by the auditing agency. If the DS manufacturer successfully passes one or more necessary audits, it gets a "CGMP Compliant" or "CGMP Certified" certificate from the auditing agency. DS manufacturers use these certifications to trumpet their quality. The comprehensive nature of the audit process and criteria applied to receive a pass varies from auditing body to auditing body. All certification programs contain some value, but some may have serious limitations and may not tell clinicians all they need to know to trust a DS manufacturer and their products. Be aware that certification does not guarantee quality, and also that lack of certification does not mean lack of quality.

There are items to consider regarding these independent CGMP certifying bodies. First, the FDA CGMPs trump all of these

auditing bodies because compliance with the FDA legally required regulations are currently most important. I have already described some of the "confusing and not spelled out" FDA CGMP interpretation and compliance issues. Until those issues are defined and specified, any outside auditing agency is making their best guess and applying their interpretation of what will pass with the FDA. Second, the most important quality practice to verify and understand with any DS manufacturer is how comprehensively they conduct testing to verify identity, strength/potency, purity (contamination), and shelf life dating. None of these CGMP Certified seals will give you that information. You must attempt to get that information directly from the DS company.

Quality Questionnaire, A Tool to Help Verify Quality Claims and Testing Practices

The road to ensuring high quality is successfully traveled when clinicians ask for, obtain, and evaluate DS manufacturer supplied information on CGMP compliance and valid evidence (test results) of a product's identity (authenticity), purity (maximum freedom from contamination), strength/potency, and shelf-life strength.

A questionnaire entitled "The Manufacturer Quality Assurance Self-Audit Form," is available for use.[3] The form is intended to give clinicians a basis upon which to question or request documentation from manufacturers and/or suppliers about their quality control/quality assurance practices and testing programs. There is also an attending compliance document that can be used to evaluate some of the responses obtained from DS manufacturers.

"Not having the information you need when you need it leaves you wanting. Not knowing where to look for that information leaves you powerless. In a society where information is king, none of us can afford that."

Lois Horowitz

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CHAPTER 108

Naturally Occurring Antioxidants

Robert A. Ronzio, PhD

A growing body of research implicates excessive oxidative damage in multiple disease processes as well as aging. This chapter examines the impact of free radicals and pro-oxidants, and the role of antioxidants in countering oxidative stress and imbalanced redox regulation.

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FREE RADICALS AND NONRADICAL OXIDANTS

Free Radicals

These molecules possess an unpaired electron; therefore, they participate in single electron oxidations. In the body, the hydroxyl radical (•OH) is one of the most reactive free radicals, precluding any useful physiologic role. Less reactive radicals, nitric oxide (NO•) and superoxide ($O_2•^-$), are able to participate in autocrine and paracrine functions. In isolated systems, a chain initiation event generates free radicals, such as alkyl (RO•) and peroxyl (ROO•) radicals. Radical propagation steps repeated many times can lead to chain reactions. However, it is unlikely that free radical chain reactions are propagated in vivo, due to abundant molecular targets, radical scavenging enzymes, and low-molecular-weight antioxidants.

In addition to free radicals, the body generates an array of nonradical oxidizing agents that participate in electron pair oxidations. This group includes hydrogen peroxide (H_2O_2), lipid peroxides (ROOH), hypochlorite, peroxynitrite, quinones, and disulfides. Nonradical oxidants vary in their reactivity, with hypochlorite and peroxynitrate representing potent oxidizers and H_2O_2 a much less reactive, diffusible signaling molecule.

Normal Metabolism Generates Reactive Oxygen Species

Reactive oxygen species (ROS) represent more or less reactive oxidizing agents, whether or not they are free radicals. They include NO, $O_2•^-$, and H_2O_2. Reactive nitrogen species (RNS) include peroxynitrite and its reaction products, such as NO_2. Multiple cellular processes yield ROS.

Oxidases

Nicotine adenine disphosphonucleotide, reduced (NADPH) oxidase is the only enzyme that exclusively produces superoxide; therefore, it is carefully regulated. Peroxisomes oxidize fatty acids while producing ROS. Xanthine oxidase oxidizes purines from DNA, RNA, and adenosine triphosphate (ATP). Microsomal mixed function oxidases (cytochrome P450) generate ROS in the detoxification of metabolites and xenobiotics. Drugs that cause peroxisome proliferation, such as clofibrate, can stimulate the production of H_2O_2 by this mechanism.

Cyclooxygenase and Lipoxygenase

Inflammation activates the arachidonic acid cascade, which converts arachidonate to eicosanoids that mediate inflammation and activate NADPH oxidase to increase production of ROS.[1]

Redox Cycling

Several xenobiotics, such as paraquat and alloxan, catalyze the formation of superoxide through cyclic reactions, promoting auto-oxidation.

Reactive Oxygen Species Generated Directly from Oxygen

In the presence of reduced iron or copper ions, oxygen can produce H_2O_2 and hydroxyl radicals. Oxygen can also react spontaneously with heme proteins such as myoglobin, hemoglobin, and cytochrome c to generate superoxide. Excessive iron and iron overload may cause hydroxyl radical production. Consequently, release of iron from storage sites during inflammation and injury may promote the spontaneous production of free radicals.[2]

Oxidative Stress

The term oxidative stress refers to a shift in the ratio of reducing agents and/or oxidants and its consequences in the body. Oxidative stress occurs when oxidants outweigh the various antioxidant systems as a result of excessive ROS production and/or limited antioxidant defenses. After discoveries that low-molecular-weight oxidants often serve as second messengers, an expanded definition of oxidative stress now includes dysfunctional redox signaling and imbalanced regulatory mechanisms. During oxidative stress, endogenous defenses may be consumed, or they may not be replenished by recycling. Decreased dietary intake of antioxidant nutrients or malabsorption syndromes can reduce antioxidant defenses and create chronic imbalances.

The Free Radical Theory of Aging

According to this seminal proposal, free radicals from normal metabolism or external sources gradually overcome antioxidant mechanisms, leading to cumulative oxidative damage to essential cellular elements: proteins, DNA, and lipids.[3] Accordingly, increased prevalence of chronic degenerative diseases can be viewed in terms of irreversible cellular deficits. The consequences of oxidative stress are often subtle: increased membrane fluidity and damage to membrane receptor proteins may alter cellular regulatory mechanisms such as signal transduction, inactivation of proteins required for ATP production, or calcium homeostasis. The more or less continuous production of ROS by activated phagocytes during chronic, possibly low-level, inflammation may eventually deplete antioxidant defenses, allowing ROS to attack cells with ensuing tissue injury.

More than 100 conditions provide circumstantial evidence linking oxidative damage to disease processes, although correlation cannot distinguish cause or consequence. This list includes several forms of cancer,[4,5] atherosclerosis,[6,7] hypertension, diabetes mellitus,[8] cataracts,[9] inflammation and autoimmune disease,[10,11] lung disease,[12] neurologic disorders including Alzheimer's disease and Parkinson's diease,[13,14] hepatitis,[15] obesity,[16] fibromyalgia and chronic fatigue syndrome,[17] in addition to cell death[18] and attributes of aging.[19,20] Psychological stress and responses to social stressors can affect antioxidant enzymes.[21]

Mitochondrial Deterioration

Mitochondrial deterioration poses a test of the free radical theory. An estimated 3% of oxygen molecules passing through mitochondria is converted superoxide, due to leakage of the electron transport chain.[22] Mitochondria also produce H_2O_2 and lipid peroxides, which can damage highly susceptible mitochondrial DNA and alter mitochondrial membrane permeability to release apoptogenic substances such as cytochrome c. Paradoxically, mice lacking the mitochondrial defensive enzyme, manganese superoxide dismutase (MnSOD), have increased pathology and increased DNA damage, yet life span is unchanged.[23]

Hydroxyl Radicals and Peroxynitrite

Hydroxyl Radicals from H_2O_2 and Superoxide. H_2O_2 is not very reactive; however, it spontaneously forms hydroxyl radicals in the presence of iron and copper ions. Superoxide is not highly reactive, either, and usually superoxide concentrations in the cytoplasm and mitochondria are held in check by superoxide dismutases (SODs), which yield H_2O_2. Superoxide also rapidly forms hydroxyl radicals in the presence of transition metal ions. Because hydroxyl radicals are such powerful oxidants, they probably diffuse only several angstroms before attacking cell constituents and forming characteristic decomposition products of lipids, proteins, and DNA.

Peroxynitrite from Superoxide and Nitric Oxide. High, sustained levels of NO and superoxide are associated with tissue toxicity, cancer, and inflammatory conditions, such as arthritis, juvenile diabetes, and ulcerative colitis.[24] Oxidative stress can result from increased production of superoxide, which reacts spontaneously with NO to produce peroxynitrite ($ONOO^-$). Excessive superoxide can come from upregulated xanthine oxidase or cytochrome P450. ROS uncouple nitric oxide synthase (NOS) to produce superoxide, not NO. Thus, exposure of human endothelial cells to lysophosphatidylcholine leads to downregulation of endothelial NOS and SOD, resulting in a superoxide overload.[25,26] Under inflammatory conditions, simultaneous production of superoxide and NO can increase 1000-fold, and production of peroxynitrite can increase by a million-fold.[27]

Reactive Oxygen Species: Function as Broad-Spectrum Antibiotics

Infection, toxic exposure, ischemia, and trauma activate phagocytic cells—macrophages, monocytes, neutrophils, and eosinophils to create ROS.[28] The binding of immune complexes, bacterial endotoxins, or other inflammatory agents to cell surface receptors triggers a respiratory burst, a localized production of ROS able to oxidize viruses and bacteria. Excessive superoxide from NADPH oxidase undergoes dismutation to H_2O_2 via SOD. Myeloperoxidase in lysosomes then converts H_2O_2 and the chloride ion to hypochlorite, which spontaneously produces highly reactive chloramines from amines.

Oxidative Stress and Cell Signaling Cascades

Physiologic levels of ROS influence cell regulatory processes as diverse as apoptosis, cell growth, and chemotaxis.[29,30] Many signal cascades are sensitive to redox balance and can be modulated by ROS and antioxidants. Essential to these pathways are multiple protein kinases, whose phosphorylation products are often other kinases or kinase inhibitors. Related protein phosphatases reverse those effects.

Transcriptions Factors. Nuclear factor-κB (NF-κB) and activating protein-1 (AP-1) help regulate inflammation and the response to oxidative stress. The factors bind to antioxidant response elements (AREs) in the promoter regions to induce transcription of inflammatory cytokines and adhesion molecules.

Nuclear Factor-κB. Proinflammatory cytokines and lipopolysaccharide (LPS) promote NF-κB activation. NF-κB upregulation may contribute to chronic oxidative stress and diseases, such as rheumatoid arthritis, hypertension, and even overweightness and obesity.[31] In contrast, transcription factors can boost defenses against ROS, depending upon which signaling cascade is activated, to increase transcription of glutathione-S transferase (GSH S-transferase), metallothionein-1, and manganese-dependent SOD.

Nuclear Factor Erythroid Related Factor 2. Nuclear factor erythroid related factor acts as a master redox switch to activate cell-protective proteins and detoxifying enzymes, which include NADPH:quinone

reductase, glutamate cysteine ligase, GSH S-transferase, GSH peroxidase (GPx), and thioredoxin. Release from its inactive cytoplasmic complex is redox-dependent.[32]

AP-1. This transcription factor controls additional processes impacting cell proliferation and apoptosis suppression, including cyclooxygenase-2 (COX-2) expression. As an example of AP-1 activation, epidermal growth factor and platelet-derived growth factor bind to their receptors, activating phosphatidylinositol kinase, followed by Rac (guanosine triphosphatase [GTPase]) activation, in turn stimulating NADPH oxidase to produce superoxide.[33]

Protein Kinases and Protein Phosphatases. The kinase family includes the protein kinase C (PKC) group, which includes serine/threonine kinases that are dependent on calcium and phospholipids; the mitogen-activated protein kinase (MAPK) family (extracellular signal-regulated kinases, Jun N-terminal kinase [JNK], and p38 kinases); and tyrosine protein kinases. Related phosphatases reverse their actions. Members of these broad families can participate in post-transcriptional control due to their redox-sensitive cysteinyl domains.[34] As an example, vasocontraction occurs when angiotensin II binds to its receptor and activates PKC, in turn activating NADPH oxidase to produce superoxide, which destroys NO. As another example, H_2O_2 from SOD can oxidize catalytic cysteinyl moieties of tyrosine phosphatases, thereby preventing inactivation of tyrosine kinases, including Src, to stimulate AP-1.[33]

Proinflammatory Cytokines. Transcription factors can be activated by inflammatory cytokines, such as tumor necrosis factor-α (TNF-α). Inhibition of NF-κB and AP-1 activation block transcription of proinflammatory cytokines, including interleukin (IL)-1β, IL-2, IL-4, IL-6, and TNF-α.

Inflammatory Eicosanoids. The arachidonate cascade features proinflammatory hydroperoxides and endoperoxide eicosanoids: prostaglandins such as PGG_2, PGH_2, and PGE_2 (via COX); leukotrienes; and hydroxyeicosatetraenoic acid (via lipoxygenase). COX-2 can be induced by superoxide, H_2O_2, and inflammatory cytokines such as IL-1 and TNF-α. Stimulated lipoxygenase can trigger ROS production through sequential activation of GTPase (Rac), PKC, phosphorylation of the NOx subunit of NADPH oxidase, leading to activation of plasma membrane NADPH oxidase and ultimately superoxide synthesis.[35]

Calcium Homeostasis. Transcription factors may be regulated through calcium signaling mechanisms, and H_2O_2 can stimulate calcium release from mitochondria.[33] H_2O_2 can increase L-type calcium channels and calcium influx by vascular smooth muscle cells linked to hypertension.[36]

Apoptosis and Cell Cycle Regulation. Programmed cell death is regulated by complex pathways involving transcription factors; therefore, it too relies on the cellular redox balance. Oxidative stress triggers apoptosis in several model systems, and apoptosis may be regulated by antioxidants.[37,38] Conditions ranging from diabetes mellitus and heart failure to HIV infection may entail altered apoptosis.[39]

Regulation of Xenobiotic, Phytochemical, and Carcinogen Metabolism. ROS modulate components of the cytochrome P450 system to activate potential carcinogens. Phase II detoxification enzymes (sulfotransferases, quinone reductase, GSH S-transferase, uridine diphosphate glucuronyl transferase) can block carcinogenic effects and modulate detoxification.[40]

Specific Reactive Oxygen Species as Secondary Messengers for Signaling Cascades

Nitric Oxide. NO is synthesized by NOS, and physiologic NO levels regulate multiple processes; thus, NO produced by the endothelial isoform (eNOS) regulates vasodilation. In contrast, large amounts of NO are produced during inflammation by phagocytic cells by an inducible isoform (iNOS) in response to proinflammatory cytokines.[41] NO is involved in S-nitrosylation of proteins by reacting with cysteinyl residues to form S-nitrothiols, which possess vasodilation activity and resist superoxide in plasma. As an example, ROS such as H_2O_2 can inhibit protein tyrosine phosphatase and its downstream actions via activation of NOS, with increased NO production and reversible active site cysteinyl S-nitrosylation.[42] High levels of NO induce apoptosis by stimulating release of cytochrome c from mitochondria, activating the AKDK1, cyclic dependent kinase 1 (CDK1) and JNK pathway, leading to active caspases that trigger cell death.[43]

Hydrogen Peroxide. The primary source of H_2O_2 is superoxide, constitutively produced by mitochondria and NADPH oxidases. To control H_2O_2, catalase and peroxidases specifically degrade H_2O_2, whereas SOD limits superoxide to curtail H_2O_2 accumulation. A high steady-state level of H_2O_2, associated with inflammation, increases production of NF-κB and AP-1. In post-transcriptional mechanisms, H_2O_2 oxidizes cysteinyl moieties in redox switching enzymes. This process activates tyrosine kinases and inhibits related phosphatases,[44] leading to nuclear factor translocation and increased expression of adhesion molecules, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), to promote neutrophil binding. ROS, like H_2O_2, can oxidize GSH peroxidase, peroxiredoxins (Prx), and inactive transcription factors directly by the formation of protein disulfides or sulfenic acid derivatives.[45]

Regulatory Roles for Superoxide and Peroxynitrite

The importance of superoxide in regulatory cascade mechanisms is restricted by its short half life and limited diffusion. Studies with SOD inhibitors suggest that superoxide may mediate sympathetic excitation in rabbit brain and regulate cardiovascular responses to stress.[46] Some authors propose that peroxynitrite participates in control mechanisms.[47] At low concentration in vitro, peroxynitrite may modulate signaling pathways by nitrating tyrosine residues in target enzymes, such as tyrosine kinases. The inhibition of phosphotyrosine-dependent signaling to block cell adhesion molecule production suggests a role in modulating signal transduction. Furthermore, peroxynitrite can promote tyrosine phosphorylation (activation) in various cell types, for example, by activating MAPKs or by inhibiting phosphotyrosine phosphatases. This upregulation can be transient and reversible, and achievable at relatively low peroxynitrite concentrations in vitro.[48]

Laboratory Assessment of Oxidative Stress

Currently used methods measure a small fraction of potential oxidation products, given the wide range of ROS and possible cell targets. These markers include urinary and/or plasma products of lipid peroxidation, such as F_2 isoprostanes,[49] and aldehydes, such as malondialdehyde from lipid fragmentation; products of protein degradation as protein carbonyls and nitrosylated adducts; and products of purine oxidation, such as 8-oxo-2-deoxyguanosine.[19,50,51] Inflammation and oxidative stress are related mechanistically. The C-reactive protein serves as a marker for systemic inflammation, as well as liver dysfunction,[52] and can be reduced by antioxidant supplementation.[53] Gamma-glutamyltransferase (γ-glutamyltranspeptidase [GTT]) is linked to the redox state and to GSH/ oxidized GSH (GSSH) balance, therefore it promotes GSH production. GTT may be useful in assessing oxidative stress associated with type 2 diabetes, the

metabolic syndrome,[54] and Alzheimer's disease,[55] in addition to coronary heart disease and stroke.[56] The ferric ion reducing ability (FRAP) assay has been used to correlate serum total antioxidant capacity (TAC) with metabolic risk factors. Ingestion of foods with high TAC values reduced markers of systemic inflammation and liver dysfunction.[52,57]

ANTIOXIDANTS

Antioxidants inhibit the oxidation of target molecules by radicals and ROS.[58] There is an apparent "pecking order" among antioxidants; some are more readily oxidized than others and will be consumed rapidly unless replenished or recycled.[59] Certain antioxidants are preventive inhibitors that block the initiation of free radical attack. Preventive inhibitors include defensive enzymes such as catalase, SOD, and peroxidases (GPx), as well low-molecular-weight compounds, including reduced GSH. Beta-carotene, chelating agents such as organic acids, and plant polyphenols represent preventive antioxidants when they quench singlet oxygen or sequester metal ion catalysts. Antioxidants can function as chain breakers, which convert free radicals to stable products and thus block free radical chain reactions. Vitamin E and ascorbic acid are chain-breaking antioxidants.

Laboratory Assessment of Antioxidant Activity

Studies of ROS and radical quenching by antioxidants frequently employ single time points (end-point assays). A more reliable approach evaluates the IC_{50}, the concentration of antioxidant yielding 50% inhibition of a given oxidant or radical. It also is important to compare antioxidant activities in several assay systems. Studies showed that procyanidolic oligomers (PCOs) found in numerous foods and used in supplements (e.g., pine bark and grape seed extract) effectively quench diphenyl picrylhydrazyl radicals.[60] Galloyl catechins were shown to be more effective than simple catechins in inhibition of NADPH-dependent lipid peroxidation of rat liver microsomes.[61]

The oxygen radical absorbance capacity (ORAC) is often used to compare antioxidant activity of foods and complex mixtures. This assay measures the decay in fluorescence (possibly from peroxyl radicals), and results are expressed as "trolox equivalents."[62] ORAC values for foods have been published by the U.S. Food and Drug Administration (FDA).[63] In addition the FRAP assay is sometimes used. This method assesses ferric to ferrous reduction to evaluate TAC. The TAC content of more than 3000 foods and supplements has been published.[64] To establish cell functionality, preliminary studies explored the feasibility of measuring antioxidant protection of erythrocytes and chemoattractant activity of polymorphs after oral supplementation.[65] Cellular antioxidant activity (CAA), as measured by the ability to quench peroxyl radical-induced fluorescence of a fluorescein probe in cultured hepatoma cells, was developed to account for update and metabolism of antioxidants.[66] It is worth noting that CAA values of flavonoids do not correlate with ORAC values.

Enzymes as Antioxidants

Superoxide Dismutase: Antioxidant Role for Manganese, Copper, and Zinc

SODs rapidly convert superoxide to H_2O_2. The mitochondrial enzyme (SOD2) requires manganese, whereas the cytoplasmic (SOD1) and extracellular (SOD3) enzymes require both copper and zinc. SOD2 is induced during acute inflammation,[67] whereas SOD3 in vessel walls plays a major role in regulating vascular ROS.[68] Knockout mice lacking SOD2 die several days after birth due to massive oxidative damage. Mice lacking SOD1 develop ROS-related pathologies with reduced lifespan. SOD may be effective in treating experimental ulcerative colitis.[69] High risk, premature infants treated with prophylactic recombinant human SOD1 had reduced early pulmonary injury at 1 year.[70] Preliminary evidence suggests that SOD can reduce free radical damage to skin after radiation treatment for breast cancer.[71]

Several lines of evidence suggest an involvement of SOD in neurologic abnormalities. Mutations in the SOD1 gene account for 20% of patients with a familial dominant form of amyotrophic lateral sclerosis, although the mechanism is unknown.[72] Overexpression of SOD2 in a mouse model of Alzheimer's disease was shown to reduce brain superoxide and prevent memory losses.[73]

Catalase

This iron-dependent enzyme converts H_2O_2 to diatomic oxygen extremely efficiently. It occurs widely in cells and is a component of peroxisomes. Animal studies with catalase, usually in conjunction with SOD, suggest protection against ischemic injury to the lung,[74] intestinal ROS damage,[75] and radiation.[76] Examination of human atherosclerotic coronary arteries revealed that vascular antioxidant enzymes, including catalase, were selectively elevated in smooth muscle cells and macrophages in atherosclerotic lesions.[77] In contrast, knockout mice lacking catalase were phenotypically normal, possibly due to effective scavenging by peroxidases.[78]

The Peroxidase Family

Glutathione Peroxidases: Antioxidant Role for Selenium. GPxs reduce H_2O_2 as well as lipid peroxides in the presence of reduced GSH. Unlike catalase and SOD, GPxs require selenocysteine. GPxs exist as several isoforms. GPx1 is a cytoplasmic isoform that prefers H_2O_2 as a substrate. GPx4 has a high affinity for lipid hydroperoxides, reducing membrane lipid peroxides to nontoxic fatty acid alcohols.[79] Antioxidant enzymes, including extracellular GSH peroxidase, are induced by oxidative stress associated with lung diseases.[80] Mice lacking GPx1 have a normal life span; however, they develop early cataracts. In contrast, GPx4 knockout mice do not survive early embryonic development.[81] Curiously, reduced levels of GPx4 may increase the mouse life span.[82]

Peroxiredoxin. This group of six thiol peroxidases reduces H_2O_2, lipid peroxide, and peroxynitrite via an active site cysteinyl, –SH. The PrxII isoform is one of the most abundant proteins in erythrocytes. Prxs control intracellular levels of H_2O_2 to regulate cell signaling in various cell types. Mice lacking PrxI or PrxII develop severe hemolytic anemia and are prone to cancer due to elevated H_2O_2. Prx1 knockout mice exhibit atherosclerotic lesions due to endothelial cell dysfunction.[83] NO may protect macrophages against oxidative and nitrosative stress by inducing Prx.[84]

Storage and Transport Proteins

Ferritin, Transferrin, and Ceruloplasmin. Free iron and copper ions catalyze the conversion of H_2O_2 to hydroxyl radicals; therefore, proteins that bind these ions help protect tissues against ROS. Iron stored in ferritin does not participate in generation of free radicals. Under normal circumstances, little unbound iron is present in cells. However, with chronic inflammation, unbound iron may be released from ferritin, posing a potential hazard. Iron storage disease is linked to oxidative damage. Transferrin (which has a high affinity for iron) and ceruloplasmin (which binds copper) can be considered part of the antioxidant defenses.[85]

Metallothionein. This cysteine-rich protein binds many metals. It is induced by cytokines, toxic metals, and oxidative stress. Mitochondrial-specific ROS generators can increase the production of metallothionein in the liver by 3.7- to 11.8-fold in mice, far more than SOD or GSH peroxidase.[86] Similarly acute ethanol-induced hepatotoxicity and associated oxidative stress were curtailed in mice that had been genetically manipulated to overexpress metallothionein, compared with wild-type mice.[87]

Selenoprotein P. Nearly 60% of plasma selenium is represented by selenoprotein P, which transports selenium to tissues. In vitro, selenoprotein P protects against peroxynitrite-induced damage and reduces phospholipid hydroperoxides.[88]

Redox Regulation: The Glutathione System

Glutathione. This sulfhydryl-reducing agent is a tripeptide containing cysteine that occurs in millimolar concentrations in most cells, where it acts as a detoxifying agent, assists amino acid transport, and quenches free radicals, in addition to regulating the internal redox environment of cells. Together with ascorbate, GSH participates in the regeneration of vitamin E, which emphasizes the cooperation of antioxidants. Reduced GSH reacts directly with singlet oxygen, hydroxyl radicals, and superoxide radicals to form oxidized glutathione (GSSG). With aging, there is a general decline in GSH levels, and low GSH levels are associated with a variety of chronic conditions, such as diabetes, age-related macular degeneration, gastrointestinal disorders, and neurodegenerative diseases.[89]

GSH reductase reduces GSSG with NADPH, linking thiol regulation to a robust glucose metabolism. GSH reductase helps maintain a high GSH/GSSG ratio. Oxidative stress reduces this ratio, activates transcription factors, and increases production of IL-1 and TNF.[90] NADPH and GSH are cofactors for other reductases that help regenerate tocopherol and ascorbate, demonstrating the principle that overall metabolic balance is a prerequisite for adequate antioxidant defense.

GSH S-transferase adds GSH to potentially toxic substances and is considered a component of phase II detoxification enzymes, although it also functions in the synthesis of prostaglandins and leukotrienes. Like GSH peroxidases and Prxs, GSH S-transferase requires an ample supply of reduced GSH.

Redox Regulation: The Thioredoxin System: Antioxidant Role for Selenium

Thioredoxin (TRX) is a small sulfhydryl protein that acts as a reducing agent for Prxs and ribonucleotide reductase, and TRX also promotes the activation of several transcription factors.[91] TRX reductase is a selenocysteine-containing enzyme that specifically catalyzes the reduction of TRX. Together, TRX and TRX reductase represent a widespread endogenous redox-regulating system with multiple roles in intracellular signaling and resistance to oxidative stress. Thus, thioredoxin activates apoptosis signal-regulating kinase-1. It reduces redox factor-1 (REF-1), which then reduces oxidized (inactive) transcription factors such as NF-κB and Nref-2. Apurinic/apyrimidinic endonuclease 1 (APE-1), a dual functional DNA repair enzyme that can also reduce transcription factors (such as AP-1 and p53) is regenerated by thioredoxin, linking DNA repair to cellular redox balance.[92]

Antioxidant Enzymes in Response to Oxidative Stress

Antioxidant enzyme levels tend to decrease with age-related conditions.[93,94] In contrast, several antioxidant enzymes are often induced during oxidative stress. In human atherosclerotic coronary arteries, catalase, GSH peroxidase, and SOD were upregulated in atherosclerotic lesions, possibly as the result of oxidative stress.[77] These enzymes are part of a battery of proteins regulated by defensive genes. Nuclear transcription factors such as Nfr2 can be regarded as a cell-sensing system for oxidative and electrophilic stress, which is responsive within 15 minutes after exposure to a stressor.[95] Transactivation of AREs is regulated by redox balance, in which nuclear factor Nrf2 migrates to the nucleus in response to ROS, where it activates genes responsible for a battery of antioxidant enzymes, including Prx-6, GPx, GSH transferase, TRX, as well as phase II detoxifying enzymes.[32]

Micronutrients as Antioxidants

Vitamin C

Ascorbic acid can react with a wide range of ROS, including superoxide, singlet oxygen, hypochlorite, and sulfur radicals.[96] Ascorbic acid is an efficient chain-breaking antioxidant in human plasma,[97] where it protects lipids and membranes by scavenging peroxyl and hydroxyl radicals.[98] The recommended dietary allowance (90 mg for men >19 years old; 75 mg for women >19 years old) is probably an underestimate. Healthy young women may require at least 400 mg/day of ascorbic acid according to tissue saturation studies.[99] Vitamin C can reduce heavy metal toxicity.[100] Dehydroascorbate is reduced back to ascorbate via GSH and NADPH. In animal models, high levels of ascorbate compensated for low GSH production and vice versa. A combination of ascorbate with vitamin E is possibly more effective than ascorbate alone for older adults.[101] Ascorbic acid functions with GSH and lipoic acid to regenerate α-tocopherol.

Cardiovascular Disease. Observational studies suggest that ascorbic acid has, at best, modest effects on the risk of coronary heart disease. Although a meta-analysis found no benefit with vitamin C supplementation on survival and cardiovascular disease (CVD) risk,[102] others reported benefits with high supplemental vitamin C.[103] The Nurses' Health Study suggested that vitamin C intake of more than 359 mg/day (diet plus supplements) reduced the risk of CVD.[104] For diabetic postmenopausal women, high vitamin C supplementation correlated with an increased risk of CVD mortality.[105] The Physicians' II study found that vitamin C supplementation at 500 mg/day was not cardioprotective for middle-aged men.[106]

Hypertension. In young healthy women, a higher level of plasma vitamin C was associated with decreased blood pressure.[107] A randomized controlled study of hypertensives supplemented with ascorbic acid 500 mg/day found a significant reduction of blood pressure only during the first month of treatment, suggesting a short-term benefit.[108]

Cancer. High ascorbic acid intake has been linked to a reduced risk of cancers of the oral cavity and esophagus,[109] ovaries,[110] stomach,[111] and colon. However, pooled analysis of eight prospective studies found vitamin C intake unrelated to lung cancer.[112] Treatment of male physicians aged equal to or more than 50 years with 500 mg ascorbic acid daily for 8 years found no reduced risk of prostate cancer or total cancer.[113] Several studies suggested that extracellular ascorbate at millimolar concentrations (achieved via intravenous or intraperitoneal administration) acted as an antitumor agent in animals and humans via a pro-oxidant mechanism. A plausible mechanism involves ascorbate reduction of transition metals (cupric to cuprous, ferric to ferrous), which react with oxygen, yielding superoxide and H_2O_2, to which tumor cells are susceptible.[114]

Neurodegeneration. The Rotterdam Study suggested a high intake of ascorbic acid and vitamin E was associated with a reduced

risk of Alzheimer's disease, especially among cigarette smokers.[115] Although ascorbate in plasma or cerebrospinal fluid of 32 patients with Alzheimer's disease did not correlate with cognitive decline over 1 year, the ratio of cerebrospinal fluid ascorbate/plasma ascorbate increased, which was possibly related to an impaired ability of the brain to concentrate neuroprotective nutrients.[116]

Cataract. Although some investigations reported the risk of cataracts and retinal damage with lowered vitamin C status, a prospective study employing 500 mg of vitamin C, 400 IU of vitamin E, and 15 mg of β-carotene found no effect on the development or progression of cataracts.[117]

Diabetes. A 12-year prospective study of nondiabetic participants in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk Study noted those with the highest 20% of plasma vitamin C had a 62% lower risk of developing type 2 diabetes compared with those in the lowest 20%.[118]

Vitamin C: A Cell Response Modifier? Vitamin C was able to increase the efficiency of generating mouse and human pluripotent stem cells from somatic cells, in part by attenuating cell senescence.[119] In other research, expression of five functional protein groups related to signaling, apoptosis, and activated transcription, among others, was detected in vitamin C–treated T cells.[120] Generally, vitamin C appears to function primarily as an antioxidant in modulating redox balance in a variety of situations, such as attenuating cytochrome P450 detoxification or plasma C-reactive protein levels.

Vitamin E (Tocopherols)

Vitamin E refers to four tocopherols (α, β, γ, δ) and tocotrienols (α, β, γ, δ) that possess an unsaturated isoprenoid side chain. Vitamin E represents a primary chain-breaking antioxidant of lipids, lipoproteins, and membranes, where it acts as a peroxyl radical scavenger, creating a tocopheryl radical. This radical will decompose unless converted back to tocopherol by ascorbic acid, GSH, and coenzyme Q_{10} (CoQ_{10}), illustrating that antioxidant defenses complement one another.[97,121] Vitamin E can exacerbate hypertension in susceptible people. High levels may antagonize other fat-soluble vitamins, thus decreasing bone mineralization. This vitamin may be contraindicated in patients receiving anticoagulants or in those with a vitamin K deficiency.

Vitamin E supplements often incorporate synthetic α-tocopherol, a mixture of D and L isomers, but only the D form (RRR-α-tocopherol) is active in the body. Esterified α-tocopherol is considerably more stable than unesterified tocopherol, and supplements often use esters of vitamin E, which are readily hydrolyzed and absorbed. As with other fat-soluble vitamins, supplementation is prudent in patients with malabsorption syndromes.

Immunity. Supplementing healthy elderly people (consuming an otherwise typical diet) with 60 to 800 mg vitamin E improved several aspects of cell-mediated immunity within 6 to 12 months.[122] In other research, ingestion of 268 mg/day of natural vitamin E for 8 months significantly reduced serum immunoglobulin-E, with apparent normalization of most lesions in patients with atopic dermatitis.[123]

Cardiovascular Disease. Hypothetically, the oxidation of low-density lipoprotein (LDL) and other lipoproteins can initiate atherosclerosis. Increasing dietary vitamin E intake to more than 20 times the usual intake in a Western-type diet was suggested to reduce the risk of heart disease and its manifestations, such as myocardial infarction, among low-risk populations.[124] However, randomized, placebo-controlled clinical trials with α-tocopherol (200 to 800 IU/day) in Western populations have been mainly negative.[125]

Only 5 of 12 clinical studies on vitamin antioxidants and CVD reported reduced cardiovascular death and nonfatal myocardial infarction. These include the Cambridge Heart and Antioxidant Study (CHAOS), the Womens' Health Study (reduced risk of sudden death from CVD), and the Secondary Prevention with Antioxidants of CVD in End Stage Renal Disease (SPACE) study of hemodialysis patients, who were at high risk of oxidative stress. Inconsistent results with vitamin E may reflect compounding variables including the heterogeneity of risk factors for coronary heart disease, treatment for late course of disease versus treatment for early-onset oxidative stress,[126] and genotypic differences among subgroups, for example, the haptoglobin 2-2 genotype in type 2 diabetic patients.[127] More generally, it is unrealistic to expect that dosing with one or two antioxidants can substitute for multiple synergistic factors that support interlocking regulatory pathways in reducing risks of chronic degenerative disease.

Neurodegenerative Disease. A high intake of vitamin E and vitamin C was found to be associated with a reduced risk of Alzheimer's disease according to the Rotterdam study.[115] In a controlled trial of patients with moderately severe Alzheimer's disease, α-tocopherol administered at a daily level of 2000 IU delayed the onset of severe dementia or death in comparison with controls.[128] However, a controlled clinical study of patients with mild cognitive impairment found that treatment with 2000 IU vitamin E failed to slow mental decline.[129]

Cancer. Effects of antioxidant supplementation often depend on the subject's nutritional status. Clinical studies with vitamin E illustrate this principle. The Shanghai Breast Cancer Study observed a 20% reduction in breast cancer risk with vitamin E supplementation among women with low dietary intake.[130] The Linxian General Population Nutrition Intervention Trial, which included adults deficient in several micronutrients, examined the effects of 50 mcg/day of selenium, 30 mg/day of vitamin E, and 15 mg/day of β-carotene. Supplementation led to decreased all-cause mortality, including overall cancer risk.[131] In contrast, U.S. studies of vitamin E on cancer rates reported negative results for breast cancer,[132] endometrial cancer,[133] lung cancer (pooled analysis of eight studies),[134] or cancer incidence and cancer mortality.[135] Although earlier studies suggested an inverse association between vitamin E intake and risk of prostate cancer, the Physician's Health Study II of men aged fifty years or older found no reduction in risk with vitamin E supplementation at 400 IU after eight years.[113] Supplementation of men equal to or greater than fifty-five years with vitamin E 400 IU per day for up to twelve years increased the risk of prostate cancer by 17%. Men who took vitamin E together with selenomethionine (200 mcg per day) had no higher risk than those taking a placebo.[136] Compounding variables in such studies included status of vitamin D, ω-6 fatty acids, and γ-tocopherol, testosterone status in addition to polymorphisms for α-tocopherol–associated protein.[137]

Diabetes. Whether α-tocopherol can benefit diabetes has not been established through well-controlled clinical studies. Treatment of elderly patients with impaired glucose regulation with α-tocopherol 1000 IU and vitamin C 1000 mg/day reduced markers of oxidative stress and inflammation while improving insulin sensitivity.[138]

Gamma-Tocopherol. Although the typical U.S. diet supplies twice as much γ-tocopherol as the α form or tocotrienols, α-tocopherol predominates in the body, due to selection by liver tocopherol-transfer protein. Gamma-tocopherol is also rapidly degraded. It selectively blocks reactive nitrogen species and complements antioxidant actions of α-tocopherol.[139] Gamma-tocopherol can protect pancreatic β-cells against NO inhibition

in vitro.[140] Mice supplementation with a mixture of α- and γ-tocopherol (not α-tocopherol alone) reduced age-related transcriptional changes in the brain.[141] Clinical findings using γ-tocopherol are limited. Patients with metabolic syndrome treated with γ-tocopherol 800 mg and α-tocopherol 800 mg/day for 6 weeks had significantly decreased markers of inflammation and oxidative stress (high-sensitivity C-reactive protein and nitrotyrosine) compared with placebo.[142] The EPIC Study found no correlation between plasma levels of either α- or γ-tocopherol and risk of prostate cancer.[143]

Tocotrienols. Tissue distributions of tocotrienols and tocopherols differ, which is perhaps indicative of selective mechanisms in various tissues.[144] Tocotrienols can induce apopotosis in prostate cancer and breast cancer cells.[145] Tocotrienols can suppress inflammatory markers, such as IL-6, TNF-α, and NO, by stimulated macrophages.[146] Clinical studies are in their infancy. Hypercholesterolemic subjects treated with mixtures of tocotrienols daily for 28 days did not have improved serum lipid or glucose concentrations or lipid peroxidation (urinary 8-iso-prostaglandin F2a).[147] In contrast, treatment of healthy adults with tocotrienols 160 mg/day for 6 months according to a randomized, double-blind protocol resulted in reduced DNA damage.[148]

Vitamin E: A Specific Cellular Response Modifier? Several studies suggest that vitamin E administration can increase expression of genes related to Th1/Th2 ratios in older mice.[149] Alpha-tocopherol can block upregulation of NF-κB, PKC, and p38 MAPK pathways to prevent inflammatory cytokine production in stimulated human monocytes and in human dendritic cells.[150] Variation in cytokine responses to vitamin E in elderly populations seems to reflect polymorphisms in cytokine genes.[151] Nonetheless, such observations reflect the altered redox state of cells and tissues. Because other antioxidants yield similar effects as α-tocopherol, some authors contend that vitamin E protects membrane domains and polyunsaturated fatty acid pathways from ROS as its underlying mechanism of action, rather than involvement in specific signaling actions.[152]

Carotenoids

These plant pigments are conveniently divided into carotenes and xanthophylls (oxygenated carotenes). The best-known carotenoid, β-carotene, represents only 25% to 33% of plasma carotenoids. In general, carotenoids are versatile antioxidants. Beta-carotene is especially effective at low oxygen tension, as found in tissues.[153] Increased carotenoid levels have been associated with decreased LDL oxidation.[154] They can quench ROS produced during inflammation and modulate levels of proinflammatory prostaglandins and leukotrienes.[155,156]

Lung Cancer. Although retrospective studies suggested an inverse correlation, analysis of pooled results from six prospective cohort studies found no relationship between dietary β-carotene and lung cancer risk reduction.[157] A recent systematic review of prospective studies concluded that dietary intake of total carotenoids did not significantly reduce the risk of lung cancer.[158] Supplementation was studied in three large randomized controlled trials (RCTs). The two studies (Alpha-Tocopherol, beta Carotene Cancer Prevention Trial and the beta Carotene and Retinol Efficacy Trial) reported an increased risk of lung cancer in high-risk groups supplemented with β-carotene. In contrast, the Physicians' Health Study (only 11% smokers) found no effect with β-carotene supplements.

Prostate Cancer. A meta-analysis of 11 case–control studies and 10 prospective studies found that the highest intake of lycopene or tomatoes accounted for a 11% to 19% reduction in prostate cancer risk.[159] Dietary lycopene intake was not related to prostate cancer risk in a more recent large prospective study.[143]

Breast Cancer. The inverse relationship between consumption of carotenoid-rich fruits and vegetables for the risk of breast cancer was strongest among premenopausal women.[160] For women who were smokers and did not use supplements, dietary α-carotene and β-carotene intake was inversely associated with the risk of breast cancer.[161] In contrast, the Women's Health Study found no link between lycopene intake and reduced risk of breast cancer.

Cardiovascular Disease. Although several prospective studies found that higher carotenoid-rich foods correlated with reduced risk of CVD, others did not.[103] Four RCTs found no effect of oral β-carotene, ranging from 20 to 50 mg/day, in preventing CVD.

Adult Macular Degeneration. The xanthophylls lutein and zeaxanthin are the only carotenoids in the retina and macula, where they filter blue light. Cross-section and retrospective case–control studies suggested that increased consumption of carotenoids, especially lutein and zeaxanthin, correlated with a lower risk of advanced, age-related macular degeneration.[162] Individuals with intermediate risk of adult macular degeneration (AMD) or with advanced AMD in one eye should consider using a combination of vitamin C, vitamin E, β-carotene, and zinc, as recommended by the Age-Related Eye Disease Study (AREDS). A large scale clinical trial of lutein, zeaxanthin, and ω-3 fatty acids is in progress (AREDS-2).[163]

Carotenoids: Cell Response Modifiers?

Interpretation of effects of β-carotene and other provitamin A carotenoids is complicated by their potential formation of retinoids, which are well-known regulatory species. Although they are effective antioxidants, non-provitamin A carotenoids (lycopene, lutein, canthaxanthin, and astaxanthin) do not present this complication. Much of lycopene's activity relates to its antioxidant actions; however, its metabolites could provide regulatory effects.[164] The non-provitamin A carotenoids may affect cancer cells by increased apoptosis, decreased cell cycle progression, or decreased production of cytokines. Alternatively, lycopene's inhibition of cancer cell proliferation may involve increased gap junction-mediated intercellular communication.[165]

Coenzyme Q_{10} (Ubiquinone)

Ubiquinones contain side chains with isoprene units, and the predominant form in humans is ubiquinone 10 (CoQ_{10}). It functions as an essential electron carrier in mitochondrial ATP production. As the only lipophilic antioxidant synthesized in the body, CoQ_{10} also stabilizes membranes and functions as an important antioxidant that can recycle α-tocopherol.[166] Ubiquinol, the reduced form of CoQ_{10}, protects LDL against lipid peroxidation.[167] CoQ_{10} synthesis requires vitamins B_2, B_6, B_{12}, and folate, and synthesis may not be optimal in people with a low intake of these important vitamins.

Immunity. CoQ_{10} may enhance the immune system. Supplementation of healthy volunteers with CoQ_{10} 3 mg/kg daily for 12 weeks was found to increase white cell levels and decrease lymphocyte DNA damage.[168]

Cardiovascular Disease. In a mouse model for atherosclerosis, large doses of CoQ_{10} reduced plaque formation.[169] In a RCT of patients at risk for CVD, 6 month treatment with a combination of vitamins C and E, CoQ_{10}, and selenium increased arterial elasticity, lowered glycosylated hemoglobin, and increased high-density lipoprotein cholesterol compared with controls.[170] CoQ_{10} has been used with conventional therapy in treatment of congestive heart failure. Studies employing doses ranging 100 to

200 mg/day for up to 3 months reported minor improvements.[171] Drugs such as β-blockers and 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors lower serum levels of CoQ_{10}.[172] However, the necessity of CoQ_{10} supplementation in these situations remains uncertain. A meta-analysis of 12 clinical trials of various protocols suggested a reduction in elevated systolic and diastolic blood pressure among hypertensive patients supplemented with CoQ_{10}.[173] Large, well-controlled trials of CoQ_{10} are needed. Results of a multinational RCT of patients with cardiac failure (New York Heart Association Classes III & IV) receiving standard therapy and 300 mg of CoQ_{10} daily can be expected in the near future.[174]

Thiols as Antioxidants

Alpha-Lipoic Acid

As a coenzyme of pyruvate dehydrogenase and α-ketoglurate dehydrogenase, α-lipoic acid (ALA) is required in mitochondrial catabolism of carbohydrates and fatty acids. ALA also scavenges hydroxyl radicals, peroxynitrite, superoxide, and peroxyl radicals, and it can regenerate endogenous antioxidants, including ascorbic acid and GSH.

Diabetes. Meta-analysis of four RCTs with intravenous ALA indicated significant improvement in diabetic neuropathy.[175] Whether oral ALA supplementation offers benefits is less clear. The highest tissue level likely attainable from oral doses is less than 10% of other intracellular antioxidants such as GSH.[176] Using a rat model of diabetes, investigators showed that month long ALA intraperitoneal treatment worsened energy balance and increased fat accumulation.[177]

Aging. Animal studies suggested that high-dose ALA and/or acetyl-L-carnitine can improve brain function,[178] reduce brain lipid peroxidation, and increase brain antioxidant enzyme activities in the brains of aged rats,[179] especially in the hippocampus.[180] Aged mice supplemented orally with ALA had increased glucose tolerance, energy expenditure, and skeletal muscle mitochondria biogenesis, but also had increased loss of lean body mass.[181] It is not clear that these results can be extrapolated clinically.

Cardiovascular Disease. Feeding high-dose ALA also reduced myocardial oxidant production to levels observed in healthy young rats.[182] ALA supplementation was used in mouse models of ischemia reperfusion and atherosclerosis, where it slowed the formation of atherosclerotic lesions.[183] In a rat model of diabetes, intraperitoneal ALA reduced cardiac apoptosis, caspase expression, and enhanced MnSOD activity and GSH levels.[184]

Obesity. Preliminary data are suggestive. A study of 1127 of obese and pre-obese subjects supplemented for 4 months with ALA 800 mg/day reported significant reduction in weight, blood pressure, body mass index, and abdominal circumference.[185]

Neurologic Disease. Clinical results are preliminary. Patients with varying stages of Alzheimer's disease administered 600 mg/day of ALA for 48 months showed slowed disease progression in patients with mild, not moderate, dementia.[186]

Alpha-Lipoic Acid: A Cell Response Modifier? ALA can induce several phase 2 antioxidant and thiol-protective enzymes, including enzymes needed for GSH synthesis. Old rats treated with ALA intraperitoneally were found to have increased γ-glutamylcysteine ligase (GGL) activity, reflecting induced Nrf2 binding to ARE and increased transcriptional levels of GGL subunits, thus reversing the age-related losses.[187] ALA activated protein kinase B (Akt) to increase survival of cultured neuronal cells exposed to oxidative stress.[188]

N-Acetylcysteine and Glutathione

GSH synthesis is regulated in part by cysteine availability. As a supplement, *N*-acetylcysteine is an effective precursor for GSH. It is deacetylated in the gut to free cysteine, and oral supplementation can efficiently raise intracellular GSH[189] in model systems and in healthy individuals.[190] *N*-acetylcysteine would be expected to play a supportive role to improve GSH status and maintain cell redox balance, counter ROS, and attenuate drug toxicity as a conjugating agent in drug metabolism.[191] Orally administered GSH may increase intestinal GSH levels via a GSH transport system.[192]

Oxidative Stress. Supplementation of healthy, trained men with *N*-acetylcysteine 1800 mg/day for 3 days before exhaustive resistance exercise significantly increased plasma thiols and TAC and reduced lipid peroxidation and protein oxidation.[193] A RCT of hypertensive patients with type 2 diabetes reported that 6 month treatment with *N*-acetylcysteine and arginine significantly reduced systolic blood pressure and lowered levels of oxidized LDL, C-reactive protein, VCAM, and protein oxidation (plasma nitrotyrosine), suggesting improved endothelial function along with reduced oxidative stress.[194]

Minerals and Oxidative Stress

Magnesium

As a cofactor for nearly all ATP-requiring reactions, magnesium is integral to intermediary metabolism. Low magnesium status is linked to inflammation and activation of the systemic stress response. Subclinical magnesium deficiency is common in the United States, and magnesium deficiency is correlated with chronic diseases associated with aging.[195]

In rodents, low magnesium status caused release of substance P, leading to increased circulating inflammatory cells, cytokines, and ROS, with depletion of antioxidants associated with cardiomyopathy.[196] Furthermore, magnesium deficiency promoted senescence in primary human fibroblasts.[197] Experimental magnesium deficiency created systemic inflammation with leukocyte and macrophage activation, inflammatory cytokine release, formation of acute phase proteins, and oxidative stress. Possible mechanisms included opening calcium channels and activation of NF-κB.[198] High fructose intake, for example, from excessive high fructose corn syrup intake, coupled with low magnesium status, could set the stage for oxidative stress, insulin resistance, and metabolic syndrome in susceptible individuals.[199]

Zinc

Beyond its role in SOD, zinc is required by many transcription factors, including tumor suppression protein p53. "Zinc fingers"—domains that bind multiple zinc atoms—stabilize these proteins. In addition to stabilizing membranes, zinc is involved in apoptosis, hormone release, and nerve transmission.[200] Subclinical zinc deficiency manifests as inflammation and oxidative stress, and it often accompanies aging.[201] That zinc deficiency diminishes immune function, especially Th1 activity, is well established. Zinc is essential for IL-2 mediated T-cell activation. The mechanism seems to rely on activation of NF-κB, resulting in increased expression of TNF-α, IL-1B, and IL-8 cytokines.[202] Although a RCT of subjects over 65 years old found that supplementation with zinc 25 mg/day for 3 months increased levels of cytotoxic T cells and CD4 T cells, other clinical studies reported negative results.[203,204]

Metabolites as Secondary Antioxidants

L-Carnitine

This metabolite is synthesized mainly by the liver and kidney, then transported to tissues using fatty acids and carbohydrate as

fuel. Fatty acid transport into mitochondria relies on a carnitine shuttle for β-oxidation. A decline in carnitine correlates with the age-related decline in mitochondrial energy production and increased ROS.[205] After demonstrations that supplementation with acetyl-L-carnitine reversed age-related decline in tissue carnitine level in rats, later experiments showed that animals supplemented with high doses of ALA and acetyl-L-carnitine for 1 month exhibited improved substrate binding of brain carnitine acetyltransferase,[178,206] improved memory,[207] and decreased DNA damage.[208] Whether such improvements with high doses of acetyl-L-carnitine translate into long-term benefits for patients remains to be investigated.

Uric Acid (Urate)

Uric acid is a waste product of a purine metabolism that occurs in high levels in plasma. Urate is a broad-spectrum antioxidant capable of scavenging free radicals, and it can chelate transition metals.[209] Uric acid is responsible for 21% to 34% of the total plasma antioxidant activity, in which it appears to protect α-tocopherol from peroxyl radicals.[210] Also, assays of TAC indicated that 49% of the TAC of human plasma is due to uric acid.[211] Although a ubiquitous antioxidant, elevated urate is not necessarily beneficial.

Does a Bilirubin–Biliverdin Cycle Protect Against Reactive Oxygen Species? Bilirubin bound to albumin can act as an antioxidant in vitro, although the in vivo mechanism is unclear. Earlier cell culture studies suggested a protective role of bilirubin–biliverdin cycling via heme oxygenase and biliverdin reductase. However, more recent data indicated that bilirubin is degraded by ROS, rather than being converted to biliverdin and recycled.[212]

Melatonin: A Hormone with Antioxidant Potential

In addition to helping set the circadian rhythm and sleep patterns, this hormone also acts as an antioxidant in vitro and in vivo.[213] In senescence-accelerated mice, long-term administration of physiologic levels of melatonin corrected hepatic mitochondrial dysfunction, suggesting that melatonin may reduce oxidative damage associated with aging.[214] Melatonin can act by inhibiting the expression of eNOS in laboratory animals.[215] It can also upregulate SOD and catalase in the brain and liver of rats exposed to carcinogens.[216] In an experimental model of diabetes, melatonin was shown to reduce lipid peroxidation and upregulate GSH reductase, GPx, and γ-glutamylcysteine synthetase.[217]

Non-Nutritive Antioxidants

Flavonoids

Flavonoids (bioflavonoids) represent one of the largest classes of polyphenols, and more than 4000 different flavonoids have been identified. Their antioxidant properties, physiologic activities, and bioavailability vary according to major subclasses.[218]

Dietary Patterns. For typical Western diets, the estimated daily consumption of total flavonoids is in the range of 100 to 200 mg,[219] although intake reflects cultural and even regional preferences. As examples, simple phenolic acids (caffeic acid, ferulic acid, gallic acid, and coumaric acids) accounted for 75% of total phenolic intake among Finnish adults, whereas flavonoids accounted for 24% of the total.[220] In an adult Spanish population, the mean intake of total flavonoids was shown to be 313 mg/day, with proanthocyanidins accounting for 60% of the total.[221]

Flavonoid Bioavailability/Biotransformation. The uptake of individual flavonoids is generally quite limited. Most flavonoids have very low water solubility. Phosphatidylcholine complexes of poorly soluble flavonoids may improve uptake.[222] Absorbed aglycone flavonoids are rapidly conjugated (sulfates, glucuronides) or methyated by intestinal and liver systems, then excreted. Such flavonoid derivatives may have different biological effects than parent compounds. Additionally, gut bacteria can degrade polyphenols by ring session, and absorbed monophenols may act differently than parent compounds. Enterohepatic and enteric recycling of flavonoid metabolites is another complication.[223] Analysis of plasma and urine of healthy volunteers 2 hours after ingesting 200 mg quercetin or green flavonoids failed to detect increases in any of the 71 aromatic metabolites observable at 5 hours after ingestion, suggesting that flavonoid metabolites are not responsible for the rapid responses to ingested flavonoid-rich foods or beverages.[224]

Are Flavonoids Important Antioxidants In Vivo? In vitro, various flavonoids scavenge a variety of radicals[225,226] and block LDL oxidation.[227] As chelators, flavonoids can inhibit spontaneous generation of hydroxyl radicals[228] catalyzed by copper and iron ions. Although data are conflicting, it appears that flavonoids and their derivatives probably make small contributions as direct antioxidants in vivo.[229] The observed increased antioxidant capacity in plasma after ingestion of fruits, fruit juice, and flavonoid-rich foods may be due to increased production of the antioxidant uric acid, rather than due to flavonoids.[230,231] Peak plasma concentrations of flavonoids and their metabolites after acute ingestion are often less than 1 μmol/L, several orders of magnitude lower than plasma or intracellular concentrations of ascorbic acid, uric acid, and GSH.

Flavonoids in Cancer Prevention

Evidence for a relationship between flavonoids and cancer incidence is conflicting. Among healthy postmenopausal women, there was an inverse association between the incidence of lung cancer intake of flavanones and proanthocyanidins for current or past smokers[232]; the highest intake of quercetin had a lower incidence of lung cancer, and those with the highest intake of myricetin had a reduced risk of prostate cancer. In contrast, among elderly Dutchmen, dietary catechins mainly from tea were not associated with a reduced risk of lung cancer or epithelial cancers.[233] In earlier studies flavonoid consumption was not associated with reduced cancer risk in this population[234] although it was inversely related to mortality due to CHD.[235]

Soy. Soy isoflavones can suppress tumors in animal models. Genistein can induce apoptosis via downregulation of Bcl-2 and Bcl-XL, antiapoptotic proteins in human hepatoma cell lines,[236] as well as in breast, prostate, pancreatic, and non-small lung cancer cells. Genistein also inhibits activation of NF-κB and Akt signaling pathways that normally balance cell survival and apoptosis.[237] A recent meta-analysis suggested a significant association between consumption of soy-based foods and reduction of the risk of prostate cancer.[238] Epidemiologic studies on the relationship between a reduced risk of breast cancer and soy intake have yet to provide definitive evidence for taking soy supplements. RCTs are in progress.

Tea. Green tea contains epigallocatechin, epigallocatechin-3 gallate (EGCG), and epicatechin-3 gallate. These flavonoids may block signal transduction pathways and induce apoptosis in various tumor cells, including skin, prostate, colon, breast, and lung.[239] EGCG blocked the growth of human cervical cancer cells via cell cycle arrest and induced apoptosis.[240] It did so by inhibiting tyrosine kinases, thus blocking MAPK signaling pathways and NF-κB and AP-1.[241] Green tea catechins can limit DNA oxidation, lipid peroxidation, and free radical production in smokers.[242]

Analysis of nearly 200 epidemiologic studies examined associations between green tea consumption and risks of cancer at different sites and found that the majority of reports did not show a preventive effect. Inhibition with green tea consumption was more frequent among Asian populations according to case–control studies.[239,243] Tea consumption may help specific subgroups, rather than a general population, such as lowering the risk of breast cancer only among women with low catechol-*O*-methyl transferase.[244] Intervention studies are a more effective way to establish protective effects of tea on cancer risk. In a double-blind study, patients at risk for prostate cancer treated with green tea catechins 600 mg/day for 1 year had a cancer rate of 3% compared with a 30% rate for the placebo group.[245] A prospective study of patients after resection for colon cancer or polypectomy employed a daily dose of EGCG 20 mg and apigenin 20 mg for up to 4 years. The recurrence rate of neoplasia was 7% for treated patients versus 47% for untreated patients.[246]

Flavonoids in Cardiovascular Protection

Whether increased consumption of flavonoid-rich foods can reduce the risk of CVD is not clear. For example, a study of postmenopausal American women found significant reductions in the risk of CVD and all-cause mortality with increased flavonoid intake.[247] Results of the Cancer Prevention Study II Nutrition Cohort suggested an inverse relationship between total dietary flavonoid intake and the risk of stroke and total CVD, especially for men.[248] In contrast, a study of women reported no significant relationship between consumption of flavanols and flavones and coronary heart disease,[249] and there was no strong relationship between flavonoid intake and total coronary heart disease among American male health professionals.[250]

Antioxidant-Rich Beverages. Short-term investigations suggest that regular consumption of fairly large amounts of cocoa, green and black tea, wine, grape juice, and soy can improve vascular and endothelial cell functions. Whether these results translate into long-term reductions in risk of CVD is not known.

Wine and Grape Juice. Wine contains abundant polyphenols, and drinking red wine can increase the antioxidant capacity of serum.[251,252] A meta-analysis of 133 RCTs studying effects of flavonoids and flavonoid-rich foods suggested that red wine consumption did not improve flow-mediated dilation, alter blood pressure, or change LDL levels.[253] Results for grape juice consumption were also mixed. Overweight volunteers who consumed 480 mL/day grape juice for 12 weeks did not have improved plasma antioxidant capacity or lipid profiles.[254]

Cocoa. A double blind study of postmenopausal, hypercholesterolemic women found that high cocoa flavonol consumption daily for 6 weeks improved endothelial functions.[255] Overweight adults who ingested cocoa beverages experienced significantly improved flow-mediated dilation in a randomized trial.[256] Furthermore, administration of 40 g/day cocoa powder for 4 weeks significantly reduced ICAM-1 and P-selectin in high-risk patients with CVD.[257]

Tea. In laboratory animals, green tea prevented loss of liver SOD, GSH peroxidase, and catalase activities due to alcohol intoxication, while protecting membrane lipids from peroxidation.[258] In apolipoprotein-E gene knockout mice, an animal model of atherosclerosis, theaflavin with quercetin reduced formation of atherosclerotic lesions and vascular superoxide and ILB-4, while increasing vascular endothelial NOS activity, NO production, and vasodilation.[259] A meta-analysis of seven cohort and case–control studies reported an 11% decrease in the risk of myocardial infarction with daily consumption of three cups of tea.[260] A later meta-analysis of nine observational studies suggested that consumption of the equivalent of three cups of green or black tea daily was associated with a significantly reduced risk of ischemic stroke.[261]

Soy. Studies with vascular cells suggest that soy isoflavones can increase eNOS activity[262] while activating the redox regulated Nfr2-Keap1 signal pathway to increase transcription of phase 2 enzymes and antioxidant enzymes.[263] Some epidemiologic studies implicated soy, especially soy protein, with reduced risk of coronary heart disease.[253] Several RCTs reported cardiovascular benefits with improved systemic arterial function after a meal enriched with soy isoflavones.[264] In a RCT, supplementation of postmenopausal women with genistein for up to 36 months decreased homocysteine and fasting glucose.[265] However, results were inconsistent.

Quercetin

This well-studied flavonol acts as a strong antioxidant in vitro, and possesses anti-inflammation in cultured cells.

Inflammation. Experiments with guinea pig epidermal cells suggest that flavonoids, such as quercetin, can inhibit COX-2 and 5-lipoxygenase pathways to curtail production of inflammatory eicosanoids.[266] Flavonoids may reduce expression of adhesion molecules needed to recruit white cells to arterial walls, a property unrelated to their antioxidant potential. Quercetin and kaempferol inhibited adhesion molecule expression induced by TNF-α in human aortic endothelial cells. Pre-exposure of hepatocytes to flavonoids blocked this inhibitory effect, suggesting that liver biotransformation reduces the ability of flavonoids to influence endothelial cells.[267] Quercetin supplementation of healthy volunteers with quercetin (500 or 1000 mg) together with vitamin C (125 mg or 250 mg) daily over 12 weeks significantly increased plasma quercetin without changing plasma oxidant capacity (FRAP and ORAC).[268]

Oxidative Stress. Stress induced by strenuous exercise increased plasma cortisone and lipid peroxides and decreased SOD, GPx, and catalase in rat brains. Treatment with quercetin significantly increased these activities, while lowering plasma peroxides.[269] In contrast, long-term quercetin supplementation (1000 mg/day) in athletes did not protect against exercise-induced oxidative stress, although supplementation might lead to a modest improvement in maximal oxygen uptake in untrained individuals.[270,271]

Cardiovascular Disease. Short-term consumption of flavonoid-rich foods and beverages can improve CVD risk factors, including endothelial function in healthy volunteers and patients with coronary artery disease. Interest was stimulated by the Zutphen study, which reported an inverse relationship between the incidence of stroke and coronary artery disease and consumption of flavonoids, particularly quercetin.[235]

Using a RCT with crossover design, healthy men who ingested 200 mg of quercetin experienced lowered plasma endothelin-1 and increased plasma nitrite and S-nitrothiols, which are biomarkers of NO production.[272]

Chemoprevention. Quercetin can induce apoptosis and stimulate production of antioxidant enzymes such as NADPH quinone oxidoreductase activity in human breast cancer cells.[273,274] With induced lung carcinogenesis in mice, quercetin pretreatment effectively prevented losses of SOD, catalase, GPx, GSH S-transferase, GSH reductase, while limiting tumor formation.[275] A case–control study found an inverse relationship between the intake of quercetin-rich foods and lung cancer risk, especially for heavy smokers. This effect corresponded to

upregulation of GSH transferase isozymes and downregulation of cytochrome P450 isoforms.[276]

Proanthocyanidins (Oligomeric Proanthocyanidins)

Pine Bark Extract. Pine bark extract (PBE) represents a complex mixture of polyphenols enriched in procyanidolic oligomers (PCOs), containing two to seven monomers of catechin and epicatechin. PCOs are effective antioxidants in vitro and can protect and/or regenerate α-tocopherol and vitamin C. PBE can also upregulate antioxidative enzymes in cultured cells.[277]

Inflammation. PBE can inhibit production of ROS by macrophages blocking the expression of proinflammatory cytokines, such as IL-1β.[278] Plasma from subjects treated with PBE can block NF-κB activation and production of matrix metalloproteinases in human monocytes.[279] Rodents fed diets supplemented with PBE had increased plasma antioxidant capacity and reduced lipid peroxidation (thiobarbituric acid reactive substances).[280] Plasma taken from healthy subjects 30 minutes after ingestion of a single dose of 300 mg PBE had inhibited COX-1 and COX-2 in human monocytes.[281] These observations suggest that PCOs may be useful in reducing inflammation; standardized PBE has been used to treat capillary dysfunction in patients with diabetes, venous abnormalities,[270] and knee osteoarthritis.[282]

Grape Seed Extract

Oxidative Stress. Wine flavonoids including PCOs are effective antioxidants in vitro. They can reduce lipid peroxides and decrease susceptibility of isolated LDL to oxidation. Grape seed extract (GSE) treatment led to significant postprandial reduction in plasma lipid hydroperoxides and increased antioxidant capacity in healthy volunteers.[283] Male smokers administered GSE had significantly decreased platelet reactivity compared with control subjects given a placebo.[284] Type 2 diabetic patients received GSE 600 mg/day according to a controlled double-blind protocol. After 4 weeks, significant decreases were observed for plasma fructosamine and high-sensitivity C-reactive protein, and significant increases were seen for whole blood GSH compared with placebo.[285]

Neurologic Disease. After animal experiments indicating that GSEs can limit lipid peroxidation in the brain,[286] GSE polyphenols were found to inhibit protofibril formation and protofiber oligomerization in a mouse model of Alzheimer's disease.[287]

Chemoprevention. GSE is able to inhibit proliferation of a variety of cancer cell lines involving regulatory targets such as MAPKs, NF-κB, phosphoinositide 3-kinases (PI 3-kinases), and angiogenesis.[288] Furthermore, pretreatment with GSE protected rodents against experimentally induced hepatotoxicity, pulmonary toxicity, and doxorubicin-induced cardiotoxicity by suppressing oxidative stress.[286,289]

Other Potential Phytochemical Antioxidants

Silymarin. Silymarin, a flavonoid concentrate from milk thistle, and silibinin, a principal constituent of silymarin, can scavenge ROS and decrease inflammation.

Hepatoprotection. Silymarin reduced oxidative stress and prevented liver necrosis in mice exposed to toxic agents.[290] Silymarin blocked production of TNF-α, interferon-γ, and IL-2 by stimulated peripheral blood mononuclear cells and T cells isolated from hepatitis C virus infected and noninfected subjects.[291] Phase I to II trials have not demonstrated consistent reduction in liver function tests, viral load, or improved liver histology in patients with hepatitis C.[292]

Diabetes. An open trial with cirrhotic diabetic patients treated with 600 mg/day silymarin for 12 months reported significant reduction in glucosuria, glycosylated hemoglobin, and malondialdehye levels compared with controls.[293] Similar positive results were found in a RCT of treatment of patients with type 2 diabetes with 600 mg/day silymarin for 4 months.[294]

Cancer. Androgen-responsive prostate cancer cells can be inhibited by silymarin. Using a transgenic mouse prostate cancer model, dietary phosphatidylcholine-silibinin complex inhibited tumor growth and metastasis by reducing expression of metalloproteinases and vascular endothelial growth factor and its receptor, while blocking epithelial to mesenchymal associated with metastasis.[295]

Resveratrol. Grapes, blueberries, and peanuts contain resveratrol and methylated resveratrol belonging to the stilbene family of polyphenols. Resveratrol can act as an antioxidant to protect human erythrocytes against H_2O_2–induced lipid peroxidation in vitro.[296] Stilbenes exhibit low solubility and rapid clearance, and ingestion of acute doses of resveratrol by healthy subjects achieved only nanomolar plasma concentrations, concentrations several orders of magnitude less than those used for in vitro or animal studies.

Inflammation. Possible mechanisms relating to anti-inflammatory effects include inhibition of COX and lipoxygenase and blocking the action of NK-κB and AP-1 in cultured cells.[297]

Cardiovascular Protection. Exposure to resveratrol correlated with decreased myocardial damage associated with ischemia reperfusion and inhibition of LDL oxidation.[298] Proteomic and immunoblot study revealed upregulation of five different redox-regulated proteins, including MAPKs.[299] Resveratrol may also promote vasodilation. Resveratrol activated human platelet eNOS, increased NO production, and reduced NOx activity, thus lowering superoxide production.[300]

Diabetes. Using experimentally-induced diabetes in rats, resveratrol reduced glucose levels compared with untreated animals. Cardioprotection of diabetic rats involved induction of eNOS, vascular endothelial growth factor, and heme oxygenase.[301]

Chemoprevention. In various cancer cell lines, resveratrol exposure can stimulate apoptosis and inhibit cell proliferation.[302] A study of rats fed resveratrol demonstrated that high-dose resveratrol suppressed a transgenic rat model of spontaneous prostate cancer.[303]

Aging. Resveratrol can increase longevity in a variety of organisms, including mice.[304] It may modulate transcription of the sirtuin gene family implicated in senescence, endothelial function, and angiogenesis. Sirt1, a deacetylase that silences transcription, can be induced by resveratrol in vitro. It is worth noting that low doses of resveratrol can improve cell survival by upregulating anti-apoptotic and redox regulating proteins, whereas high doses induce cell death by downregulating redox proteins and inducing production of apoptotic proteins.[305] Questions of bioavailability, long-term safety, effective dosage, and optimal duration of treatment have not yet been established.[306]

Ginkgo biloba. A variety of evidence suggests benefits of *Ginkgo biloba* extract for vascular insufficiency, cerebral insufficiency, and improved cognition. Most studies utilized a standardized extract, EGb 761.

Oxidative Stress. In part, beneficial effects appear related to antioxidant and anti-inflammatory actions, and it is likely that active constituents, ginkgolides, and related flavonoids reduce oxidative stress.[307,308] Cell culture studies suggest that EGb 761 can raise GSH levels and induce γ-glutamylcysteinyl synthetase, the rate-limiting enzyme in GSH synthesis.[309] Damage to human endothelial cells exposed to oxidized LDL could be prevented by EGb 761.[310] Rats treated with EGb 761 had increased catalase and

SOD activity and reduced lipid peroxidation in the hippocampus, striatum, and substantia nigra compared with controls.[311]

Aging. Mice supplemented with EGb 761 also had less ROS-induced apoptosis in lymphocytes than untreated mice; this result was greater in old mice than in young animals.[312] In clinical studies, type 2 diabetic patients treated with EGb 761 for 3 months were found to have reduced markers of lipid peroxidation in platelets, potentially through inhibition of the COX-1 mediated cascade.[313] A RCT of elderly subjects administered EGb 761 long-term found no benefit in reducing the risk of CVD.[314]

Curcumin. Curcuminoids are bright yellow pigments found in turmeric, a family of lipophilic diketones. Curcumin, the principal curcuminoid, is poorly absorbed with serum concentrations in the nanomolar to micromolar range after oral ingestion of up to 8 g.[315] Extending the observation that curcumin scavenges ROS and RNS in vitro, consumption of 200 mg/day of curcuminoids decreased serum lipid peroxide levels and LDL lipid peroxidation in healthy subjects.[316]

Inflammation. In cultured colonic cells, curcumin inhibited iNOS and blocked lipoxygenase, COX-2, and phospholipase A, and reduced production of proinflammatory prostaglandins, thromboxanes, and leukotrienes by inhibiting NF-κB activation.[317] Clinical studies are preliminary. For example, a RCT of patients experiencing remission of ulcerative colitis examined high-dose curcumin supplementation in addition to standard treatment. After 6 months, 2 of 43 patients relapsed compared with 8 of 39 patients in a placebo group.[318]

Cancer. Curcumin can induce apoptosis and inhibit angiogenesis and production of matrix metalloproteinases in several cancer cell lines. Oral curcumin administration inhibited a mouse model of familial adenomatous polypsis,[319] and it inhibited the growth of human tumors in xenotransplant animal models. Clinical studies are limited. Two of 21 patients with advanced pancreatic cancer administered 8 g/day curcumin until cancer regressed experienced some anticancer activity.[320] Several Phase II and III clinical trials are near completion (Curcuminoids in colon cancer prevention, University of Pennsylvania; curcumin and capecitabine in rectal cancer, MD Anderson Cancer Center; curcumin for pancreatic cancer, MD Anderson Cancer Center; and for pediatric oral mucositis, Hadassah Medical Organization).

Neurodegeneration. Curcumin can bind to amyloid deposits. A mouse model of Alzheimer's disease treated with curcumin 7 days reduced existing plaques and structural irregularities in dystrophic dendrites.[321] Of four clinical trials of curcumin supplementation for Alzheimer's disease, the two that have been reported found no significant differences in cognitive performance between treated and placebo groups.[322]

Garlic. Many health attributes of garlic are derived from multiple organosulfur compounds, including allicin and its derivatives in garlic. Some may influence antioxidant status.

Oxidative Stress. Rabbits fed an atherogenic diet and garlic extract had significantly better antioxidant status and reduced plaque area compared with animals not fed garlic.[323] S-allyl cysteine inhibited oxidative damage and blocked the formation of H_2O_2 in cultured endothelial cells.[324] Using an animal model of type 2 diabetes, investigators found that aged garlic extract lowered lipid peroxidation and increased SOD and GPx activity compared with controls.[325]

A pilot study of smokers and nonsmokers found that daily supplementation with aged garlic extract for 2 weeks reduced lipid peroxidation (8-iso-prostaglandin F_2).[326] A study of hypertensive patients supplemented 2 months with garlic observed significant reduction of DNA oxidation (8-hydroxyguanosine), NO production, and lipid peroxidation compared with controls.[327] However, using a RCT and crossover protocol, investigators observed that supplementation of men with coronary artery disease with aged garlic extract for 1 month increased arterial flow-mediated dilation without lowering markers of oxidative stress (oxidized LDL) inflammation (C-reactive protein).[328]

Inflammation and Detoxification. Garlic can attenuate inflammatory cytokine production in stimulated macrophages by suppressing NO production.[329] Garlic also upregulates phase II detoxification enzymes in vitro. Human hepatoma cells exposed to diallyl sulfides activated the AREs and Nerf2 family of detoxification enzymes, possibly through calcium-dependent signaling.[330]

Specific Antioxidant Mechanisms for Polyphenols In Vivo?

Interpretation of polyphenolic "antioxidant effects" is complicated by several factors. Most data regarding polyphenol activities come from cultured cells and tissues and often test concentrations of individual flavonoids that far exceed those found in vivo. Flavonoids such as quercetin and green tea catechins rapidly produce H_2O_2 under typical cell culture conditions, thereby complicating interpretation. Identity of the polyphenolic species affecting cells and tissues is uncertain due to their biotransformation. Localized concentrations of active species in vivo are also uncertain.

Mechanism. Depending upon the experimental design, polyphenols can inhibit COX, lipooxygenase, telomerase, xanthine oxidase, cytochrome P450, and protein glycation, as well as modulating drug transport systems and platelet function. Flavonoids may influence multiple signaling pathways, making it difficult to assign specific actions. As an example, red wine polyphenols administered to rats for 16 weeks inhibited chemically induced colon cancer.[331] In the process, responses to oxidative stress were downregulated. Microarray analysis of cellular changes after polyphenol treatment for 14 days revealed the following frequencies of downregulated genes: receptors and signal transduction, 22%; transport and binding proteins, 14%; inflammatory and immune response, 11%; metabolic enzymes, 4%; gene expression/control, 4%; xenobiotic metabolism, 3%; and cell cycle regulation, 3%. In the final analysis, observed protective effects of flavonoid-rich foods in humans may be independent of flavonoids.

Gastrointestinal Tract as Primary Target for Polyphenols

The GI tract is continuously exposed to ROS and RNS from multiple sources. The gut epithelium may not adapt to long-term oxidative stress, and because of low initial levels of defensive enzymes, it may be susceptible to oxidative damage with even moderate inflammation.[332] After ingestion of flavonoid-rich foods, phenolic compounds are present in the stomach and intestinal lumen at much higher concentrations than those found in plasma.[333] Of particular interest are inflammatory bowel disease, gastric ulcers, and liver disease.[334,335] ROS are present at high levels in the colons of patients with ulcerative colitis.[336] Green tea polyphenols can reduce inflammation in models of inflammatory bowel disease.[337] Polyphenolic by-products of intestinal metabolism, such as hydroxybenzoic acid and protocatechuic acid, exhibit important properties. As an example, they can induce apoptosis in gastric cancer cells.[338]

THERAPEUTIC USE OF ANTIOXIDANTS

Immunodeficiency, Oxidative Stress, and Antioxidants

Supplementation with antioxidants, including vitamins C and E, and carotenoids, along with selenium, copper, and zinc, has been

reported to improve aspects of innate and humoral immunity. Used alone or in combination, these nutrients may improve lymphocyte proliferation, delayed hypersensitivity responses, and immune cell functions. These include Th1 cytokine-mediated responses. Adequate levels of proinflammatory cytokines help balance anti-inflammatory Th2-mediated responses.[339,340] However, a small RCT of allergic individuals found no change in immune responses, serum antioxidant capacity, or markers of oxidative stress after 4-week supplementation with vitamins C and E, β-carotene, selenium, and zinc at levels several-fold higher than recommended dietary allowances.[341]

The growing literature suggests that HIV infection is associated with oxidative stress. Sero-positive HIV patients were shown to have significantly reduced plasma TAC compared with healthy controls, a finding that correlated with significantly elevated lipid peroxidation and reduced levels of vitamins C and E, SOD342, and oxidative stress, which may relate to HIV dementia.[342,343] A cross-sectional study demonstrated increased plasma lipid peroxide levels along with depleted GSH levels in HIV-infected individuals compared with healthy controls.[344] Low levels of reduced GSH could activate transcription factor NF-κB to increase transcription of the HIV genome.[345]

It is logical to propose that antioxidant treatment could benefit HIV-positive individuals. Polyphenols can inhibit HIV infectivity of cells in vitro.[346] However, results of clinical studies are mixed. A review of 6 RCTs concluded that β-carotene/vitamin A did not change overall mortality, morbidity, or CD4 and CD8 counts, whereas 4 RCTs of other micronutrients did not improve overall mortality.[347] Benefits of micronutrient supplementation in improving mortality among HIV-positive patients appears to involve correcting nutrient deficiencies.[348] High vitamin C or high vitamin E levels can potentially interfere with indinavir therapy.[349]

Exercise, Oxidative Stress, and Antioxidants

The health benefits of regular physical activity are well established, but the exact mechanisms are uncertain. Some data suggest that long-term exercise increases antioxidant defenses as an adaptation. Clearly, strenuous physical exercise increases ROS production and muscle fiber damage. Although vitamin C, vitamin E, ALA, L-carnitine, and flavonoids can attenuate certain of the signs and symptoms due to resistance training, they do not eliminate tissue injury. Green tea extracts appear to have marginal effects on metabolism and performance in trained athletes.[350] Supplementing with antioxidant vitamins such as E, C, and CoQ_{10} may decrease associated oxidative damage in untrained individuals, especially in older people.[351] Nonetheless, optimal doses of putative beneficial antioxidants and pretreatment intervals are unknown.[352] The field is confusing because a variety of markers of antioxidant status and different training levels have been used. Furthermore, many studies use blood levels of antioxidant and ROS-induced by-products as end points to assess antioxidant status after exercise, contributing to variable test results. It is questionable whether these endpoints represent tissue level changes. Benefits of supplementation are most often seen in untrained populations rather than in athletes, especially when there are nutrient deficiencies. For example, in resistance-trained men, supplementation with 1000 mg/day of vitamin C and 378 mg/day of mixed tocopherols or placebo for 14 days did not change markers of muscle injury or oxidative stress (blood protein carbonyls and peroxides).[353] Currently, there does not appear to be enough evidence for recommending antioxidant supplements for well-trained and well-nourished athletes.[354,355] Antioxidant supplementation may actually be counterproductive. A RCT of kayakers given standard antioxidants (vitamin C 400 mg, α-tocopherol 272 mg, β-carotene 30 mg, lutein 2 mg, selenium 400 mcg, zinc 30 mg, magnesium 600 mg) daily for 4 weeks found that supplementation failed to lower lipid peroxidation induced by strenuous exercise, and it reduced muscle recovery times.[356]

Do Antioxidants Explain the Health Benefits of Plant-Based Foods?

Consumption of plant-based foods rich in antioxidants was reported to decrease oxidative damage in humans by some authors,[333] although others found little effect.[357] Recent analysis of data from the EPIC study found that eating five portions of fruits and vegetables daily lowered the overall risk of cancer by 9%, far less than expected.[358] Nonetheless, previous studies concluded that five servings could reduce the risk of stroke by 26%; reduce the risk of cancers of the oral cavity, bowel and lung; and reduce the risk of obesity. Do antioxidants account for such benefits? Results of assays of antioxidants and assessments of oxidative stress are suggestive, but as yet there is no firm demonstration that in vitro measurements translate into specific health benefits. The U.S. FDA and the European Food Safety Authority concluded that claims cannot be made linking foods and food constituents to protection of body cells and molecules, such as DNA, proteins, and lipids from oxidative damage.[359]

Supplementation with Antioxidants

Specific Goals

A primary goal is to adjust supplementation to correct any imbalances in an individual's nutritional status. Overall, studies suggest that the recommended dietary allowances for antioxidants are inadequate for optimal immune function for certain groups. Table 108-1 provides a summary of a recommended intake of antioxidants for maintenance as compiled by the European Federation of Health Product Manufacturers.[301] For most adults, intakes of vitamin C up to 2000 mg/day are believed to be safe.[360] The levels of vitamins and minerals often prescribed in treatment protocols may be considerably higher than those listed in Table 108-1.

A second goal is to support the body's defense systems. Antioxidant requirements should be balanced against oxidant burden. Multiple, complementary antioxidants are far more effective than large amounts of a single antioxidant, because antioxidants often work synergistically.[361] Animal studies suggest that consumption

TABLE 108-1 **Recommended Safe Upper Intake Levels for Antioxidant Nutrients**

Vitamin E	1000 mg*
Vitamin C	2000 mg*
Vitamin A	3000 mcg*
Beta carotene	None established (5 or more servings of fruits and vegetables would provide an estimated 3-6 mg β-carotene daily.)
Copper	10 mg*
Magnesium	250 mg†
Selenium	300 mcg*
Zinc	40 mg*

Data from Flynn A, Moreiras O, Stehle P, et al. Vitamins and minerals: a model for safe addition to foods. Eur J Nutr 2003;42:118-130.
*U.S. Food and Nutrition Board, Institute of Medicine Tolerable Upper Intake Levels.
†European Commission Scientific Committee on Food, Tolerable Upper Intake Level.

of a greater diversity of antioxidants is more effective than use of single antioxidants. Daily supplementation with vitamin C (500 mg), vitamin E (400 IU), β-carotene (15 mg), zinc (80 mg), and copper (2 mg) significantly slowed the progression of advanced AMD, although this regimen did not affect the risk of cataracts or loss of visual acuity.[362] In other research, the combination of CoQ_{10}, vitamin E, and ALA were shown to act synergistically in protecting LDL against lipid peroxidation in vitro.[363]

How Common Are Antioxidant Deficiencies?

The prevalence of subclinical deficiencies of nutrients with antioxidant roles may be quite high—magnesium (56%), zinc (12%), vitamin E (93%), and vitamin C (31%) for general populations, as judged by intakes less than an estimated average requirement.[19] More than 90% of Americans do not consume the dietary reference intake (DRI) for vitamin E of 15 mg, which is judged as adequate to prevent myopathy and neuropathy.[364] Success with antioxidant supplementation is most notable when there are deficiencies, overt or not. According to a metabolic "triage" hypothesis, low micronutrient intake can increase the risk of chronic degenerative diseases without overt deficiencies, because the body's homeostatic mechanisms direct essential nutrients to support the most critical functions.[19]

Limits to Antioxidant Supplementation

The use of antioxidant supplementation to completely quench free radicals is counterproductive. As discussed earlier, physiologic levels of ROS are essential in maintaining homeostasis for multiple physiologic systems, for example, superoxide and NO play essential roles in maintaining the body's defenses and homeostatic mechanisms. Antioxidant supplementation may be counterproductive, as examples, acute supplementation with vitamins C, E, and α-lipid acid negated the reduction of blood pressure and the improvement in flow-mediated vasodilation due to exercise in elderly hypertensive men.[365] Transient oxidative stress, induced by short-term physical activity, can ameliorate insulin resistance. However, pretreatment with α-tocopherol 400 IU/day and vitamin C 1000 mg/day for 4 weeks prevented exercise-induced insulin sensitivity and blocked induction of endogenous antioxidant enzymes in healthy volunteers.[366] Quercetin and myricetin efficiently inhibited TRX reductase to induce apoptosis and cell cycle arrest in tumor cell lines by direct binding and by semiquinone radical oxidation.[367] However, the TRX system broadly affects redox balance in normal cells and tissues, and its inhibition may be detrimental to health.

No single supplement, nutrient, or food can maintain the body's antioxidants, prevent disease, or be effective in treatment. There are simply too many oxidants to be neutralized, too many layers of antioxidant defenses to be sustained, and the range of reactivity of water- and lipid-soluble ROS is far too great. Nor can antioxidant supplements substitute for a prudent diet and supportive lifestyle changes, including cessation of smoking, regular exercise, and effective stress management. The frequent negative or conflicting results from clinical trials may reflect wide variations in the nutritional status and heterogeneity of antioxidant intake in study populations, as well as biochemical individuality (genetic polymorphisms), and medical history, especially for an aging population for whom multiple pharmaceuticals are prescribed.

What is the most effective way to increase intake of a broad spectrum of defined and undefined antioxidants? The increased consumption of a variety of antioxidant-rich foods—especially colored fruits, vegetables and legumes, and beverages such as green tea—remains a prudent strategy. Because short-term interventions with vitamins C or E, β-carotene, or flavonoids have not demonstrated consistent health benefits, the data suggest that other plant food factors may account for such protection.[368] As an example, flavonoids seem to account for only a small percentage of the oxidant capacity of apple extracts.[230]

Additional Considerations for Antioxidant Supplementation

Does Vitamin E Increase Mortality Risk? Meta-analysis of 68 randomized trials found that supplementation up to 800 IU/day did not change the risk of all-cause mortality.[102] A more recent meta-regression analysis of 29 clinical trials representing a total of 138,462 participants and vitamin E dosages ranging from 16.5 to 5000 IU/day found no causal relationship between high-dose vitamin E and mortality.[369] Indiscriminant use of high doses of vitamin E is not recommended.[136,370] Vitamin E can interfere with vitamin K-dependent clotting factors, and high doses increase the risk of bleeding in at-risk individuals.

Does Excessive Beta-Carotene Contribute to Disease? Beta-carotene may act as a pro-oxidant for those at risk for oxidative stress (smoking, alcohol consumption); β-carotene may also raise the risk of lung cancer in high-risk populations unless protected by antioxidants like vitamin E.[371] When β-carotene is supplemented during oxidative stress, cleavage products are produced, which are genotoxic, and these may account for the carcinogenic effects observed in the Alpha Tocopherol, Beta Carotene Cancer Prevention Study (ATBC) and Beta Carotene and Retinol Efficacy Trial (CARET).[372] High levels of β-carotene may be contraindicated in smokers with myocardial infarctions. In one study, the rate of fatal coronary heart disease rose in patients receiving 20 mg/day β-carotene (with or without α-tocopherol).[373] Carotenoids generally lose their effectiveness at high concentrations and at high partial pressures of oxygen. This feature may account for the possible benefits of consumption of carotenoid-rich foods, although therapeutic doses of isolated carotenoids may be deleterious.[374]

Can Antioxidants Contribute to Oxidative Stress? The potential pro-oxidant activity of polyphenolic radicals is well documented.[375] Flavonoids are metabolized and detoxified by liver enzymes, and pharmacologic doses can induce phase I detoxification enzymes, increasing the ability to transform toxins. The tradeoff lies in the possibly greater sensitivity to mutagens. Vitamins C and E exhibit pro-oxidant activity in vitro under certain conditions. When exposed to catalytic levels of iron or copper ions, ascorbate promotes the formation of H_2O_2 and hydroxyl radicals.[376,377] In vitro studies suggest that ascorbic acid can decompose lipid peroxides to genotoxins.[378] In vivo, these effects would likely require high ascorbate concentrations coupled with the depletion of tocopherol.[379] Excessive dietary iron or iron accumulation could promote ascorbate-induced oxidation, and ascorbate could act as an oxidant in the presence of iron or copper released during inflammation or injury. In a RCT, hypertensive patients were treated with 500 mg ascorbic acid and/or 1000 mg grape seed polyphenols daily for 6 weeks. Although ascorbic acid alone reduced elevated systolic pressure, the combination significantly increased both systolic and diastolic blood pressure.[380]

Antioxidants as Adjuvant Cancer Therapy. A systematic review found that 24 of 33 randomized, controlled studies reported decreased toxicity of chemotherapy with concomitant use of antioxidants, including vitamin E and vitamin C, with one study of vitamin A reporting increased toxicity.[381] As a recent example, a study of pediatric patients with acute lymphoblastoma being treated with chemotherapy and concurrent supplementation with 400 IU vitamin E and 600 mg *N*-acetylcysteine daily for

28 days found that children taking the supplements experienced less liver toxicity, fewer blood abnormalities, and fewer blood transfusions.[382] The use of α-tocopherol succinate to inhibit tumor growth in vivo remains unproven. Because this derivative possesses no antioxidant activity, presumably its inhibition of cancer cell proliferation and induction of apoptosis in tumor cells relies on other mechanisms.

Caveats Regarding Potential Nutrient–Drug Interactions and Phytochemical–Drug Interactions

The popularity of antioxidant supplementation comes with additional concerns regarding interactions with over-the-counter and prescription medications. Literature in these areas is steadily growing, and several useful compendia are available.[383-386] In addition, the editors of the *Pharmacist's Letter* publish the Natural Medicines Comprehensive Database, which is updated frequently.

FUTURE DIRECTIONS

The broad outlines for antioxidant defenses against oxidative stress are established. However, our understanding of the inner workings of these mechanisms remains incomplete, and details of the body's response to oxidative stress remain poorly understood. Use of newer research tools, such as genetically manipulated laboratory animals (e.g., SOD−/− or GPx1−/− animals) and analysis of global changes in gene expression induced by oxidative stress, offer powerful approaches to understanding in vivo responses.[387] Incorporation of a systems biology analysis can also provide powerful insights.[388]

In general, the consumption of a broad spectrum of antioxidants in amounts geared to meet an individual's oxidant burden and nutritional status may minimize the effects of genetic predisposition that compromise defenses against aging and degenerative disease and promote optimal health. Yet for most antioxidants, used singly or in combinations, the dosage, duration, efficacy, safety, and levels needed to sustain optimal health remain unknown. This is especially true for polyphenols.[389] In addition, a therapeutic window for antioxidant action is often inferred, although not defined. Target dietary reference intakes for phytochemicals may eventually reflect composites beyond the currently recommended five daily servings for fruits and vegetables.[390]

Nonetheless, essential data needed to support the therapeutic use of antioxidants cannot be obtained from in vitro or from animal studies. Future claims for the impact of antioxidants on health must await additional studies, including intervention clinical trials demonstrating better function with supplementation and prospective studies exploring risk reduction for degenerative diseases.[391] A "nutrigenomics" strategy embraces the large-scale analysis of gene expression, individual proteins, and lipid markers, as well as metabolic pathways integrated using functional analysis software.[392] This approach demonstrated that a diet enriched in putative antioxidants can modulate low grade oxidative stress and inflammation in overweight men. The potential of herbs and botanicals in the prevention and treatment of conditions involving free radical pathology further enriches the future of antioxidant research.[393]

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CHAPTER 109

Opuntia Species (Prickly Pear)

Kathy Abascal, BS, JD, RH(AHG), and Eric L. Yarnell, ND, RH(AHG)

Opuntia spp. (family: Cactaceae)
Common names: prickly pear, nopal

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GENERAL DESCRIPTION

There are about 260 species of *Opuntia.*[1] These cacti are shrubs, and their flat, pear-shaped pads are stems or branches, not leaves, as many suppose. Some prickly pear varieties form thickets many feet tall and many feet across. Prickly pear's flowers range from yellow to orange and red to rose. Their fruits come in shades of yellow through red to purple. Most species have glochids, sometimes referred to as tiny spines, although they are actually leaf hairs with tiny barbs.[2] The stems, fruits, and flowers are all used as medicines.

CHEMICAL COMPOSITION

Comparisons of the constituents of the many prickly pear species are sparse, and there is no indication that any particular species is a better medicinal plant. The pad is high in mucilage, consisting of carbohydrate-containing polymers.[3] The pads also contain a mixture of saturated and unsaturated long-chain aliphatic esters; daidzein; genistein; β-sitosterol; and vanillic, ferulic, myristic, palmitic, and stearic acids.[3-6] Prickly pear fruits are high in carbohydrates and contain the pigments indicaxanthin and betanin.[7] The flowers contain flavonoids such as quercetin and isorhamnetin-3 glucosides in varying amounts.[8]

HISTORY AND FOLK USE

Prickly pear has a long history of medicinal use. The Aztecs used prickly pear root with *Geranium* spp. (cranesbill) as a febrifuge, to alleviate hernias, and to soothe irritated livers.[9] The fruit and seeds were used to prevent diarrhea. Indigenous peoples along the Yaqui River used the fluid from roasted prickly pear pads to relieve pain.[10] In New Mexico, prickly pear pads were used as poultices for painful, inflamed skin conditions, for swollen glands in the neck, and for congested, purplish breasts in lactating women. The pads were also used as emollients for tumors, warts, and calluses. The Tarahumara used the pads for the pain of bites and burns, and the Paipai used them to heal festering wounds. The Yaqui and the Hispanics in New Mexico soak diced pads in water and drink the liquid for thirst and diabetes; they also use the roasted pad to treat diabetic infections. Prickly pear was brought from the Americas to Africa and Europe, and its medicinal uses followed.[11]

Today, the Moors apply the heated pads to swellings on the body, the South African Bantu use prickly pear for a variety of tumors, and Zimbabweans use prickly pear internally as a treatment for pain in gouty arthritis.[12,13] In the Canary Islands, prickly pear fruits are used topically for a variety of inflamed wounds and internally for gastrointestinal and bronchial problems. In the Mediterranean region, prickly pear pads are used to treat gastric ulcers, and in Sicilian folk medicine, a flower infusion is used for its diuretic and relaxant action on the kidneys.[14]

PHARMACOLOGY

Analgesic Effect

Prickly pear fruits and pads had significant analgesic effects in mice.[15] Prickly pear fruit injected intraperitoneally (400 mg/kg) had an analgesic effect comparable to that of aspirin (70 mg/kg) in vivo.

Antiinflammatory Effect

Prickly pear significantly reduced edema in rat paws and showed an antiinflammatory effect in a mouse model of chronic inflammation.[16] The active constituent was identified as β-sitosterol. Another study showed that prickly pear *(O. dillenii)* fruit extract injected intraperitoneally had antiinflammatory action.[17] Pretreatment with prickly pear significantly reduced edema dose-dependently, and its maximal effect was similar to that of indomethacin.

Antiviral Effect

After reports that a woman stopped frequent recurrent outbreaks of herpes genitalis by taking 2 g prickly pear a day, studies investigated the plant's antiviral effects.[18] In hamster kidney cells, prickly pear specifically reduced herpes simplex virus type 2 (HSV-2) replication at 3.5 mg/mL, and completely inhibited replication at 15 mg/mL. Prickly pear also inhibited other herpes viruses (pseudorabies virus, bovine mammillitis virus, equine herpes virus type 1, as well as the more cell-associated human herpes virus, cytomegalovirus, and varicella zoster virus).

Prickly pear inhibited replication by HSV-2 in infected human cervix tissue and inhibited RNA virus replication.[18] Testing included a laboratory strain of influenza A virus, an isolate of respiratory syncytial virus, and strains of encephalomyocarditis (EMC) virus, and HIV-1. The only virus that prickly pear failed to inhibit was the picornavirus EMC. The researchers found prickly pear to be a promising antiviral agent because it combines a breadth of in vitro reactivity with a high index of clinical safety. However, prickly pear pads combined with fresh *Capsicum frutescens* (cayenne) fruit and fresh *Citrus limon* (lemon) did not protect chickens from Newcastle virus.[19]

Cicatrizant Effect

When administered by mouth, dried prickly pear pad *(O. ficus indica)* significantly inhibited hydrochloride-induced, aspirin-induced, and ethanol-induced gastric lesions in rats.[20,21] Prickly pear did not affect gastric juice secretion, acid output, or stomach pH in the rats. Extracts of *O. ficus indica* showed significant wound healing activity in rats.[22]

Diuretic and Other Renal Effects

Fruit and flower infusions of *O. ficus indica* significantly increased diuresis in rats, and the fruit infusion had an antiuric effect.[23] Prickly pear pads (20 mg/100 g body weight daily for 5 weeks) significantly decreased uric acid levels and increased water intake while only slightly raising urine output in rats.[24] Although the rise in urine flow was slight, the investigators suggested that it could account for the greater excretion of uric acid. *O. megacantha* pads (20 mg/kg daily for 5 weeks) significantly increased urinary sodium output in diabetic rats and normal rats compared with controls.[25] Prickly pear did not alter plasma aldosterone concentrations. In earlier studies, prickly pear extract administered orally (20 mg/100 g body weight) increased creatinine clearance in diabetic rats and raised plasma creatinine and urea levels in all rats.[24,26]

Hypoglycemic Effect

Animal studies showed prickly pear pad had a hypoglycemic effect in streptozotocin-induced diabetes in rats and rabbits, although one study showed no effect if the rabbits' pancreatic β-cells were completely obliterated.[26-29] In one study, prickly pear's hypoglycemic effect was comparable to that of tolbutamide.[27] Prickly pear and insulin equivalently reduced, but did not normalize, glucose and insulin levels in diabetic rats. Prickly pear combined with insulin had a synergistic effect. Diabetic rats given the combination rapidly achieved normal glucose levels, and at 7 weeks became hypoglycemic. At that point, prickly pear alone was sufficient to maintain normal glucose levels.[28]

Hypocholesterolemic Effects

Prickly pear pectin had a hypocholesterolemic effect in guinea pigs.[30,31] Prickly pear consistently reduced blood cholesterol levels, reduced low-density lipoprotein (LDL) cholesterol, and increased its density.

CLINICAL APPLICATIONS

Alcohol Intoxication

Prickly pear extract administered 5 hours before alcohol consumption reduced symptoms of hangover. It appeared to act by inhibiting the production of inflammatory mediators.[32]

Diabetes (Adult-Onset Non–Insulin-Dependent)

There are a number of clinical trials on the effect of prickly pear pad in non–insulin-dependent diabetes mellitus (NIDDM).[33-39] A preliminary meta-analysis of the clinical trials on prickly pear's benefit in NIDDM concluded that the intervention data showed it to lower blood glucose levels by 10 to 30 mg/dL and supported claims that prickly pear had a true metabolic effect in diabetes.[40] Although the control data were insufficient for a full meta-analysis, a statistically significant reduction of blood glucose and, when tracked, in insulin levels, was seen consistently when broiled prickly pear was administered. The magnitude of the hypoglycemic effect varied from mild to moderate depending on dose. For example, a 300-g dose of broiled pad acutely lowered blood glucose levels by 30 mg/dL in eight subjects, whereas 500 g lowered levels by an average of 45 mg/dL in the same subjects.

Most studies used broiled pads. One that used homogenized prickly pear pad preparation did not find a hypoglycemic effect.[39] However, when the pad was ground in a regular blender rather than ultrahomogenized, it had an effect equivalent to that of broiled pads.[33] Capsules of dried prickly pear did poorly in a small, crossover, single-blind study in which a single dose of 30 capsules had no hypoglycemic effect.[41] Only a mild effect was seen in volunteers taking 30 capsules per day for 10 days—an impractical dose for most people.

In contrast, prickly pear has been shown to affect glucose levels mildly or not at all in normal individuals.[34,36,42] In two studies, prickly pear pad did not reduce glucose or insulin levels in healthy

volunteers. In a third study, nondiabetic individuals who ate broiled prickly pear pads before meals for 10 days showed a mild but significant reduction in fasting glucose levels, but prickly pear pad had a significant hypoglycemic effect in volunteers in an induced hyperglycemic state.[41-44] In a small study, a proprietary extract of prickly pear pad and fruit skin had an acute blood glucose lowering effect.[45]

Hyperlipidemia

Prickly pear pads lowered cholesterol and triglyceride levels, and improved cholesterol ratios in a small, non–placebo-controlled trial.[36] Eight healthy patients, fourteen obese patients, and seven patients with NIDDM ate 100 g of broiled prickly pear pads before meals three times a day for 10 days. Each group experienced a significant reduction in total cholesterol levels; triglyceride levels also diminished significantly in obese and diabetic patients (23% to 27%). An 8-week pilot study found that prickly pear pulp normalized blood fats as well as other indicators of metabolic syndrome in 24 hypercholesterolemic men.[46] In another 6-week study of 68 women with metabolic syndrome, an extract of prickly pear significantly improved blood fat levels.[47] In 10 patients with familial hypercholesterolemia, prickly pear upregulated LDL binding.[48]

Prostatic Hyperplasia

Dried prickly pear flowers improved subjective symptomology of prostatic hyperplasia in a preliminary open study.[49] Eighty-eight patients at two centers took two 250-mg capsules of flower extract three times daily for 2 to 6 months. Many patients reported decreases in urgency, emergency urinations, and the sensation of fullness in the bladder, but not all patients experienced relief.

Weight Loss

In a small, open-label study, prickly pear pads significantly reduced body weight of obese and diabetic subjects and showed a trend toward weight loss in normal subjects.[36] Fourteen obese patients, seven patients with NIDDM, and eight healthy patients ate 100 g of broiled prickly pear pad before meals three times a day for 10 days. Each group showed a mean reduction in weight of 1.5 kg while maintaining their usual diets.

DOSAGE

Studies of the use of this plant have used a variety of forms of prickly pear pad. Most have used broiled or grilled pads, whereas some studies have used juiced slurries. These studies used 100 to 500 g (3 to 17 oz) of pads three times a day, taken before meals. There is little information on dried preparations, but as mentioned previously, such preparations did not achieve results in some small trials.

TOXICOLOGY

Prickly pear showed a high degree of safety in studies of mice, horses, and humans.[29] It has a long history of use as a food, a factor that also indicates a high level of safety. Most adverse events involving the plant are the result of its glochids (tiny, nearly invisible spines), which can become embedded in the skin.[50] Sabra dermatitis is an occupational disease among prickly pear fruit handlers, in which the glochids cause a widespread skin eruption resembling scabies, which in chronic cases involves granuloma formation. However, in two animal studies, prickly pear significantly raised blood urea and creatinine levels in rats, and increased urinary creatinine clearance rates in diabetic rats only.[24,25] The researchers expressed concern that prickly pear perhaps caused an early stage of kidney dysfunction in rats. However, the same researchers did not report similar results in a subsequent study, and no other studies have reported such effects.[26]

DRUG INTERACTIONS

No human data on drug interaction are available for prickly pear. All herbs rich in complex carbohydrates may affect transit time and thus may alter absorption of practically any medication.

Many of the diabetes trials of this plant included patients who were taking oral hypoglycemic agents (tolbutamide, glyburide, chlorpropamide), and no adverse interactions were reported.[34-36,38,51] Prickly pear and insulin had a synergistic effect in rats, first normalizing blood sugar levels and then inducing hypoglycemia.[28] The effect of combining prickly pear and insulin in human subjects has not been studied.

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CHAPTER 110

Panax ginseng (Korean Ginseng)

Michael T. Murray, ND

Panax ginseng C.A. Meyer (family: Araliaceae)
Synonym: *Panax schinseng Nees*
Common names: Korean ginseng, Chinese ginseng, Asiatic ginseng, Oriental ginseng

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GENERAL DESCRIPTION

Korean or Chinese ginseng is a small perennial plant that originally grew wild in the damp woodlands of northern China, Manchuria, and Korea. Wild ginseng is now extremely rare. However, ginseng is a widely cultivated plant, especially in Korea, but also in Russia, China, and Japan. In addition to *Panax ginseng* C.A. Meyer, the following four other, closely related species are often used:

- *Panax quinquefolius* (American ginseng)
- *Panax japonicus* C.A. Meyer (Japanese ginseng)
- *Panax pseudoginseng* (Himalayan ginseng)
- *Panax trifolium*

P. ginseng C.A. Meyer is the most widely used and most extensively studied species.[1,2] Its pharmacology is the major focus of this chapter.

Fully mature, Korean ginseng is an herbaceous plant with a taproot, five-lobed palmate leaves, and greenish-white flowers in an umbel. In its first year, ginseng bears only a single leaf with three leaflets. In the second year, it bears a single leaf with five leaflets, and in its third year, it bears two leaves with five leaflets. It usually starts flowering in its fourth year, while bearing three leaves. The roots of the cultivated plant are 3 to 4 mm in diameter and 10 cm long, and the roots of wild plants may attain 10 cm in diameter and a length of 50 to 60 cm.

Ginseng is often processed in two forms, white and red. White ginseng is the dried root whose peripheral skin is frequently peeled off. Red ginseng is the steamed root, which has a caramel-like color.[2]

There are many types and grades of ginseng and ginseng extracts, which vary according to the source, age, and parts of the root used, where it was grown, the time of harvesting, and the methods of preparation.[1-3] Old, wild, well-formed roots are the most valued, whereas rootlets of cultivated plants are considered the lowest grade. High-quality preparations are usually in the form of extracts of the main root of plants between 4 and 6 years old that have been standardized for ginsenoside content (see later) and ratio to ensure optimum pharmacologic effect.

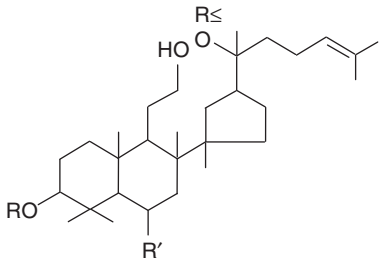
CHEMICAL COMPOSITION

Ginseng contains at least 13 different triterpenoid saponins, collectively known as ginsenosides, which are believed to be the most important active constituents. The usual concentration of ginsenosides is between 2% and 3%. The ginsenosides have been designated R_0, R_{b1}, R_{b2}, R_{b3}, R_c, R_d, R_e, R_f, 20-gluco-R_f, R_{g1}, and R_{g2}. The ginsenosides originate from the following three fundamental aglycones:

- Oleanolic acid (ginsenoside R_0)
- 20-S-protopanaxadiol (ginsenosides R_{b1} to R_d)
- 20-S-protopanaxatriol (ginsenosides R_e to R_{g2})

As can be seen from Figure 110-1, the ginsenosides differ primarily in their sugar groups.

Ginsenosides R_{b1}, R_{b2}, R_c, R_e, and R_{g1} are present in significant concentrations in Korean ginseng. In contrast, American ginseng (*P. quinquefolius*) contains primarily



Ginsenoside	R	R′	R≤
R_{a1}	Clc-^{2}Glc	H	Xyl-^{4}Ara(p)-^{6}Glc
R_{a2}	Clc-^{2}Glc	H	Xyl-^{4}Ara(f)-^{6}Glc
R_{b1}	Clc-^{2}Glc	H	Glc-^{6}Glc
R_{b2}	Clc-^{2}Glc	H	Ara(p)-^{6}Glc
R_{b3}	Clc-^{2}Glc	H	Xyl-^{6}Glc
R_{c}	Clc-^{2}Glc	H	Ara(f)-^{6}Glc
R_{d2}	Clc-^{2}Glc	H	Glc
R_{e}	H	Rha-^{2}Glc-O	Glc
R_{f}	H	Glc-^{2}Glc-O	H
R_{g1}	H	Glc-O	Glc
R_{g2}	H	Rha-^{2}Glc-O	H
20-Gluco-R_{f}	H	Glc-^{2}Glc-O	Glc
R_{h1}	H	Glc-O	H

Ara, Arabinose; *Glc,* glucose; *Rha,* rhabinose; *Xyl,* xylose.

FIGURE 110-1 Ginsenosides of *Panax ginseng.*

ginsenosides R_{b1} and R_{e} and does not contain ginsenosides R_{f}, R_{b2}, or, in some instances, R_{g1}.[4] These features allow for easy detection of species with high-pressure liquid chromatography.

Other components of ginseng are as follows[1,2]:

- Panacene, a volatile oil
- Free and glucoside-bound sterols (e.g., β-sitosterol and its β-glucoside)
- Polyacetylene derivatives β-elemene and panaxynol
- 8% to 32% starch
- Low-molecular-weight polysaccharides
- Pectin
- Vitamins (e.g., thiamine, riboflavin, B_{12}, nicotinic acid, pantothenic acid, biotin)
- 0.1% to 0.2% choline
- Minerals (including germanium)[5]
- Simple sugars (glucose, fructose, sucrose, maltose, trisaccharides, etc.)
- Unique proteins (e.g., panaxagin, a protein that possesses antifungal, antiviral, translation-inhibiting, and ribonuclease activities)[6]
- Various flavonoids

Although it was reported that ginseng contains large amounts of germanium (i.e., 300 ppm), a follow-up study using highly sensitive (detection limit of 1 ppb), flameless atomic absorption spectrometry combined with solvent extraction demonstrated that the highest concentration of germanium measured in samples of ginseng purchased in the Osaka market was only 6 ppb.[5] More research is needed to accurately determine the germanium content of botanical medicines, because the reported concentrations vary widely. Such low levels suggest that a connection between the pharmacology of ginseng and its germanium content is unlikely.

HISTORY AND FOLK USE

Perhaps the most famous medicinal plant of China, ginseng has been generally used alone or in combination with other herbs to restore the "Yang" quality. It has also been used as a tonic for its revitalizing properties, especially after a long illness. Conditions for which ginseng is used in folk medicine are shown in Box 110-1. It has been used as an alterative, anodyne, aperitif, aphrodisiac, cardiotonic, carminative, emetic, estrogenic, expectorant, gonadotrophic, nervine, sedative, sialogogue, stimulant, stomachic, and tranquilizer.[1,2] As can be seen from this list, ginseng has been used for most conditions, reflecting a broad range of nutritional and medicinal properties.

BOX 110-1 Conditions for Which Ginseng Is Used in Folk Medicine

- Amnesia
- Anemia
- Anorexia
- Asthma
- Atherosclerosis
- Boils
- Bruises
- Cachexia
- Cancer
- Convulsions
- Cough
- Debility
- Diabetes
- Diuretic
- Divination
- Dysentery
- Dysmenorrhea
- Dyspepsia
- Enterorrhagia
- Epilepsy
- Epistaxis
- Fatigue
- Fear
- Fever
- Forgetfulness
- Gastritis
- Hangover
- Headache
- Heart
- Hemoptysis
- Hemorrhage
- Hyperglycemia
- Hypertension
- Hypotension
- Impotence
- Insomnia
- Intestinal complaints
- Longevity promotion
- Malaria
- Menorrhagia
- Nausea
- Neurasthenia
- Palpitations
- Polyuria
- Pregnancy
- Puerperium
- Rectocele
- Rheumatism
- Rhinitis
- Shortness of breath
- Sores
- Spermatorrhea
- Splenitis
- Swelling
- Vertigo

PHARMACOLOGY AND CLINICAL INDICATIONS

Since the 1950s, a great amount of research has been conducted worldwide to determine whether the therapeutic properties attributed to ginseng belong in the realm of legend or fact. Unfortunately, inconsistent results (due mostly to different procedures in the preparation of extracts, use of nonofficial parts of the plant, use of adulterants, and lack of quality control in the ginseng used) have made determination of ginseng's true properties difficult. Nonetheless, enough good research does exist to indicate that ginseng possesses pharmacologic activity consistent with its near-legendary status, especially when high-quality extracts, standardized for active constituents, are used.

Over the years, ginseng has been reported to have numerous pharmacologic effects in humans and laboratory animals, including the following[1,2,7]:

- General stimulatory effects during stress
- Decrease in sensitivity to stress

- Increase in mental and physical capacity for work
- Improved endocrine system function
- Amelioration of radiation sickness, experimental neurosis, and cancer
- Enhanced protein synthesis and cell reproduction
- Improved glucose control in diabetes
- Modulation of various immune system parameters
- Lowering of serum cholesterol
- Protection of the liver from hepatotoxins

Some of these actions are discussed in greater detail in the following sections.

Adaptogenic and Antistress Activity

Ginseng was originally investigated for its adaptogenic qualities. An adaptogen was defined in 1957 by the Russian pharmacologist I.I. Brekhman[2] as a substance with the following properties:

- It must be innocuous and cause minimal disorders in the physiologic functions of an organism.
- It must have a nonspecific action (i.e., it should increase resistance to adverse influences through a wide range of physical, chemical, and biochemical factors).
- It usually has a normalizing action irrespective of the direction of the pathologic state.

According to tradition and scientific evidence, ginseng possesses this kind of equilibrating, tonic, antistress action, and so the term adaptogen is quite appropriate to describe its general effects.[2,7,8]

From a clinical perspective, ginseng can be used as a general tonic, especially in debilitated and feeble individuals. Use in this manner is consistent with its historic application. It can also be used as an antistress aid because it has been shown to enhance the ability to cope with various stressors, both physical and mental.

Ginseng delays the alarm phase response in Selye's classic model of stress. Animal studies found that adrenal cholesterol levels were many times higher in animals given ginseng than in their matched controls, indicating greater tolerance of stress and delayed alarm phase response.[9-11]

Italian researchers studied the effect of a standardized ginseng extract, the ginsenoside composition of which was accurately determined, on the adrenal functions of rats exposed to cold.[10] The ginseng extract significantly counteracted body temperature decline without affecting blood glucose or cortisone levels. In a group of adrenalectomized rats, the ginseng extract had no significant effects. Administration of hydrocortisone to the adrenalectomized rats did, however, cause body temperature to be maintained when the rats were exposed to cold.

Histologic findings in this study were as follows:

- Evidence of hyperfunctioning in the supraoptic and paraventricular nuclei of the hypothalamus in rats fed the ginseng extract
- Remarkable increase in corticotropic basophilic cells (adrenocorticotropic hormone [ACTH] producing) in the pars distalis of the pituitary gland
- Hyperplasia of the adrenal zona fasciculata, indicating that hyperfunctioning of the adrenal was promoted by the administration of the ginseng extract

Other researchers demonstrated that ginseng saponins significantly increased plasma ACTH and corticosteroids (in a parallel kinetic pattern).[12,13] Because this effect could be blocked by dexamethasone (which acts on the hypothalamus and pituitary to prevent ACTH release), it was concluded that ginsenosides act predominantly on the hypothalamus or pituitary to promote secretion of ACTH. This conclusion was confirmed further by indirect studies. ACTH first stimulates an increase in cyclic adenosine monophosphate (cAMP) in the adrenal and then promotes corticosteroid synthesis. Ginseng administration was shown to increase adrenal cAMP in normal rats, but not in hypophysectomized rats.

These investigations make quite clear that ginseng's antistress action is mediated by the hypothalamic-pituitary-adrenal axis, as follows:

- The antistress action of ginseng is greatly reduced by adrenalectomy.
- Ginseng continues to exert its antistress action after hypophysectomy only if ACTH is administered.
- Histologic and chemical evidence demonstrates a strong link between ginseng and the hypothalamic-pituitary-adrenal axis.
- Dexamethasone blocks the effects of ginseng.

This release of ACTH and associated pituitary substances (e.g., β-lipoprotein, endorphins, enkephalins) coupled with their end-organ effects is probably responsible for many of the antifatigue and antistress actions of ginseng, because ACTH and corticosteroids have been shown to bind directly to brain tissue to increase mental activities during stress. From a clinical perspective, it is apparent that ginseng has a balancing effect or alterative action on the hypothalamic-pituitary-adrenal axis through adjustment of metabolic and functional systems governing hormonal control of homeostasis. This effect assists the body's response to the challenge of stress and, therefore, is indicated when disruption of this axis is apparent.

Ginseng may prove especially effective in restoration of normal adrenal function and prevention of adrenal atrophy associated with corticosteroid administration. In rats, ginseng was found to inhibit cortisone-induced adrenal and thymic atrophy.[14]

Antifatigue (Mental and Physical) Activity

Some of the first studies of ginseng's adaptogenic activities were performed during the late 1950s and early 1960s by Brekhman and Dardymov[7,8] in the Soviet Union and by Petkov[15-17] in Bulgaria.

In one of Brekhman's experiments, Soviet soldiers given an extract of ginseng ran faster in a 3-km race than those given a placebo. In another, radio operators tested after administration of ginseng extract transmitted text significantly faster and with fewer mistakes than those given placebo. These and similar results reported by European researchers, who demonstrated improvement in human physical and mental performance after administration of ginseng extracts, prompted researchers to confirm the results in experimental models using mice.[2,7,8,15]

In perhaps the best known of these experiments, mice were subjected to swimming in cold water or running up an apparently endless rope to determine whether ginseng could lengthen the time to exhaustion. The results indicated that ginseng possessed significant antifatigue activity, because a clearly dose-dependent increase in time to exhaustion was noted in mice receiving ginseng.[2,8,18-20] In one study, the time to exhaustion was lengthened by up to 183% in the mice given ginseng 30 minutes before exercising compared with controls.[8]

Experimental animal studies indicated that much of the antifatigue action of ginseng was due to the stimulant effect of ginseng on the central nervous system (CNS). Stress coupled with ginseng ingestion induced alterations in energy metabolism during prolonged exercise.[9,16-20]

Ginseng has been shown to improve locomotor activity,[21] modify electroencephalographic (EEG) tracings,[16] improve metabolic activity in the CNS,[22] and affect the hypothalamic-pituitary-adrenal axis (discussed later), all of which could be largely responsible for

ginseng's antifatigue activity in mental and physical performance. The CNS activity of ginseng is essentially different from that of usual stimulants. Although stimulants are active under most situations, ginseng reveals its stimulatory action only with the challenge of stress.[22]

On the physical level, ginseng's antifatigue properties appear to be closely related to its ability to spare glycogen utilization in exercising muscle.[9] Exercise physiologists clearly established that during prolonged exercise, the development of fatigue is closely related to the depletion of glycogen stores and the buildup of lactic acid, both in skeletal muscle and in the liver. If an adequate supply of oxygen is available to the working muscle, nonesterified fatty acids are the preferential energy substrate, thus sparing utilization of muscle glycogen, blood glucose, and, consequently, liver glycogen. The greater the ability to conserve body carbohydrate stores through mobilization and oxidizing of fatty acids, the greater the amount of time to exhaustion. Ginseng enhances fatty acid oxidation during prolonged exercise, thereby sparing muscle glycogen stores.[9]

Mental and physical antifatigue activity effects were demonstrated in both animal studies and double-blind clinical trials in humans. In one double-blind clinical study, nurses who switched from day to night duty rated themselves for competence, mood, and general well-being, and were evaluated with an objective test of psychophysical performance, blood cell counts, and blood chemistry analysis. The group administered ginseng demonstrated higher scores in competence, mood parameters, and objective psychophysical performance than those who received a placebo.[23]

From a clinical standpoint, ginseng's antifatigue properties may be useful whenever fatigue or lack of vigilance is apparent. In particular, cancer patients who underwent chemotherapy, patients with chronic obstructive pulmonary disease (COPD), and athletes were all shown to benefit from ginseng use. In regards to COPD, in one double-blind study, 92 adults with COPD were randomly assigned to receive either ginseng or placebo.[24] Pulmonary function tests, maximum voluntary ventilation, maximum inspiratory pressure, and maximal oxygen consumption were studied before treatment and every 2 weeks for the 3-month study. In the ginseng group, but not in the control group, all parameters were significantly higher than baseline and higher than the parameters in the placebo group. Maximum increases, in comparison with baseline, were forced vital capacity 32.5%, forced expiratory $volume_{1.0}$ 27.0%, maximum voluntary ventilation 40.4%, maximum inspiratory pressure 47.0%, and maximal oxygen consumption 37.5%. No side effects were observed.

In a large study in 290 cancer patients, subjects were randomized in a double-blind manner to receive American ginseng in doses of 750, 1000, or 2000 mg/day or placebo given in twice daily dosing over 8 weeks. Over twice as many patients on ginseng perceived a benefit and were satisfied with treatment over those on placebo.[25] In another double-blind trial, 53 cancer patients were randomly assigned to receive ginseng (3000 mg/day) or placebo for 12 weeks. Quality of life was assessed using the World Health Organization Quality of Life Assessment-BREF (WHOQOL-BREF) and the General Health Questionnaire-12.[26] After 12 weeks of therapy, the "psychological domain " score of the WHOQOL-BREF was significantly improved in patients randomized to ginseng, compared with those randomized to placebo. There was a tendency for ginseng to improve the "physical health" and "environment" domain scores of the WHOQOL-BREF, compared with placebo. The General Health Questionnaire-12 total score was significantly improved in patients treated with ginseng than in those with placebo. These results from clinical trials indicate ginseng is of benefit in improving some aspects of mental and physical functioning in cancer patients.

Cognitive Performance

Standardized extracts of *P. ginseng* alone or in combination with *Ginkgo biloba* (a formula called Gincosan) were shown to improve cognitive performance in animal and clinical studies.[27-36] In one of the earlier studies (a double-blind, crossover design) in university students in Italy, ginseng extract alone was compared with placebo in various tests of psychomotor performance. A favorable effect of ginseng relative to baseline performance was observed in attention (cancellation test), mental arithmetic, logical deduction, integrated sensorimotor function (choice reaction time), and auditory reaction time. However, statistically significant superiority of the ginseng group over the placebo group was noted only for mental arithmetic. It was interesting to note that during the course of the trial, the students taking ginseng reported a greater sensation of well-being.[29] Later studies in college-aged students showed similar results with a clear dose dependency.[30-32] However, unlike studies in older subjects, no positive effect on mood or quality of life has yet been demonstrated with ginseng administered to healthy young adults.

The benefits of ginseng on cognitive performance, mood, and quality of life assessment are considerably greater in middle-aged adults than in younger adults. In several studies of the administration of ginseng alone or in combination with *G. biloba* extract, significant improvements were noted, not only in tests of cognition and memory, but also in social functioning and mental health.[33-35] In one study, however, the results attenuated after 4 weeks of use, indicating that cotherapy with *G. biloba* may be more efficacious or that cycling of the ginseng dosage may be necessary to produce a prolonged effect.[35]

Both *G. biloba* and *P. ginseng* have been shown to modulate aspects of cognitive performance, including effects on EEG recordings. One double-blind, placebo-controlled, balanced crossover experiment assessed, in 15 healthy volunteers, the effects of single doses of *G. biloba* extract (360 mg), a proprietary *P. ginseng* extract (200 mg G115), and an identical placebo on auditory-evoked potentials, contingent negative variation, and resting power within the δ, θ, α, and β wavebands.[36] The results showed that ginseng use led to a significant shortening of the latency of the P300 component of the evoked potential. Both ginseng and ginkgo also led to significant reductions in frontal "eyes closed" θ and β activity, with additional reduction for ginseng in the α waveband. These findings demonstrated for the first time that *P. ginseng* can directly modulate EEG activity, and that these effects are more pronounced than those that follow ingestion of *G. biloba*. Additional studies with G115 also showed an ability to enhance cognitive function in normal subjects.[37-39]

In regards to improving cognitive performance in Alzheimer's disease (AD), there appears to be some benefit based upon the results from an open label study.[40] In the study, consecutive AD patients were randomly assigned to the ginseng (n = 58) or the control group (n = 39), and the ginseng group was treated with *P. ginseng* powder (4.5 g/day) for 12 weeks. Cognitive performances were monitored using the Mini-Mental State Examination (MMSE) and Alzheimer's disease assessment scale (ADAS) during 12 weeks of the ginseng treatment and for 12 weeks after the ginseng discontinuation. MMSE and ADAS scales showed no baseline difference between the groups. After ginseng treatment, the cognitive subscale of ADAS and the MMSE scores began to show improvements and continued up to 12 weeks. After discontinuing

ginseng, the improved ADAS and MMSE scores declined to the levels of the control group. These results suggest that *P. ginseng* is clinically effective in the cognitive performance of AD patients.

As an Ergogenic Aid

The benefits of ginseng on athletic performance are not clear. Results of later double-blind studies were negative. For example, one study, in which 36 healthy young men received a standardized ginseng extract (Ginsana) at a dosage of 400 mg/day, showed that ginseng had no effect on any exercise-related parameter (e.g., blood lactic acid concentration, heart rate, and perceived exertion).[41] Similar results were seen in a study in women, and an even more comprehensive laboratory evaluation in 38 healthy adults also showed no improvement in any parameter.[42,43] The totality of results at this time do not offer support for claims that ginseng improves athletic performance. However, other benefits were noted, such as an ability to protect against muscle injury and inflammation in athletes, reduced exercise-induced oxidative stress, reduced post-exercise plasma creatine kinase levels, as well as improved psychomotor performance at rest during a graded exercise test.[44-47]

Diabetes

Ginseng, used either alone or in combination with other botanicals, has a long folk use in the treatment of diabetes. This hypoglycemic activity was confirmed in both experimental and clinical trials. In one double-blind study in type 2 diabetes, ginseng therapy reduced fasting blood glucose levels, elevated mood, improved psychophysical performance, and lowered body weight and glycosylated hemoglobin.[48]

The chief constituents responsible for this effect are as follows[49-53]:

- Five glycans (polysaccharides designated panaxans A to E)
- Adenosine
- A carboxylic acid
- A peptide
- A fraction designated DPG-3-2

The ratio of ginsenosides also appears to be an important factor. In one human study, the ratio of protopanaxadiol/protopanaxatriol was the sole predictor of whether or not a ginseng preparation would exert hypoglycemic effects.[54] It appears that it is important to utilize crude, standardized extracts having a higher protopanaxadiol/protopanaxatriol ratio, such as those from American ginseng extract, to produce the desired benefit.

Powdered American ginseng root *(P. quinquefolius)* at a dosage of about 3 g before each meal was shown to reduce postprandial blood sugar significantly in patients with type 2 diabetes. It was determined that American ginseng worked through the stimulation of pancreatic β-cells, with a subsequent increase in insulin secretion. This substance also has significant antioxidant properties and improves cognitive function. In addition, American ginseng was shown to possess nerve protection and regeneration properties. This could prove to be valuable in diabetes, in which peripheral and autonomic nerve damage so often occurs.[55-57]

It is interesting to note that ginseng raises serum cortisol levels in nondiabetic individuals but reduces serum cortisol levels in patients with diabetes.[58] Because cortisol antagonizes insulin, this is presumably a beneficial effect. This action again demonstrates ginseng's nonspecific balancing effect, which is baffling to researchers accustomed to investigating compounds with consistent pharmacologic effects.

In double-blind, randomized, crossover design study in 19 patients with well-controlled type 2 diabetes, each participant received the selected ginseng preparation (rootlets) and placebo at the selected dose (2 g/meal = 6 g/day) and mode of administration (preprandial oral agent [–40 minutes]) for 12 weeks as an adjunct to their usual antidiabetic therapy (diet and/or medications). Although there was no change in the primary end point, glycosylated hemoglobin, ginseng treatment decreased 75 g oral glucose tolerance test plasma glucose (OGTT-PG) indexes by 8% to 11% and fasting plasma insulin (PI) and 75 g OGTT-PG indexes by 33% to 38%, and increased the fasting insulin sensitivity index and 75 g OGTT-insulin sensitivity index by 33%, compared with placebo.[59]

In another double-blind study, improvements were seen with American ginseng supplementation on fasting blood sugar levels and insulin resistance in type 2 diabetic patients. Proposed mechanisms included effects on insulin release from pancreatic β-cells, insulin-stimulated glucose disposal, and increasing insulin sensitivity related to the peroxisome proliferator-activated receptor.[60]

Based upon current information, ginseng appears useful as an adjunctive therapy in the treatment of diabetes, both for its antihyperglycemic effect and for its ability to decrease the atherogenic index (see later). Although the root has received the most attention, animal studies indicate that extracts from the ginseng berry may even be more beneficial due to a higher concentration of ginsenoside R_e.[58,61]

Reproductive Effects

Although it is claimed to be a "sexual rejuvenator" and aphrodisiac, human studies supporting this belief are scanty. In animal studies, however, ginseng was shown to have the following effects[62,63]:

- Promotes the growth of the testes and increases spermatogenesis in rabbits
- Accelerates the growth of the ovary and enhances ovulation in frogs
- Stimulates egg-laying in hens
- Facilitates lordotic response in female rats
- Increases gonadal weight in both male and female rats
- Raises testicular nucleic acid content in rats
- Increases sexual activity and mating behavior in male rats

These animal study results seem to support ginseng's use as a fertility and virility aid.

In other experimental animal studies, ginseng was shown to increase testosterone levels while reducing prostate weight.[64] This finding suggests that ginseng should have favorable effects in the treatment of benign prostatic hyperplasia; however, no clinical trials have yet been reported.

Ginsenosides were also shown to bind to human myometrial receptor proteins, and they apparently exert estrogen-like action on the vaginal epithelium. These activities are significant enough to prevent the atrophic vaginal changes associated with postmenopause and other menopausal symptoms.[65]

Other clinical indications involving the reproductive system (based on historical use and experimental evidence) are decreased sperm counts, testicular atrophy or hypofunction, other organic causes of male infertility, ovarian atrophy or hypofunction, amenorrhea, and other organic causes of female infertility. It should be noted that several reports of mastalgia were reported in women taking ginseng.[66,67]

Most of the later clinical studies involving reproductive effects focused on ginseng's effect on erectile dysfunction (ED). A plausible

mechanism involves evidence that ginsenosides can facilitate penile erection by directly inducing the vasodilatation and relaxation of penile corpus cavernosum, which is mediated by the release and/or modification of the release of nitric oxide from endothelial cells and perivascular nerves.[68-70]

In one double-blind, crossover study, 45 patients with clinically diagnosed ED showed significantly higher mean International Index of Erectile Function (IIEF) scores with Korean red ginseng than those who received placebo. In response to the global efficacy question, 60% of the patients answered that Korean red ginseng improved erection.[70]

In a double-blind, placebo-controlled trial, a tissue-cultured mountain ginseng extract (TMGE) or placebo was given to 86 male patients with ED. Over the course of 8 weeks, one group took 1000 mg of TMGE twice a day, and the other group took 1000 mg of placebo twice a day. The effects of the TMGE and the placebo were analyzed using the IIEF questionnaire. All 86 patients completed 8 weeks of treatment. The scores on the five domains of the IIEF after medication were significantly higher than the baseline scores in the group treated with TMGE, whereas no significant improvement was observed in the placebo group. Erectile function and overall satisfaction scores after medication were significantly higher in the TMGE group than in the placebo group.[71]

In another double-blind study, 60 patients presenting with mild or mild to moderate ED were given either *P. ginseng* at a dosage of 1000 mg three times daily or a placebo. The IIEF score after treatment was significantly higher in the ginseng group compared with that before the treatment. In contrast, there was no difference before and after the treatment in the placebo group.[72]

Menopause

Ginseng has also been a popular treatment for menopausal symptoms; however, clinical research is unconvincing. One double-blind study in 384 menopausal women was performed to compare the effects of a standardized ginseng extract with those of a placebo on quality of life, menopausal symptoms, and physiologic markers of menopause (follicle-stimulating hormone and estradiol levels, endometrial thickness, maturity index, and vaginal pH). Although the ginseng extract showed no statistically significant effects on the physiologic parameters, including vasomotor symptoms (hot flashes), it was associated with statistically significant improvements in mood and well-being.[73]

Cell-Proliferating, Antioxidant, and Antiaging Effects

Ginseng has a dual effect on cell growth: it stimulates cell division in an adequate nutritional environment but acts cytostatically under adverse conditions (as described in "Diabetes" section).[73] Furthermore, ginseng yielded impressive results in lengthening the lifespan of cells in culture.[74]

This enhancement of cellular proliferation and function was shown in a variety of cell types (epithelial, hepatic, lymphocyte, fibroblast, thymic, etc.), but especially in nerve cells, which appears to be a result of potentiation of nerve growth factor by ginsenosides.[3,75-77]

Clinically, these results indicate a potential use of ginseng in healing damage to virtually all tissue types, but especially the brain. In animal studies, ginseng was shown to reduce oxidative stress, scavenge free radicals directly, protect endothelial cells from damage, and increase cellular antioxidant enzymes like superoxide dismutase.[78-83] Again, these effects demonstrate ginseng's nonspecific action. Its effect on improving arterial endothelial function is especially novel.[84]

Immunomodulating Effects

That ginseng possesses immunomodulating activity is evidenced by its ability to enhance the following immune functions[85-92]:

- Antibody plaque-forming cell response
- Circulatory antibody titer against sheep erythrocytes
- Cell-mediated immunity
- Natural killer (NK) cell activity
- The production of interferon
- Lymphocyte mitogenesis
- Reticuloendothelial system proliferative and phagocytic functions

In addition to these immunostimulatory aspects, ginseng components were shown to exert antiallergy and anti-inflammatory effects in experimental models.[93,94]

From a clinical perspective, the long-term ingestion of ginseng by individuals with mild immunodeficiency may reduce the risk of viral infection. Its use in this manner is consistent with the historic use of ginseng by debilitated individuals. There is clinical evidence of benefit in these applications. Extracts of *P. ginseng* were found to stimulate NK function in normal individuals and patients with either chronic fatigue syndrome or AIDS.[95] Ginseng was shown to prevent respiratory viral infections in a nursing home environment (89% relative risk reduction) and potentiate influenza vaccinations.[96,97]

It should be noted that large dosages of ginseng may be contraindicated in acute infections. The reason may be its in vitro inhibition of lymphocyte transformation (similar to cortisone) at high (i.e., more than 1 mg/mL), but not low concentrations.[98,99] In vitro, ginseng at 1.6 mcg/mL was shown to inhibit phytohemagglutinin-induced transformation of peripheral blood lymphocytes to a greater degree than cortisone at 500 mcg/mL.[98] The greatest level of inhibition, however, was observed when ginseng was used in combination with cortisone. These results suggest that ginseng at high doses may be effective against T-cell–mediated inflammatory diseases without producing glucocorticoid-like side effects. It also suggests that a lower dose of cortisone could be used if ginseng were given simultaneously.

When using ginseng, the clinician must remember: (1) that ginseng's in vitro effect on lymphocyte proliferation is biphasic, that is, it exerts a strong inhibition at high concentrations and a moderate stimulation at low concentrations; and (2) that although ginseng has demonstrated significant inhibition of lymphocyte proliferation in vitro, this has not been the observed effect in vivo, in which lymphocyte proliferation has been enhanced.[87] These effects may be related to a dose-dependent ginseng-induced elevation of interferon (which inhibits lymphocyte proliferation).

Anticancer Properties

Regular ginseng consumption may protect against cancer. In two large population studies, the risk for development of cancer was significantly lower among people who consumed ginseng on a regular basis. Ginseng extract and powder were shown to be more effective than fresh sliced ginseng, ginseng juice, or ginseng tea in reducing cancer risk. A statistically, highly significant dose–response relationship between ginseng intake and cancer risk was observed. These results support the preventive and anticancer effects of ginseng demonstrated in animal and in in vitro studies.[100-102]

Long-term oral administration of ginseng to newborn mice was shown to reduce the incidence and also to inhibit the proliferation of tumors induced by various chemical carcinogens, including 7,12-dimethylbenz[*a*]anthracene, urethane, and aflatoxin B_1.[45]

The anticancer effects of ginseng in other experimental models can be summarized as follows[102-106]:

- Ginseng promotes apoptosis.
- The effect is observed only in slow-growing tumors, such as Ehrlich and sarcoma 180 ascites tumor.
- The effect is not observed in rapidly growing tumors, such as l1210, p388, and Walker carcinoma.
- There is no dose–response relationship or cumulative effect.

The lack of a dose–response relationship suggests that ginseng's anticancer effects are indirect and subject to a threshold mechanism. Thus, ginseng once again appears to demonstrate nonspecific effects.

In addition to a possible role in cancer prevention, some researchers are investigating *P. ginseng* extracts as a possible adjunct in cancer treatment.[107] Exerting some direct and indirect anticancer actions, ginseng may also offer protection against chemotherapy-induced damage to normal cells. In one animal study, *P. ginseng* extract was shown to protect against cisplatin nephrotoxicity.[108]

Cardiovascular Effects

From a clinical perspective, ginseng may offer some protection against atherosclerotic disease, further supporting its use as a general tonic. It may also possess a blood pressure–regulating effect via improvement in the endothelial dysfunction underlying many cases of hypertension.[109]

Ginseng administered to human subjects with hyperlipidemia was shown to reduce total serum cholesterol, triglycerides, and nonesterified fatty acid levels while raising serum high-density lipoprotein cholesterol levels. Platelet adhesiveness was also decreased.[110]

These results in humans confirmed earlier studies on rats fed high-cholesterol diets.[111,112] The mechanism of action appears to be through accelerated degradation, conversion, and excretion of cholesterol and triglycerides despite increased lipogenesis and cholesterogenesis. Ginseng was also shown to be effective in inhibiting platelet aggregation and the conversion of fibrinogen to fibrin.[113]

Hepatic Effects

Obviously, any adaptogenic substance must affect the liver because of this organ's central role in metabolic and detoxification reactions. Ginseng affects the liver in several ways. Perhaps the most important is its ability to produce a marked hyperplasia of the Kupffer cells of the liver and of the folliculi in the spleen and lymph nodes.[10] The hyperplastic folliculi show an increase in the number and volume of light centers, thus demonstrating morphologic evidence of increased host defense capacity against a wide variety of external assaults. Because these cells are responsible for filtering out much of the toxins and debris from the portal circulation, increasing their number and activity could have profound effects.

Ginseng was also shown to increase nuclear RNA biosynthesis, indicating greater protein synthesis.[3,114] Ginseng was shown to increase not only nuclear RNA synthesis, but also ribosomal and messenger RNA, the amount of rough endoplasmic reticulum, and the activity of RNA polymerase.[3,114-116] These results indicate that ginseng activates virtually every step in protein biosynthesis. Since protein synthesis is often reduced in the elderly, the significance of the described effects on enhancement of hepatic protein synthesis could be extremely high. However, these results have yet to be confirmed by clinical studies.

Ginseng was also shown to reverse diet-induced fatty liver in animals and to possess significant antihepatotoxic action.[117] The clinical indications of these hepatic actions of ginseng are quite broad and support its general tonic/adaptogen properties.

Radiation-Protecting Effects

Ginseng was shown to offer some protection against harmful radiation, both in vivo and in vitro, and to hasten recovery from radiation sickness.[118,119] In the presence of ever-increasing environmental radiation contamination, ginseng may be an appropriate prophylactic against radiation exposure.

TOXICOLOGY

The problem of quality control makes toxicology difficult to address. This is exemplified by a 1979 article in the *Journal of the American Medical Association* titled "Ginseng Abuse Syndrome."[120] In this article, a number of side effects of commercial preparations of ginseng were reported, including the following:

- Hypertension
- Euphoria
- Nervousness
- Insomnia
- Skin eruptions
- Morning diarrhea

Given the extreme variation in quality of ginseng in the American marketplace and the use of both nonofficial parts of the plant and adulterants, it is not surprising that side effects were noted. None of the commercial preparations used in the trial were subjected to controlled analysis. Furthermore, the species of ginseng used included *P. ginseng*, *Panax quinquefolius*, *Eleutherococcus senticosus*, and *Rumex hymenosepalus* in a variety of different forms—roots, capsules, tablets, teas, extracts, cigarettes, chewing gum, and candies. It is virtually impossible to derive any firm conclusions from the data presented in the *JAMA* article. The author's final words do, however, seem sensible and appropriate:

> *An important caveat is that these GAS [ginseng abuse syndrome] effects are neither uniformly negative nor uniformly predictable. Nevertheless, long-term ingestion of large amounts of ginseng should be avoided, as even a panacea can cause problems if abused.*

Studies performed on standardized extracts of ginseng demonstrated the absence of side effects and mutagenic or teratogenic effects.[121-123] These studies differed markedly from the trial reported in *JAMA,* in that high-quality extracts were used. An extensive review of the safety of *P. ginseng* concluded, "Data from clinical trials suggest that the incidence of adverse events with ginseng monopreparations is similar to that with placebo."[120]

DOSAGE

The dosage of ginseng is inversely proportional to the ginsenoside content; that is, if an extract or ginseng preparation contains high concentrations of ginsenosides (and presumably other active components), a lower dose suffices. The standard dose for ginseng is in the range of 4.5 to 6 g/day.

Currently, there is almost a total lack of quality control in ginseng products marketed in the United States. Independent research and published studies clearly documented a tremendous variation in the ginsenoside content of commercial preparations.

Many products on the market contain only trace amounts of ginsenosides, and some formulations contain no ginseng at all. This situation has led to several problems, ranging from toxicity reactions (discussed later) to lack of medicinal effect. The widespread disregard for quality control in the health food industry has done much to tarnish the reputation of ginseng as well as other important botanicals.

We recommend the use of standardized ginseng preparations to ensure sufficient ginsenoside content, consistent therapeutic results, and reduced risk of toxicity. Products should be standardized in their ginsenoside content. The typical dose (taken one to three times daily) for general tonic effects should contain a saponin content of at least 5 mg of ginsenosides with an R_{b1}/R_{g1} ratio of 2:1. For example, for a high-quality ginseng root powder containing 5% ginsenosides, the dose would be 100 mg.[123]

Because each individual's response to ginseng is unique, the patient should be monitored for signs of possible ginseng toxicity (see later). It is best to begin at a lower dose and increase it gradually. The Russian approach for long-term administration is to use ginseng cyclically for a period of 15 to 20 days followed by a 2-week interval without any ginseng.

DRUG INTERACTIONS

Taking ginseng preparations may increase the effectiveness of insulin and drugs that lower blood sugar levels such as glyburide (Diabeta, Micronase). It is important to discuss proper monitoring of blood sugar levels with patients who have diabetes before prescribing ginseng. *P. ginseng* may potentiate the monoamine oxidase inhibitor phenelzine (Nardil) to produce manic-like symptoms.[123]

Ginseng may reduce the effectiveness of Coumadin (warfarin). In one double-blind study designed to evaluate the interactions between American ginseng and Coumadin (warfarin), twenty healthy volunteers received warfarin for 3 days during weeks 1 and 4.[124] Beginning in week 2, patients were assigned to receive either American ginseng or placebo. The peak international normalized ratio statistically significantly decreased after 2 weeks of ginseng administration compared with placebo, with the difference between ginseng and placebo being zero. The international normalized ratio area under the curve, peak plasma warfarin level, and warfarin area under the curve were also statistically significantly reduced in the ginseng group compared with the placebo group. These results indicate a potential for ginseng reducing the effectiveness of warfarin; however, in a study in stroke patients, no interaction was noted.[125] Until this interaction is further clarified, ginseng should only be used with careful monitoring, if at all, in patients on Coumadin.

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CHAPTER 111

Pancreatic Enzymes

Anthony J. Cichoke, Jr., MA, DC, DACBN, PhD

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INTRODUCTION

Pancreatic enzymes produced by the body are well known for the integral role they play in the digestion of the foods we eat. Pancreatic juice contains numerous enzymes, including amylase, lipase, cholesterol esterase and phospholipase, and the proenzymes trypsinogen, chymotrypsinogen, and procarboxypolypeptidase, which are converted in the small intestine to their active forms trypsin, chymotrypsin, and carboxypeptidase, respectively.[1]

Foods in the human diet are composed primarily of protein, carbohydrates, and fats. Protein leaves the stomach predominantly in the form of proteoses, peptones, and large polypeptides.[2] Upon reaching the small intestine, these are further digested by the proteolytic enzymes trypsin, chymotrypsin, and carboxypolypeptidase. Protein digestion primarily occurs in the duodenum and jejunum. Carbohydrates are digested by α-amylase in the pancreatic juice, which breaks starches (converting them into maltose and other small glucose polymers), whereas pancreatic lipase, cholesterol esterase, and phospholipase digest fats.[1,3]

Although critical for proper digestion, pancreatic enzymes also aid in a surprising variety of bodily functions, including detoxification, immunity, aging, blood fluidity, and tissue repair. Unfortunately, an inadequate production of, or an excessive requirement for, pancreatic enzymes can occur for a variety of reasons, including genetics, illness, injury, exercise, aging, and toxins (both endogenous and exogenous). Many authorities believe that a deficiency of pancreatic enzymes, for whatever reason, may be the cause of numerous illnesses and degenerative conditions. When a deficiency occurs, enzymes from an external source may be necessary.

HISTORY

Pancreatic enzymes have a long history of clinical use. In the early twentieth century, John Beard, a Scotch embryologist, successfully treated cancer using a pancreatic extract, which he described in his book, *The Enzyme Treatment of Cancer and Its Scientific Basis*. Beard injected pancreatic juice (freshly extracted from young animals) into cancer patients and, when possible, directly into their tumors. He found that the pancreatic juice could inhibit the growth of cancer cells.

In 1934, Dr. Ernst Freund, a Viennese physician, studied the blood of people who were free from cancer and discovered a substance that had the ability to dissolve cancer cells. Patients with cancer did not have this material, which Freund called "normal substance." In the early 1930s, Professor Doctor Max Wolf worked with Freund in Vienna and successfully identified "normal substance" as an enzyme that decomposes fatty materials and proteins. For his work in the field of enzymes, Wolf is generally considered the father of modern enzyme therapy. The work of Freund and John Beard sparked Wolf's interest in the possibilities of treating malignant diseases with enzymes. He subsequently founded the Biological Institute of New York City and, after studying various enzymes and enzyme combinations,

developed what he regarded as an optimal preparation for the treatment of various acute and chronic conditions. His preparation was a combination of a fractionated hydrolysate of beef pancreas, calf thymus, *Pisum sativum* (common pea), *Lens esculenta* (edible lentil), mannitol, and *Carica papaya* (papaya, a source of the enzyme, papain).

In the 1960s, Irving Innerfield conducted landmark research in the area of pancreatic enzymes, primarily relating to the clinical use of trypsin, chymotrypsin, and pancreatin as well as streptokinase (a microbial proteolytic enzyme). Professor Heinrich Wrba, who for many years was head of the Austrian Cancer Research Institute at the University of Vienna, believed that enzyme therapy should be considered a highly-effective causal anti-cancer compound. Dr. Wrba's interest in cancer was piqued when he lost a daughter to leukemia. He devoted his life to educating oncologists in Germany and around the world about enzyme therapy.

It was the late Karl Ransberger, however, who continued and refined Wolf's research, bringing it to doctors, hospitals, and patients throughout the world. Ransberger encouraged and funded research projects in numerous hospitals and universities in Europe, the Americas, and elsewhere. His research, and that of others, validated enzyme therapy's effectiveness in treating numerous conditions, including arthritis, cancer, multiple sclerosis, cardiovascular disease, human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS).

PANCREATIC ENZYME SUPPLEMENTS

The pancreatic enzyme supplements most commonly used in health care are chymotrypsin, trypsin, pancrelipase, and pancreatin. Chymotrypsin and trypsin are proteolytic enzymes that break proteins into peptides. Chymotrypsin liberates the amino acids, L-tyrosine, L-tryptophan, and L-phenylalanine, and other molecules, including several synthetic esters and amides.[4] Trypsin hydrolyzes primarily lysyl and arginyl residues. Pancreatin contains amylase (which breaks down starch), lipase (which breaks down fats), and protease (which breaks down proteins). Pancrelipase is similar to pancreatin, but with a higher concentration of lipase.

These enzymes are primarily obtained from hog or ox pancreas, but some (such as lipase) can also be obtained from microbial sources (e.g., *Aspergillus niger* and *Aspergillus oryzae*). Nevertheless, only enzymes isolated from animal pancreatic glands can be considered pancreatic enzymes.

According to the *U.S. Pharmacopeia* (USP), chymotrypsin and trypsin are routinely crystallized from ox pancreas gland extract, and pancreatin from both hog and ox sources, whereas pancrelipase is derived from hog pancreas.[5] Porcine pancreas is especially rich in amylase and lipase, and is similar to the human pancreas.[4] Bovine pancreas contains considerable amounts of proteolytic enzymes, but substantially lower amounts of lipase and amylase.[4] Germany, Japan, England, India, and other countries utilize their own pharmacopeia, and foreign companies may use other sources to formulate their enzyme products.

Enzyme concentration and activity levels can vary depending on the age, sex, and species of pork or ox used to produce the supplement. For example, sow glands (from pork) are high in lipase, whereas butcher hogs (young male hogs, up to 90 kg in weight and 6 months of age) are high in protease. Beef cows and bulls have different enzyme levels from those in steers or heifers. Beef, although it provides all three basic enzyme types, does not exhibit the activity levels of pork (which has an activity level one third to one half higher). Furthermore, the physiology of hogs is more similar to that of humans than to that of any other animal.

Enzymes extracted from animal sources are sensitive to environmental changes, so manufacturers take particular care during extraction to control pH (usually with buffers), temperature (using precooled solutions and apparatus), substrate, and proteolysis (controlled through the use of inhibitors) to render a product that is enzymatically active.[6]

Enzyme Standardization

In 2010, the Food and Drug Administration (FDA) began requiring manufacturers of pancreatic enzyme products to test them in clinical trials if those products were prescribed to treat individuals with pancreatic diseases. Until that time, there were frequent inconsistencies in enzyme formulation. For example, a study of six different enzyme preparations found that, in some cases, the actual lipase activity in a product was more than twice that listed on the label.[7] Another study on nine pancreatic enzyme products found that, although within USP limits, the percentage of lipase activity after dissolution was not always equal.[8] These inconsistencies in content and activity level could unexpectedly alter patient enzyme requirements.

The FDA's ruling ensures that pancreatic enzymes are standardized with consistent activity level. Pancreatic enzymes marketed as dietary supplements, however, do not require testing or approval by the FDA. The requirements regarding activity level apply only to those pancreatic enzyme products prescribed for exocrine pancreatic insufficiency due to cystic fibrosis (CF), chronic pancreatitis, and other conditions.

ABSORPTION OF PROTEINS

In the past, it was believed that the intestinal epithelial mucosa was impermeable to large protein molecules.[9] However, research over the past several decades has shown that the intestinal epithelium can be crossed by macromolecules, including intact proteins such as proteolytic enzymes.[10]

These macromolecules normally penetrate the mucosal surface via the transcellular route as, in healthy mucosa, the tight junctions (zonula occludens) between the enterocytes prohibit paracellular passage.[11] Binding to the luminal membrane of the enterocyte is followed by phagocytosis.[12] Some of the vacuole membrane vesicles formed fuse with lysosomes, and within the resulting phagolysome, the peptides and proteins may be hydrolyzed by lysosomal enzymes.[13] Other macromolecules avoid intracellular digestion and are passed from the enterocytes through the basolateral membrane into the interstitial space.[14] In the interstitial space, the macromolecules become available to macrophages and lymphoid cells.[15] Those molecules not taken up by macrophages or lymphatic cells eventually pass from the interstitial space into the blood or lymph.[16]

The transport of macromolecular material from the lumen to the interstitium has been extensively studied in the epithelium covering the lymphatic structures, such as Peyer's patches or isolated follicles.[12] In these regions, specialized enterocytes, the follicle-associated epithelium cells[17] or M-cells[18] (so called because of their occurrence in the microfolds of the luminal surface), transport macromolecular material in both directions.[17] The gut-associated immune system is thus supplied with antigenic macromolecules from the intestinal lumen.[19] The immunoglobulins produced by the plasma cells in the lamina propria (mainly immunoglobulin-A) are transported transcellularly to the luminal surface.

TABLE 111-1 **Absorption Rate of Individual and Combined Enzymes (within 6 Hours)[27,28]**

ENZYME	ABSORPTION RATE (%)
Amylase	45
Chymotrypsin	14-16
Pancreatin	18-19
Papain	6
Trypsin	26-28
Enzyme combination (bromelain, chymotrypsin, pancreatin, papain, and trypsin, with the bioflavonoid rutin)	22

The exact level of the intestinal absorption of intact molecules or large breakdown products of dietary proteins is not yet totally clear and can vary by individual.[20] Although it is generally assumed that, apart from a very small proportion, all protein is hydrolyzed into amino acids or low-molecular-weight peptides before absorption by the mucosa, some research supports the hypothesis that a considerable proportion of dietary protein is taken up in the form of macromolecules and is only then hydrolyzed intercellularly in the peripheral tissue into amino acids (a process called "distributed digestion").[21]

Understanding the Absorption of Enzymes

Understanding the intestinal transport of macromolecules is especially important for understanding the functions and absorption of enzymes specifically. Hydrolases such as trypsin or elastase can be transported functionally intact into the bloodstream from the lumen of the gut. These circulating proteinases are bound to antiproteinases, such as alpha$_2$ macroglobulin or alpha$_1$ antiproteinase,[22] and can be resorbed from the main bloodstream by pancreatic cells (enteropancreatic circulation as an enzyme conservation process).[23] Thus, the intestinal absorption of intact enzymes appears to be important for the balance between hydrolases and antiproteinases in the intracellular space,[24] and is an important factor for the establishment and maintenance of the internal stability in the body.

Although there are a number of absorption mechanisms, the primary mechanism for the enteral absorption of enzymes and other macromolecules is pinocytotic transfer by the M-cells of the small intestinal epithelium. The enzymes connect to a receptor in the intestinal wall mucosa and are then absorbed into the wall by pinocytosis, guided through the intestinal cells in vesicles, and finally released into the blood by exocytosis.[25]

To clarify rate of absorption, Steffen et al[26] investigated the absorption of an enzyme mixture "A" (EMA), which contained 100 mg of pancreatin, 60 mg of papain, 10 mg of lipase, 10 mg of amylase, 24 mg of trypsin, 1 mg of chymotrypsin, 45 mg of bromelain, and 50 mg of the bioflavonoid rutin in rabbits. Using electrophoresis, these researchers found that entire enzyme molecules were absorbed. Although enzyme particles were also present, the ratio to the entire amount administered was not measured. EMA was found in both lungs and liver after 1 to 2 hours. After 1 to 4 hours, approximately twice as much EMA was found in the liver as in the lungs. The absorption maximum in all animals occurred approximately 1 hour after administration. After 24 hours, EMA was no longer found in either the lungs or liver.

The absorption rate of individual and combined enzymes can be found in Table 111-1.[27,28] The absorption rate of orally-ingested EMA is about 20% within 6 hours.[19]

FACTORS AFFECTING ENZYME ACTIVITY

Numerous factors including pH, temperature, substrate (and substrate concentration), cofactors, metal ions, inhibitors, and coating can affect the activity of supplemental enzymes.

Optimal pH Range

Each enzyme has an optimal pH range, depending on such variables as temperature and substrate concentration at which the enzymatic catalytic reaction occurs most rapidly. Chymotrypsin has an optimum pH of 8.0, has reversible denaturation at a pH below 3.0, and becomes inactive at a pH above 9.0.[4] Trypsin has an optimum pH between 7.0 and 9.0, is stable at a pH of 3.0 (and at low temperature), and is irreversibly denatured at a pH of 9.0 or higher.[4] The pH of the normal human stomach is 1.5 to 3.0,[29] low enough to denature or inactivate some or all of a pancreatic enzyme supplement if it is not enterically coated or otherwise treated to protect it from a low-pH environment.

The Effects of Temperature

In general, an increase of 50° F (10° C) in the enzymatic environment approximately doubles the rate of the chemical reaction.[30] However, because enzymes are proteins, excessively high temperatures can denature them, thus destroying their activity. Optimum temperature for an enzyme is the temperature at which the catalyzed enzymatic reaction progresses most rapidly without damage to the enzyme. This temperature can vary by enzyme. This is a good rationale for avoiding hot beverages when taking enzyme supplements.

The enzymes in the human body develop high levels of activity at about body temperature, increasing to maximum at about the temperature of a severe fever, that is, 104° F (40° C).

Substrate Concentration

The rate of any reaction is accelerated by raising the substrate concentration until the enzyme is saturated by substrate. At this level, the rate of reaction becomes independent of substrate concentration and is no longer accelerated by the addition of more substrate. This is why it is particularly important to ingest sufficient quantities of supplemental enzymes (which vary according to the condition being treated).

Cofactors

Although all enzymes consist of protein, some are complex proteins, that is, they have a protein component and a "cofactor." If the cofactor is removed, the protein (no longer active enzymatically) is called the apoenzyme. A cofactor might be a metal (e.g., iron, magnesium, copper, or zinc), a prosthetic group (a moderately-sized organic molecule), or a coenzyme (small organic compound). Prosthetic groups and metals can aid in the catalytic function of the enzyme, whereas coenzymes take part in the enzymatic reaction. Many vitamins, trace elements, and minerals essential to human bodily function are part of enzymatic cofactors. So the physician must ensure that his or her patients take multivitamins and multiminerals to "feed" their enzymes.

Coenzymes are essential for the activity of many enzymes and serve as a type of substrate in certain reactions. In these reactions, the coenzyme is converted to a form no longer active in catalyzing the reaction. The reaction requires a mix that contains one molecule of cofactor for every molecule of substrate to be converted.

Metal Ions

Specific metal ions are required for the activity of many enzymes. Some metal ions increase enzyme activity and others decrease or inhibit it. Calcium, cobalt, copper, iron, magnesium, manganese, molybdenum, potassium, and zinc are the most common enzyme activators in humans. Certain heavy metal ions inhibit enzyme reactions; they are barium, lead, and mercury, and they combine with the sulfhydryl reactive group (–SH) that is part of the active site of many enzymes.

Inhibitors

Ions, atoms, or molecules that terminate or retard enzyme activity are called inhibitors. They are classified as either noncompetitive or competitive. A noncompetitive inhibitor combines with the enzyme at a location other than the active site. The noncompetitive inhibitor retards the conversion of the substrate by the enzyme, although it does not affect the bonding of the substrate of the enzyme. An inhibitor is classified as competitive if it combines with the active site of the enzyme, preventing the substrate from having access to the active site.

Supplement Coating

The pH of the stomach's hydrochloric acid secretions is about 0.8.[31] This low pH inhibits bacterial growth and activates certain enzymes. This acidic nature, however, can destroy pH-sensitive supplemental enzymes. For this reason, many enzyme products are enterically coated. This coating allows the product to reach the small intestine before disintegrating. Other products are encapsulated in "microspheres," delaying disintegration. For example, pancreatic protease encapsulated with a mixture of cellulose acetate phthalate and maize starch can remain stable in simulated gastric conditions (pH of 3.97) for at least 3 hours.[32] This would theoretically provide enough time for the capsule to pass through each part of the gastrointestinal tract. The capsule then disintegrates rapidly under pH 6.82 and temperature of 39.5° C (as would occur in the small intestine).[32]

Nanotechnology is opening a new field for the delivery of enzymes and other small proteins. Nanotechnology is the study of matter as small as one billionth of a meter. According to the National Nanotechnology Initiative, nanoparticles are being used in timed-release drug delivery.[33] Enzymes can be attached to nanoparticles and actually maneuvered to destroy diseased cells. Research on nondegradable nanocapsules showed that proteins can be efficiently transported to individual cells, surviving different pH levels.[34] So, it is no wonder that enzymes (which are proteins) can also be attached to nanoparticles and used to treat disease at the cellular level.

MEASURING ENZYME ACTIVITY

When considering enzymes and enzyme applications, the physician must understand the variables affecting their performance. Selection of an enzyme for therapeutic purposes requires more than knowing whether a given product contains amylase, protease, lipase, or other enzymes. The activity levels of the enzymes are critical.

As mentioned previously, the manufacturers of pancreatic enzymes prescribed to treat specific conditions must clearly disclose content and enzyme activity levels. Unfortunately, the same is not true of enzyme products sold as dietary supplements, whose labels may not indicate enzyme activity levels. In addition, even when the activity is stated, the consumer has no way of knowing which enzyme assay the manufacturer used unless the label also indicates that the product conforms to the guidelines of the USP. This is particularly confusing because activity levels are greatly affected by the conditions under which the assay was performed (including temperature, pH, and substrate).

Adding to the confusion, enzyme manufacturers utilize diverse assay methodologies, making direct comparison of competing products difficult, if not impossible. Utilizing a single assay system (such as detailed in the USP) is necessary to directly compare competitive products. Several standardized assay systems are available for enzyme suppliers and are found in the USP (for a definitive assay), the *NFIA Laboratory Methods Compendium,* and the *Food Chemical Codex*.

Incomplete labeling and the inconsistent use of standardized assay methodologies make evaluating competitive products extremely challenging. Price could be the first indication of inequities in assay procedures. For example, if company A is selling a product at 1000 U/g for $30 a bottle, and company B is selling a product at 5000 U/g for $10 a bottle, the units are most likely not the same.

For clinical reliability, one must use only appropriately labeled products or obtain the assay procedures from each of the manufacturers. If possible, competitor products should be compared by means of assays performed in an independent laboratory.

CLINICAL APPLICATIONS

Historically, enzyme therapy has been used in a wide variety of applications, ranging from oral supplementation to treat pancreatic insufficiency, to the centuries-old external application of enzymes to treat leg ulcers, topical wounds, wrinkles, blemishes, episiotomies, scars, and so on. Usually administered in capsules or tablets, enzymes are also available as lozenges (dissolved in the mouth) or in powder. Topical enzyme ointment is currently used to debride necrotic tissue and other wound debris. Enzymes can also be administered by injection (normally in a hospital setting because of the risk of anaphylactic reaction) or rectally, by retention implant.

Enzymes can be used individually, but are typically more efficacious when used in enzyme mixtures. Enzyme combinations are not simply intensified forms of pancreatin. An enzyme combination has a number of therapeutic advantages over a preparation with only one or two components. Combining enzymes from different sources–animal, plant, and fungi–results in a wider range of optimal pH, synergism of the combined enzymes, greater absorption, higher level of effectiveness, and broader range of application. For example, one German product contains an enzyme extract consisting of proteinases, triacylglycerol lipase, and alpha-glycosidase (amylase); minor amounts of elastase, nuclease, and carboxypeptidase; and calcium ions to boost activity.

Dr. Peter Streichhan, a well-known enzyme researcher, stated that certain enzymatic mixtures have a broader range of action than pancreatin, bromelain, or any other standardized monohydrolytic preparation—this is because certain enzyme mixtures characteristically possess differences in optimal pH and also differences in reactive properties of the proteolytic, lipolytic, and/or amylolytic-acting hydrolases.[35]

BOX 111-1 Clinical Applications of Chymotrypsin

- In debridement, treatment of abscesses and ulcerations, liquefaction of mucous secretions[36]
- In ophthalmic cataract surgeries and therapy of eyeball hematomas and ophthalmorrhagias[36,37]
- Before and after tooth extractions, as well as in operative dentistry[38,39]
- After episiotomy procedures[40]
- As an anthelmintic against enterozoic worms[41]
- In early recognition of tumor cells[42]
- In histologic gastroenterologic diagnostics[43]
- In inflammatory conditions (local and systemic) to promote the dispersion of blood extravasates and effusions from fractures[37,44-51]
- Surgical trauma[40,49]
- Sporting injuries[44-48]
- Accidental soft tissue trauma[44-48,51]
- Intervertebral disc lesions[52]
- In uveitis vitreous hemorrhage, diabetic retinopathy, and asthmatic symptoms[53]

BOX 111-2 Clinical Applications of Trypsin

- In debridement of necrotizing wounds, ulcerations, abscesses, empyemas, hematomas, fistulas, and decubitus[54-57]
- To accelerate healing in injuries, inflammations, phlogistic edemas, and traumatic changes[44-51]
- As an auxiliary agent in meningitis therapy[58]
- As an ointment or dressing (wet or dry)[4]
- As a liquid or an aerosol to liquefy sputum in bronchial disorders and in the preparation of sputum for cytologic examination[4]
- As an anti-inflammatory agent; oily suspensions are injected intramuscularly[4]
- As an aid in the treatment of intraocular hemorrhage, thrombophlebitis, intestinal obstruction (due to cirrhosis or carcinoma)[59]

BOX 111-3 Clinical Applications of Amylase

- Needs calcium ions for enzymatic activity
- Acts on starch, glycogen, and related poly- and oligosaccharides.[60]
- In combination with other enzymes, as a digestant[36,61,62]
- As an anti-inflammatory[61]
- In treatment of deficiencies of exocrine pancreas, amylaceous dyspepsia, and cystic fibrosis.[4]

BOX 111-4 Clinical Applications of Lipase

- In pancreatin-containing remedies to increase pancreatic/lipolytic activities (replacement therapy)[63-66]
- When given with pancreatin (in combined preparations), it reduces fat level in stools[67-69]
- Synergistically intensifies the activity of lipoprotein-lipase in the blood[70] and migration of agranulocytes[71]
- As a digestive aid[69]

BOX 111-5 Clinical Applications of Pancreatin

- In pancreatic insufficiency, inadequate secretion of exocrine pancreas, disturbed digestion, and after gastrectomy[64,72-84]
- In chronic pancreatitis[85] and after surgery for chronic pancreatitis[86]
- After pancreatectomy[4,85]
- In ductal obstruction from neoplasm (e.g., of the pancreas or common bile duct)[85]
- To treat severe cases of steatorrhea (as found in cystic fibrosis)[87-92]

It should be remembered that, at the beginning of therapy, an individual's symptoms may occasionally become more severe. This is a sign that a therapeutic reaction is occurring and should be evaluated positively. The medication need not be discontinued, although a temporary reduction in dose might be advisable.

Clinical uses of individual enzymes can be found in Boxes 111-1 through 111-5, whereas clinical uses of combinations can be found in Box 111-6. For more information on how enzymes can treat more than 150 conditions, please see the author's book, *The Complete Book of Enzyme Therapy*.

Most conditions treated by enzymes can be assigned to one or more of the following categories:

- Digestive conditions
- Inflammatory conditions
- Cancer
- Autoimmune or immune disorders
- Cardiovascular disorders
- Viral and bacterial disorders
- Other conditions

Digestive Disorders

Supplementing the diet with pancreatic enzymes can improve food digestion and, therefore, nutrient assimilation. This is especially true if the body's own pancreatic enzyme production and/or supply is deficient, as can occur with age or because of an underlying health condition, such as pancreatic insufficiency, chronic pancreatitis, steatorrhea, biliary tract disease, celiac disease, or cystic fibrosis (CF). Pancreatic enzymes have a long history of use in treating those conditions, as well as indigestion, heartburn, gas, diarrhea, constipation—the list seems endless.

Patients with CF are routinely prescribed pancreatin or pancrelipase capsules containing enterically-coated beads. A hereditary disease, CF involves a disorder of the exocrine glands and causes the production of thick mucus, which leads to obstructions in various glands and ducts in the body. When the mucus affects the lungs, it leads to severe coughing and repeated lung infections, including bronchitis and pneumonia. When the mucus obstructs the pancreatic duct, it prevents the enzyme-rich pancreatic juice from reaching the intestine, negatively impacting food digestion and nutrient absorption. This can result in malnutrition, weight loss, steatorrhea (fatty stools), or intestinal obstruction. Poor digestion affects approximately 90% of all CF patients.[180]

Enzyme supplementation can improve the digestion of fats, proteins, and carbohydrates, thus improving nutrient absorption and, therefore, increasing weight gain,[181] controlling steatorrhea,[182] and improving serum albumin levels (low levels reflect protein calorie malnutrition).[181]

Inflammatory Diseases and Conditions

The inflammatory process is involved in numerous diseases and conditions, from sports injuries to arthritis to sinusitis to fibrositis. One of the basic concepts in systemic enzyme therapy (that is, using enzymes to treat disorders within the body) is that all kinds

BOX 111-6 Clinical Applications of Enzyme Combinations

- Soft-tissue injuries[93,94]
- Sprained ankle[94-96]
- Tendonitis[97]
- Reabsorption of hematomas[93,98]
- Sports medicine[99-106]
- Meniscectomy (pre- and postoperative therapy)[107,108]
- Traumatology[109]
- Fractures[110,111]
- Pancreatitis[112]
- Surgery[93,113]
- Lower extremity bypass surgery[114]
- Operative dentistry[115]
- Proctology[116]
- Sinusitis[117-120]
- Acute and chronic bronchitis[121-123]
- Cystitis and lower urinary tract infections[117,124,125]
- Prostatitis[117,125,126]
- Pelvic inflammatory disease[127,128]
- Post-thrombotic syndrome[129-133]
- Pathologic venous processes[129,134-138]
- Occlusive arterial disease[139]
- Lymphedema[140-146]
- Soft tissue rheumatism (nonarticular rheumatoid syndrome)[147,148]
- Rheumatoid arthritis (chronic polyarthritis)[117,122,131,142,149-164]
- Ankylosing spondylitis (Bekhterev's disease)[94,153,154,157]
- Degenerative rheumatic joint disease[102,117]
- Monoarticular, activated osteoarthrosis[102,123,165]
- Multiple sclerosis[121,166-172]
- HIV infections[173-177]
- Sepsis[178]
- Fibrocystic breast disease[144,179]
- Ulcerative colitis and Crohn's disease[117,121,122,168]

of inflammatory processes respond to enzymes. The following steps describe the postulated mechanism of action:

1. Various repair mechanisms are activated in the damaged area, resulting in fibrin surrounding the traumatized region (among other effects).
2. The injured area (after having been partly or completely sealed off by microthrombi and/or a fibrin web) is cut off from the normal circulatory system. This results in stasis, inhibiting the repair process (nutrients cannot get into the damaged area and waste products cannot be removed). Pressure rises in the damaged capillaries, the blood vessels become highly permeable, and fluid is forced out into the surrounding tissue. This causes increased pressure, swelling, and pain.
3. Supplemental enzymes, after absorption, are bound in complexes (e.g., α_2-macroglobulin hydrolase) and circulate via the bloodstream to the injured area. Enzymes have been shown to reduce interleukin-2 (IL-2), Il-6, tumor necrosis factor-α (TNF-α), and other proinflammatory cytokines, while increasing anti-inflammatory cytokines such as IL-4, thereby normalizing cytokine homeostasis.[183]
4. Proteolytic enzymes directly attack the microclots and fibrin formation, lysing the fibrin and breaking open the clogged vessels, thus reestablishing circulation.

The restoration of normal blood flow leads to a faster resolution of postinflammatory pain and edema. Equally important, the essential physiologic inflammatory repair process is not blocked or diminished (as with anti-inflammatory agents), but rather is accelerated and reinforced.

In a Canadian study, postal workers with rotator cuff tendonitis were treated with either naturopathic care (NC), which included dietary counseling, acupuncture, and an enzyme supplement (containing bromelain, trypsin, and rutin), or with physical exercise (PE), which included exercise and placebo.[97] Those participants on the NC therapy saw a decrease in their shoulder pain and disability of over 54% (as measured by Shoulder Pain and Disability Index) compared with 18% in the PE group. The NC group also had significant improvement in range of motion compared with the PE group.[97]

Fractures often require surgery to repair the broken bone. Czech researchers followed the progress of 60 patients after surgery for repair of long bone fractures. Thirty patients received an enzyme mixture (containing trypsin, bromelain, and rutin), whereas another 30 patients were treated by standard antiedema drugs. Both groups received the same pain medicine. The group who received the enzyme mixture had a significantly faster reduction in posttraumatic and postoperative swelling. In addition, those taking enzymes consumed significantly fewer pain killers.[184]

A similar study in Russia using an enzyme mixture on children with fractured long bones found that swelling and pain subsided twice as fast in the enzyme group as in the group receiving traditional therapy.[111]

Intense exercise can lead to soft tissue injury and inflammation. Researchers found that supplementing with protease mixtures could help ease muscle soreness and assist muscle healing after exercise.[106]

Even inflammatory diseases, such as arthritis[149] and herpes zoster[185] were shown to respond to the systemic application of enzymes. A double-blind, randomized study compared an oral enzyme mixture (containing trypsin, bromelain, and the bioflavonoid, rutin) with diclofenac (a nonsteroidal anti-inflammatory drug frequently prescribed for osteoarthritis and rheumatoid arthritis). Ninety patients received either the enzyme mixture or the diclofenac for a 6-week period. Results indicated that the enzyme mixture was just as effective as diclofenac.[186]

Individual enzymes and enzyme combinations (particularly those including trypsin, chymotrypsin, pancreatin, amylase, lipase, papain, and bromelain, with rutin) are effective in treating inflammation because they help limit the injury, aid its rectification, and promote new, healthy tissue formation. Enzymes effectively accelerate the inflammatory process (a necessary component of wound healing). This acceleration means, on the one hand, that the work of damage control, damage repair, and new tissue construction is carried out more actively, and thus completed more swiftly. On the other hand, it means that there can be a temporary increase in the visual and sensory effects produced by the inflammation (i.e., more redness, swelling, heat, and pain).

Despite the supportive research, the administration of enzymes in traumatology and injuries is not widely used in the United States, which is in contrast to Europe, where (because the inflammatory reaction is so universal) all types of injuries—sprains, strains, hematomas, dislocations, and even postoperative conditions—are effectively treated with enzymes. Although the inflammatory process is involved in viral and bacterial infections, those disorders are covered in a "Viral and Bacterial Disorders", separate section within this chapter.

Cancer

Just as Beard researched the effects of enzymes on cancer, so have modern researchers. Dr. William Kelley devised an anticancer program that employed detoxification, pancreatic enzymes (and other

nutritional supplements), improved enzyme-rich nutrition, and coffee enemas.[187] He initiated his treatment program in response to his own bout with pancreatic cancer.

Standard cancer therapy can often result in serious side effects. For instance, radiation therapy of the head and neck is often accompanied by acute side effects, including difficulty swallowing, mucous membrane inflammation, and skin redness or soreness. Oral enzyme preparations seem to protect against these acute side effects, reducing their severity and duration.[188]

A study on patients with laryngeal cancer receiving radiation treatment found that those patients receiving an enzyme mixture (containing trypsin, bromelain, and rutin), had no cases of radiomucositis of the second degree and were able to continue on the radiation therapy.[189] Researchers also noted that those on enzyme therapy had a mean weight loss of only 5% (compared with 10% in the control group).[189]

In another study, researchers tested an enzyme combination in patients who underwent radiation therapy for cervical cancer, a therapy that can cause numerous side effects, including bladder irritation, loose bowels, nausea, vomiting, and vaginal dryness. Results indicated that patients who received the enzyme mixture (which contained trypsin, chymotrypsin, and papain) had a significant reduction in vaginal mucosa reactions, genitourinary symptoms, and subcutaneous changes.[190]

Wobe Mugos E (which contains papain, trypsin, chymotrypsin, and thymic peptides) was found to reduce the incidence of leukopenia, nausea, vomiting, sensory neuropathy, and treatment-related depression in lung cancer patients who underwent chemotherapy.[191]

Breast Cancer

It is estimated that one of every eight women will be diagnosed with breast cancer sometime during her life.[192] Unfortunately, standard treatment, including radiation, chemotherapy, and surgery, often causes serious side effects, including gastrointestinal symptoms, headache, pain, skin disorders, and infections. Researchers in Germany evaluated whether treatment with oral enzymes could reduce some of the typical side effects of breast cancer therapy.[193] They found that 74% of the enzyme group experienced a clear reduction in chemotherapy and radiotherapy side effects, and that oral enzyme therapy could improve disease signs and symptoms, reduce side effects, and improve quality of life.[193]

Lymphedema. Treatment for breast cancer can sometimes lead to lymphedema (swelling caused by a buildup of lymph). This typically occurs after a lymph node is removed or after radiation treatment, and can develop slowly. Symptoms include swelling in the arm, hand, shoulder, chest, or breast, and may be accompanied by changes in skin texture, aching, and restricted mobility.

Typical medical therapy for lymphedema includes massage, exercising, special bandaging, manual lymphatic drainage, and the use of diuretic therapy. One clinical trial compared therapy with enzymes (the product contained pancreatin, papain, bromelain, trypsin, chymotrypsin, and rutosid) with a diuretic.[146] After 7 weeks, significantly more of the patients receiving enzymes were pain free compared with the patients receiving diuretics**.**

Pancreatic Cancer

Pancreatic cancer kills over 30,000 people every year.[194] In the past, survival rates for this disease were extremely low because treatment options were limited, and diagnosis usually did not occur until the disease was quite advanced. However, treatment improvements and earlier diagnosis have dramatically improved survival rates.[195] Standard medical treatment for pancreatic cancer involves surgery, radiation therapy, chemotherapy, and immunotherapy (also called biological therapy).

Pancreatic cancer can block the pancreatic duct and prevent enzymes from reaching the small intestine, resulting in malnutrition and weight loss. It is estimated that 80% to 90% of all pancreatic cancer patients have malabsorption and weight loss.[196] Supplementing with pancreatic enzymes is an important supportive step in treating pancreatic cancer because it can improve digestion and, therefore, nutrient absorption.[79,182,197]

Autoimmune and Immune Complex-Mediated Diseases

In autoimmune disease, tissue-bound immune complexes activate the complement system. Activation of the enzyme cascade results in an intense protein-destroying inflammatory response, leading to significant local tissue destruction. For instance, when immune complexes collect in the kidneys, complement activation causes inflammation, resulting in glomerulonephritis.

Research showed that some enzymes can inhibit immune complex-mediated diseases, such as glomerulonephritis and rheumatoid arthritis, by interrupting the complement cascade. Other disorders with similar mechanisms also respond to supplemental enzymes. Some are conditions such as Crohn's disease, pulmonary fibrosis, chronic rheumatism, and ankylosing spondylitis, which do not respond well to conventional medical treatments.

Multiple Sclerosis

The National Multiple Sclerosis Society estimates that there are approximately 400,000 people with multiple sclerosis (MS) in the United States alone.[198] Although its cause is unknown, it is generally believed to be an autoimmune disease. In MS, antibodies attack the myelin sheath that protects and covers nerve fibers. This leads to inflammation and myelin sheath damage, which in turn interferes with nerve communications.

MS patients typically have higher concentrations of circulating immune complexes (CICs) than healthy individuals. Research showed that enzyme therapy can help reduce those CICs, and thereby reduce inflammation.[199]

A Ukrainian study on an enzyme combination containing trypsin, bromelain, and rutin (a flavonoid) found that MS patients taking the combination for 1 to 3 years had fewer and less severe complications and longer remissions, and also experienced a slowing of their disease progression.[172]

Cardiovascular Disorders

Cardiovascular disorders include diseases of the heart and blood vessels (including strokes).

In the United States, heart disease and strokes kill nearly three quarters of a million people every year and account for nearly one third of all deaths.[194] However, these conditions are not limited to the elderly, because over 140,000 Americans younger than 65 years old die from these diseases every year.[194]

In normal circulation, there is a constant dynamic balance between blood clotting and fibrinolysis.[200] If fibrinolysis is impaired, clot formation is abnormal. If fibrinolysis increases, a tendency toward excessive bleeding results. Therefore, maintenance of proper equilibrium is extremely important for the circulatory system.

One study examined the effects of various enzyme combinations on fibrinolysis and fibrin formation.[121] The researchers

induced fibrin deposition with calcium ions or staphylocoagulase in the plasma of centrifuged, acellular citrated blood from humans or rabbits and treated the clot with various concentrations of enzyme suspensions. They found that the higher the enzyme content of the solution, the more rapidly clots were degraded. Inflammation is considered to play a central role in all atherosclerotic processes. Therefore, the use of enzymes is indicated because of their anti-inflammatory effect.

A German study measured the effects of a proteolytic enzyme combination (containing trypsin, bromelain, and rutin) on blood fluidity. Researchers found that even a minimum enzyme concentration resulted in a significant reduction in plasma viscosity and erythrocyte aggregation.[201]

Systemic enzyme therapy appears to be particularly effective in the treatment of phlebitis and thrombophlebitis,[202] as well as the chronic venous insufficiency (also called postphlebitic syndrome) that can occur because of phlebitis. In one study, treatment with systemic enzyme therapy led to a decrease in several symptoms, including pain, edema, and trophic ulcers.[203]

Viral and Bacterial Disorders

As more and more bacteria become resistant to antibiotics, researchers and physicians are investigating supportive treatments, including systemic enzyme therapy. Enzymes reduce inflammation, improve circulation, stimulate and balance immune system function, and enhance the antibiotic's ability to penetrate target tissues. Enzymes fortify the action of antibiotics, leading to complete healing and preventing the progression of an acute infection into its chronic form. A good example is urogenital chlamydiosis, which is a sexually transmitted disease and a major cause of infertility. According to the Centers for Disease Control, there were more than one million cases reported in the United States in 2008.[204] Standard treatment is with antibiotics, including azithromycin or doxycycline. Although antibiotic treatment appears to be highly efficacious, in some individuals the infection becomes persistent and chronic, leading to long-term disorders in females, including pelvic inflammatory disease, ectopic pregnancy, and sterility.[205] A Russian study of 227 patients with urogenital chlamydiosis found that treatment with antibiotics led to complete recovery in only 61.4% of patients, whereas enzyme therapy in conjunction with antibiotics resulted in over 90% treatment success.[206]

Many viral and bacterial conditions, including abscesses, acne, adenoiditis, adnexitis, bladder infection, boils, conjunctivitis, diarrhea, ear infections, empyemas, epididymitis, gingivitis, kidney disorders, laryngitis, pneumonia, rheumatic fever, sinusitis, staphylococcal infection, tonsillitis, and sepsis can be helped with enzymes.

Sepsis is a particularly dangerous systemic response to infection. Researchers in India found that proteolytic enzyme therapy improved recovery time in children with sepsis.[178] Thirty young boys (ages 1 month to 12 years) with sepsis were given proteolytic enzymes. Another group of 30 boys received placebo tablets. Both groups received supportive treatment and the appropriate antibiotics. Fever subsided faster in the enzyme group (3 days) than in the placebo group (4 days), and those in the enzyme group were able to begin oral feeding in 4 days, as opposed to 5 days in the placebo group. In addition, hemodynamic support was only needed for 2 days in the enzyme group (as opposed to 3 days in the placebo group), and the modified Glasgow coma scale normalized for enzyme participants in 3 days (as opposed to 5.5 days in the placebo group).[178]

Enzyme therapy can also aid in the treatment of viruses. The human body defends against viruses with the help of macrophages or natural killer (NK) cells. Oral enzyme combinations (such as papain, trypsin, and chymotrypsin) synergistically increase the antiviral effects of TNF, macrophages, and NK cells, and the breakdown of CICs. Enzymes can aid in the treatment of numerous viral conditions, including AIDS, chancre sores, chickenpox, colds and coughs, hepatitis, herpes simplex, herpes zoster, influenza, measles, pneumonia (viral), and warts.

Other Conditions

Enzyme therapy may be of value in conditions that do not easily fit into one of the preceding categories. Autism is just one example. No causative agent has been found for this developmental disease, although many theories abound, including vaccinations, a genetic link, nutritional deficiencies, and reactions to chemicals or other environmental factors. Some research indicates that enzyme therapy to improve protein digestion may be of particular benefit in autism as well as many other conditions.[207]

DOSAGE

Regardless of the condition being treated, a wide range in daily dosage has historically been used for the following reasons:

- There are individual differences in patient health.
- The level of effective absorption in tablet strength can vary.
- There are a wide variety of influencing ranges in pH.
- Enzyme activity levels vary between products.

For example, pancreatin dosage depends on the condition being treated, as well as on the patient's diet and digestive requirements. Dosage can vary because of pancreatin's susceptibility to inactivation in the stomach and duodenum.[192]

Table 111-2 indicates the composition of three enzyme combinations (A, B, and C),[208] whereas Table 111-3 lists some of the conditions effectively treated with these products, the dose required, and the treatment period.

TOXICOLOGY

Oral Enzymes

In general, side effects of orally administered enzymes are few, short-termed, and due primarily to higher dosages or hypersensitivity reactions. According to Wolf and Ransberger, high dosages

TABLE 111-2 **Composition of Enzyme Combinations (Milligrams)**

ENZYME	"A"	"B"	"C"
Pancreatin	100	100	0
Papain	60	60	100
Bromelain	45	45	0
Lipase	10	10	0
Amylase	10	10	0
Trypsin	24	24	40
Chymotrypsin	1	1	40
Rutin	50	0	0
Thymus extract	0	0	40

Data from Stauder G, Pollinger W, Fruth C. Systemische Enzymetherapie: Eine Ubersicht uber Neue Klinische Studient. Allgemein Medizin 1990;19:188-191.

(70 tablets of 17.5 g each) of a proteolytic enzyme mixture have been given without long-term side effects.[215] Studies and literature searches commissioned by regulatory authorities such as the U.S. FDA apparently confirmed that enzyme preparations obtained from suitable sources (e.g., nontoxic, nonpathogenic sources) are safe to consume.[216]

Potential side effects of pancreatic enzyme therapy include diarrhea, intestinal gas, abdominal pain or cramping, and greasy, pale, or pungent stools. Reducing the dose can usually reduce or eliminate these side effects. Hyperuricosuria (excess uric acid in the urine) and hyperuricemia (excess uric acid in the blood) have been associated with extremely high doses. Sneezing, lacrimation, rash, and other hypersensitivity reactions have been reported in sensitive individuals.

Pancreatin preparations held in the mouth or chewed before swallowing can result in stomatitis, or ulcerations and irritation of the mucosa, particularly in infants, in whom pancreatin may also cause perianal soreness.[217] However, some of the capsules containing microencapsulated enzyme beads can be opened and dispensed by the spoonful to infants or mixed into foods such as apple sauce or gelatin.

Enzyme enemas can sometimes cause the rectum or anus to itch or burn. However, these are only minimal side effects in relation to the positive benefits obtained.

Prolonged skin contact with proteolytic enzymes (i.e., in ointment form) may cause skin irritation. Care should be exercised when using powdered enzymes or enzyme capsules to avoid inhaling dust particles, because irritation of the mucous membranes of the throat, nose, and eyes may result.[216] In addition, inhalation may trigger an asthma attack.[218]

It is not known whether pancreatin or pancrelipase given to pregnant women can harm the fetus, because animal reproductive studies have not been conducted. Therefore, pancreatin should probably not be used during pregnancy.[217] Also, it is not known if pancreatin or pancrelipase is distributed into mother's milk. Therefore, caution should be exercised with use of this substance in nursing women.[217]

Enzymes should not be used by hemophiliacs or those on blood thinners (unless under a physician's care), nor immediately before or after surgical procedures with an increased risk of bleeding. Enzymes should also be avoided by those with pulmonary

TABLE 111-3 **Dosage Programs for Specific Conditions**

CONDITION	FREQUENCY × DOSAGE	TREATMENT PERIOD	COMBINATION*
Post-thrombotic syndrome[209]	3 × 5	As needed	A
Oncology[210]	2 × 11	6 wks or as needed	A
Lymphedema[141]	2 × 5	2 yr	A
Fibrocystic breast disease[177]	2 × 10	6 wks or as needed	A
Experimental hematoma[93]	3 × 10	24 hr	A
Prophylactic treatment of karate injuries[211]	3 × 5	During the season	A
Traumatology and meniscus operation[107]	3 × 10	Average of 17.7 days	A
Soft tissue injuries and distortions of the ankle joint[94]	3 × 10 initially, then 3 × 1	As needed	A
Athletic soft tissue injuries[98]	2 × 5	Spring football season	A
Dental surgery[115]	4 × 5	Day before surgery to seventh postoperative day	A
Sports injuries[101]	3 × 10	As needed	A
Chronic polyarthritis[212]	4 × 8 tablets	6 mo	A
Active arthroses[213]	4 × 7	6 wks	A
Extra-articular rheumatism[144]	3 × 10 tablets	As needed	B
Adnexitis[127]	3 × 5	10-14 days	A
Prostatitis[117,125]	3 × 5	10 days	A
Mastopathy[214]	2 × 10		A
Multiple sclerosis[168-171,199]			
Initially	2 ampules injection	Daily	C
As symptoms improve	2 ampules	Every 2 to 3 days, then at longer intervals	C
On injection-free days	3 × 10		A
Later	3 × 5		A
Finally	3 × 3		A
Herpes Zoster[185]			
Initially	2 × 1 ampules	First 2 days	C
First 2 days	3-4 tablets/day	As indicated, up to 14 days	A
HIV[175,176]	3 × 10 (ongoing studies insufficient to give effective dose levels)	As indicated	A

*For composition of combinations, see Table 111-2.

emphysema or thrombocytopenia. Pancrelipase (and any other enzyme derived from pork sources) is contraindicated in those who are hypersensitive or allergic to pork products.

There is some indication that patients with CF who are undergoing long-term high-dose pancreatic enzyme therapy may demonstrate colonic wall thickening, a condition called fibrosing colonopathy (FCP). It was once believed that the copolymer coating on the tablets might be the culprit,[219] and there have been instances of FCP in CF patients not taking any type of enzyme preparation.[220] However, it is now generally believed that FCP occurs because of prolonged treatment with very high doses of pancreatic enzymes. Many of the individuals who were first diagnosed with FCP were taking tens of thousands of units in excess of label recommendations.[221] To reduce the risk of FCP, it is extremely important that patients closely follow their physicians' recommendations regarding dosage.

A note about supplement safety: During the last few decades, there has been increased concern regarding mad cow disease (bovine spongiform encephalopathy [BSE]). Called Creutzfeldt-Jakob disease (CJD) in humans, it can be caused by eating beef that is infected with BSE, but can also be transmitted through corneal transplant tissue, from hormone extracts (such as human growth hormone), and possibly from ingesting contaminated glandular products. Unfortunately, it may take as long as 20 years after infection for the characteristic symptoms of CJD to manifest. Since 1995, the FDA has required that dietary supplement manufacturers ensure that any "high risk" animal products used in their supplements do not originate in BSE countries, in countries with inadequate surveillance, or with requirements less strict than those that would be acceptable for importation into the United States. The list is constantly updated; for the most current list of BSE countries, refer to the FDA website: www.FDA.gov. Fortunately, bovine (cow) pancreas (the source of some pancreatic enzymes) is not considered a "high risk," but rather a category III or low infectivity tissue. In addition, many manufacturers use pork sources for pancreatic enzymes. Unfortunately, there is no test to see whether a supplement is infected with BSE. Contact the supplement manufacturer for concerns about pancreatic supplement safety or to see what measures they employ to ensure BSE-free products.

DRUG INTERACTIONS

In addition to lipases and amylases, pancreatic enzymes contain proteases, so are subject to some of the same drug interaction warnings as is bromelain (see Chapter 71 on Bromelain). As with bromelain, caution should be exercised when pancreatic enzymes are used with anticoagulants (blood thinners), including Coumadin, Jantoven, Lovenox, and warfarin, as well as over-the-counter nonsteroidal anti-inflammatory drugs, including aspirin and ibuprofen. In addition, certain botanicals, including garlic, gingko biloba, and ginseng, may increase bleeding risk, and so should be monitored when used in conjunction with pancreatic enzymes.

Certain diabetes drugs such as acarbose (brand names Glyset and Precose) function as alpha-glucosidase inhibitors, lowering blood sugar levels by delaying the digestion of dietary carbohydrates. This, in turn, limits the rise of blood sugar levels. However, the amylase in pancreatic enzymes has the potential to reduce the effectiveness of alpha-glucosidase inhibitors, because amylase improves carbohydrate digestion. Therefore, pancreatic enzymes should not be taken concomitantly with acarbose and other alpha-glucosidase inhibitors.

Similarly, drugs that function as lipase inhibitors (such as Orlistat) should be avoided while taking pancreatic enzymes. Orlistat is available in prescription (as Xenical) and nonprescription (as Alli) forms. It functions by inhibiting lipase in both the lumen of the stomach and the small intestine. Although there are no known studies on Orlistat given concomitantly with pancreatic enzymes, it would seem counterproductive to take a drug designed to inhibit lipase activity while also taking a drug containing lipase. In addition, because Orlistat inhibits the activity of lipase, it may interfere with the action of pancreatic enzymes.

Any foods that contain enzyme inhibitors have the potential to decrease the activity of pancreatic enzymes. Heat inactivates enzyme inhibitors (as is the case in potatoes, legumes, and soybeans, which are rarely eaten raw).

CONCLUSION

As we can see, the use of pancreatic enzymes has been found to be extremely effective in treating a wide variety of conditions, from digestive diseases to inflammation, cancer, autoimmune diseases, viral and bacterial conditions, and more. It is my firm belief that future research will not only continue to validate, but will also reveal new and exciting applications for systemic enzyme therapy.

This chapter is dedicated to the memory of Dr. Max Wolf, the father of systemic enzyme therapy, as well as Dr. Karl Ransberger, who validated and marketed systemic enzyme therapy, making it a highly accepted worldwide treatment for a wide variety of systemic diseases and injuries.

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CHAPTER 112

Phage Therapy: Bacteriophages as Natural, Self-limiting Antibiotics

Elizabeth Kutter, PhD, Sarah J. Kuhl, MD, Zemphira Alavidze, PhD, and Bob G. Blasdel, BS

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INTRODUCTION

Phage therapy involves the use of bacteriophages—viruses that only attack bacteria and are very host specific—to kill pathogenic microorganisms. The art was first developed at the Pasteur Institute in Paris early in the twentieth century, but since the advent of chemical antibiotics in the 1940s, it has been little used in the West. Today, however, the increased prevalence of bacteria that are resistant to most or all available antibiotics is precipitating a major health crisis, as was again passionately stressed by the World Health Organization in their call to action on World Health Day, 2011.[1] Here, we summarize the evidence that the available data strongly support expedited evaluation of phage therapy to help address this serious menace.[2-14]

Extensively documented results of French and Eastern European therapeutic phage applications are encouraging, but most involved individualized applications to infections recalcitrant to all other available treatments rather than double-blind clinical trials. There have also been encouraging recent developments. In 2006, the U.S. Food and Drug Administration (FDA) and the European Union (EU) both approved phage preparations targeting *Listeria monocytogenes* on ready-to-eat foods. The Nestlé Corporation is currently carrying out an extensive project in Dhaka, Bangladesh, to study the safety and efficacy of phage therapy in treating enterotoxigenic *Escherichia coli* and enteropathogenic *E. coli* induced diarrhea in children.[15] Either of two preparations, a novel cocktail of T4-like phages used in earlier safety trials as well as a commercially available Russian anti-*E. coli* phage cocktail (Microgen), or a placebo is being added to the standard oral rehydration solution currently in use in double-blind fashion. This work demonstrates all the key elements of modern clinical trials. The phages being used for the main experimental arm of the trial were isolated from the stools of pediatric diarrhea patients in Bangladesh, with the broad-spectrum ones applicable for phage therapy all turning out to be members of the highly studied T4 family (see the following).[16] They have also reported the details of their very extensive genomic, mouse, and human safety studies of representative phages in their set.[17]

This chapter was written to put phage therapy into historical and ecologic perspective and to explore very interesting early research in France, the United States, and Eastern Europe, as well as growing recent studies worldwide, with the hope that this modality will soon be available for external applications while researchers deal with the challenges of getting funding for full-scale clinical trials of more invasive approaches.

HISTORICAL CONTEXT

Discovery and Early Research

Edward Twort and Félix d'Hérelle independently reported the isolation of filterable entities capable of lysing bacterial cultures and of producing multiple small cleared areas on bacterial cultures when diluted, rather than showing a minimum inhibitory concentration, implying that discrete particles were involved. They are jointly given credit for the discovery of bacteriophages. It was d'Hérelle, a Canadian working at the Pasteur Institute in Paris, who gave the name *bacteriophage* to these entities he discovered in the stools of soldiers recovering from dysentery—using the suffix *phage* "not in its strict sense of *to eat*, but in that of *developing at the expense of*."[18] He soon also isolated phages targeting avian typhosis and tested their application during an outbreak in French chickens, showing that three quarters of the

untreated chickens died, but all of the infected chickens treated with phages survived. He then accepted a request to treat several children battling dysentery at the Paris Hôpital des Enfantes Malades; the day before treating the first child, he and several assistants swallowed far more phages than they would be administering, thus carrying out the first known Phase I clinical trial. This trial was fully successful, but d'Hérelle turned to intense study of phages before publishing the results or carrying out further therapeutic applications. Thus, the first-known publication discussing successful phage therapy was published in 1921 from Belgians Bruynoghe and Maisin,[19] who used phages to treat staphylococcal skin infections.

In a 300-page 1922 book, *The Bacteriophage: Its Role in Immunity*,[18] d'Hérelle wrote the original, classic descriptions of plaque formation and composition, infective centers, the lysis process, host specificity of adsorption and multiplication, the dependence of phage production on the precise state of the host, isolation of phages from various sources, and the factors controlling stability of the free phage. He quickly became fascinated with the apparent role of phages in the natural control of microbial infections, and noted the frequent specificities of the phages isolated from recuperating patients for disease organisms infecting them and the rather rapid variations over time of the phage populations. Throughout his life, he worked to develop the therapeutic potential of properly selected phages against the most devastating health problems of the day, traveling to many parts of the world, teaching at Yale from 1928 to 1933, and establishing his own Laboratoire du Bactériophage in Paris, run by his son-in-law, Theodore Mazure, which produced the first commercial phage cocktails—Bacté-Coli-Phage, Bacté-Intesti-Phage, Bacté-Dysentérie-Phage, Bacté-Pyo-Phage, and Bacté-Rhino-Phage. Although France is clearly a western country, most of the literature reviews of phage therapy have ignored the successful continuation of phage therapy in France until the early 1990s, which largely used well-made phage preparations produced by d'Hérelle's laboratory or by the Bacteriophage Service of the Lyon and Paris branches of the Institut Pasteur.

Key to d'Hérelle's many successes was that he focused intensely on understanding phage biology and on applying that knowledge in his production and application of phages, including careful ongoing quality control, close work with physicians, and development of appropriate treatment modalities. He wrote several more detailed books on phages and phage therapy, two of which were also translated into English (1926 and 1930). The depth of his insights into the practice of phage therapy became more accessible via the recent publication of a translation of the appendix of his book.[18] Through much of the time, he worked closely with George Eliava, director of the Georgian Institute of Microbiology, who had seen bacteriocidal action of the water of the Koura River in Tbilisi (Tiflis) that he could not explain until he became familiar with d'Hérelle's work while spending 1920 to 1921 at the Pasteur Institute.[18] Over the years, the two developed plans to found an Institute of Bacteriophage Research in Tbilisi as a world center of phage therapy, including scientific and industrial facilities and supplied with its own experimental clinics. A large campus on the river Mtkvari was allotted for the project in 1926. D'Hérelle sent supplies, equipment, and library materials. In 1934 to 1935, he visited Tbilisi for 6 months, set up his laboratory, and wrote a book, *The Bacteriophage and the Phenomenon of Recovery*,[20] which was translated into Russian by Eliava and had a very strong impact on Stalin, and thus on the implementation of phage therapy in the Soviet Union. D'Hérelle intended to move to Georgia; his cottage still stands on the institute's grounds. However, in 1937, Eliava was arrested as a "people's enemy" by Beria, then head of the Georgian NKVD and soon to direct the Soviet NKVD as Stalin's much-feared henchman. Eliava was executed, sharing the tragic fate of many Georgian and Russian progressive intellectuals of the time, and d'Hérelle, disillusioned, never returned to Georgia. However, their Bacteriophage Institute survived under the leadership of a group of women well trained by Eliava and d'Hérelle. The Institute was put under the People's Commissary of Health of Georgia in 1938 and was transferred to the All-Union Ministry of Health in 1951, taking on the leadership role in providing bacteriophages for therapy and bacterial typing throughout the Soviet Union. Hundreds of thousands of pathogenic bacterial samples were sent to the Institute from throughout the Soviet Union to isolate and produce more effective phage strains and to better characterize their usefulness. A new five-story building provided facilities for making two tons of phage products two or more times a week, with 80% of the product going to the Soviet military. These included tablets against dysentery, pyophage cocktails targeting wound and other purulent infections, as well as intestiphage intended for a wide range of enteric pathogens. Much of the main building held research laboratories continually isolating new phages, upgrading therapeutic cocktails, working on anaerobes and defenses against potential biowarfare, and collaborating closely with military and civilian physicians to test the phage preparations and ways of administering them. These were the golden years of the Institute, when its employees were among the best paid in Tbilisi, and there were no shortages of supplies, new research targets, or potential customers. In 1988, an official Scientific Industrial Union "Bacteriophage" was formed, centered in Tbilisi with branches in Ufa, Habarovsk, and Gorki.

After the 1991 breakup of the Soviet Union, the Russian sites were gradually pulled into the developing pharmaceutical giant, Microgen (eng.microgen.ru) whose products include a wide range of phage preparations available in pharmacies, online, and in hospitals throughout the Soviet Union. What is now the Eliava Institute lost most of its markets and funding and struggled for survival as the factory portions were stripped away and privatized. Phages for Georgian use were made in 30-L batches packaged by hand in small 5-mL ampules, 10 to a box, and sold in the diagnostic clinic on the Eliava campus in laboratories that had once focused on research-scale preparations, and where laboratory leaders had done the actual testing and diagnosis, supporting the laboratories while continuing to acquire all the newest pathogenic strains for research and production purposes. Often, the power and/or gas went out, and no new young people were being trained. By 1996, help became available from the International Science and Technology Centers and the Civilian Research and Development Fund, set up by North Atlantic Treaty Organization (NATO) and the United States, the EU, the Phage Biotics Foundation, and other sources to fund civilian research by scientists formerly supported by the military. With hard work and outside help, the institute is again thriving at its original site on the Mtkvari. Their work is further discussed in the following.

Initial Attempts at Commercialization

Phage therapy has been explored extensively, with successes being reported for a variety of diseases, including dysentery, typhoid and paratyphoid fevers, pyogenic and urinary tract infections, and cholera.[4] Phages have been given orally, through colon infusion, and as aerosols as well as infused directly into lesions. They have also been given as injections: intradermal, intramuscular, intraduodenal, intraperitoneal, into the pericardium and arteries leading to infected areas, as well as intravenously. The early strong interest in phage therapy is reflected in some 800 papers published on the topic between 1917 and 1956. The reported results were

quite variable. Many of the physicians, entrepreneurs, and pharmaceutical firms who initially became very excited by the potential clinical implications, especially in the pre-antibiotic era, jumped into application efforts with very little understanding of phages, microbiology in general, or the basic scientific process. Thus, many of the studies were anecdotal and/or poorly controlled; many of the failures were predictable; and some of the reported successes did not make sense in light of current knowledge. Too often, uncharacterized phages at unknown concentrations were given to patients without previous specific bacteriologic diagnosis, and there is no mention of follow-up, controls, or placebos. Much of the understanding gained by d'Hérelle was ignored in this early work, and inappropriate methods of preparation, "preservatives," and storage procedures were often used. On one occasion, d'Hérelle reported testing 20 preparations from various companies and finding that not one of them contained active phages! Not surprisingly, a check of the product showed that one phage had out-competed all the others, and this was not a polyvalent preparation. In general, there was little essential quality control except in a few research centers. Large clinical studies were rare, and the results of those few that were carried out were largely inaccessible outside of what was then the Soviet Union.

Specific Problems of Early Phage Therapy Work

Some still believe (erroneously) that phage therapy was proven not to work; however, it simply was never adequately researched for a variety of reasons, and the work that was done well is not widely enough known. It is thus important to carefully consider the reasons for the early problems and for the questioning of efficacy:

- Paucity of understanding of the heterogeneity and ecology of the phages and the bacteria involved
- Lack of availability or reliability of bacterial laboratories for carefully identifying the pathogens involved (important considering the relative specificity of phage therapy)
- Use of too few phages in infections that involved mixtures of different bacterial species and strains
- Failure to select obligatorily lytic phages against the target bacteria before using them in patients
- Emergence of phage-resistant bacterial strains, through selection of resistant mutants (especially if only one phage strain was used against a particular bacterium) or through lysogenization (if temperate phages were used, as discussed in "Properties of Bacteriophages")
- Failure to appropriately characterize or titer phage preparations, many of which, even from major companies, were shown to be totally inactive[21,21a]
- Failure to neutralize gastric pH before oral phage administration
- Inactivation of phages by both specific and nonspecific factors in bodily fluids

All of these factors need to be taken into consideration as we now work to formally document phage efficacy and integrate phages into medical practice worldwide.

PROPERTIES OF BACTERIOPHAGES

Viral particles are like spaceships that are able to transfer their genomes between susceptible cells where they can reproduce. In the case of bacteriophages, the targets are specific kinds of bacterial cells, specific to varying degrees for each phage; they cannot infect the cells of more complex organisms. Each virus consists of a long nucleic acid polymer (DNA or RNA) containing the genetic information that determines all of the properties of the virus, which is carried around packaged in a protein coat (Figure 112-1). Unlike eukaryotic viruses, most phages have tails, the tips of which have the ability to bind to specific molecules on the surfaces of their target bacteria (Figure 112-2). The viral DNA is then ejected through the tail into the host cell, where it directs the production of progeny phages; often more than 100 are produced in just half an hour from each bacterial cell.

Each strain of bacteria has characteristic protein, carbohydrate, and lipopolysaccharide molecules present in very large quantities on its surface. These molecules are involved in forming pores, motility, and binding of the bacteria to particular surfaces. Each such molecule can act as a receptor for particular phages. Development of resistance to a particular phage generally reflects mutational alteration or loss of its specific receptor; this loss frequently has negative effects on the bacterium, often making such mutants less virulent, and does not confer protection against the many other phages that use different receptors. Each kind of bacterium has its own phages, which can generally be isolated wherever that bacterium grows: from sewage, feces, soil, even ocean depths and hot springs, but finding phages suitable for therapeutic applications is much easier for some species than for others; this relates significantly to the ability to grow the host in the laboratory. The process of isolation is straightforward for phages targeting many of our best-studied pathogens. An environmental sample is combined with an appropriate nutrient-fortified

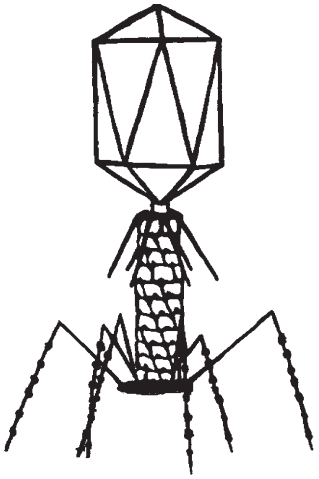


FIGURE 112-1 Phage diagram (bacteriophage T4).

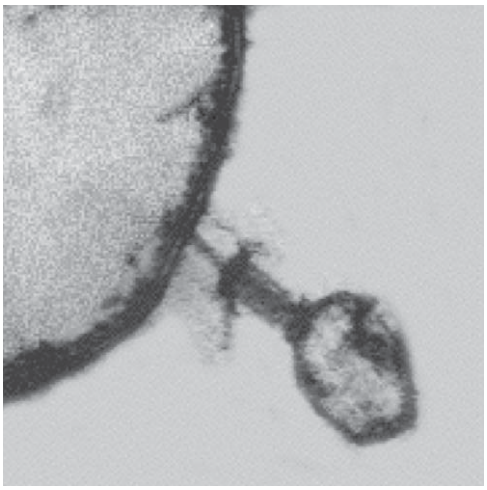


FIGURE 112-2 Electron micrograph of phage infecting a bacterium.

solution and several targeted bacteria, incubated over night, and 10 μL each of a series of ten-fold dilutions spotted on a nutrient-agar plate prepared with a single strain of target bacteria. The next day, a dense bacterial lawn is seen, hopefully with cleared spots and, at some dilution, dotted with small, cleared plaques. Each plaque contains about a billion phages, all of them progeny of a single initial phage. Individual plaques are plucked and cultured to give a homogeneous stock of that particular phage, whose host ranges and other properties can then be studied.

One major source of confusion in the early phage work was that new phages were often isolated by each laboratory, so there was little continuity or basis for comparison. Key technical developments in the 1930s to 1940s that helped clarify the general nature and properties of bacteriophages were (1) the concentration and purification of some large phages by means of very high-speed centrifugation and the demonstration that they contained equal amounts of DNA and protein; and (2) visualization of phages by the electron microscope (EM).[22,23] Phages specific for virtually every well-studied bacterial species have now been isolated, and increasingly, many are becoming well classified.

This EM work also helped resolve the major disputed question as to whether the lytic principle termed bacteriophage simply reflected an inherent property of the specific bacteria or required regular reinfection by an external agent, as claimed by d'Hérelle. During the 1930s and 1940s, it gradually became clear that in some senses both were true—that there were two quite fundamentally different groups of bacteriophages. Obligatorily lytic phages always have to infect from outside, reprogram the host cell, and release a burst of phage through breaking open, or lysing, the cell after a relatively fixed short interval. Temperate phages, in contrast, have another option; they can actually integrate their DNA into the host DNA, much as HIV can integrate the DNA copy of its RNA. For several reasons, such temperate phages are not appropriate for therapeutic applications. They generally make the host resistant to related phages, blocking treatment efficacy, and also may carry genes that actually increase the pathogenicity of the host; very specific prophages are a key factor in such diseases as cholera and diptheria.

Using the EM, each phage family was found to have its own specific shape and size, from "lunar lander"–style complexity with a contractile tail and long tail fibers attached to a baseplate, to globular heads with long or short tails, to the small filamentous phages that looked much like bacterial pili (Figure 112-3). With recent advances in DNA sequencing techniques, our understanding of various phages is exploding in powerful and important ways; the genomes of several hundred phages, infecting a variety of organisms, have now been sequenced, revealing a remarkable variety of types and properties that can be very important when considering potential therapeutic applications. In general appearance, 95% of the studied phages belong to one of the three general tailed morphotypes: the short-tailed podoviridae, the siphoviridae with long, often flexible tails; and the myoviridae, with tails composed of an inner tube and an outer contractile sheath attached to a complex baseplate. There are both obligatorily lytic and temperate phage families with each of these three general morphotypes, so other kinds of data are also needed to tell whether a newly isolated phage is temperate or lytic.

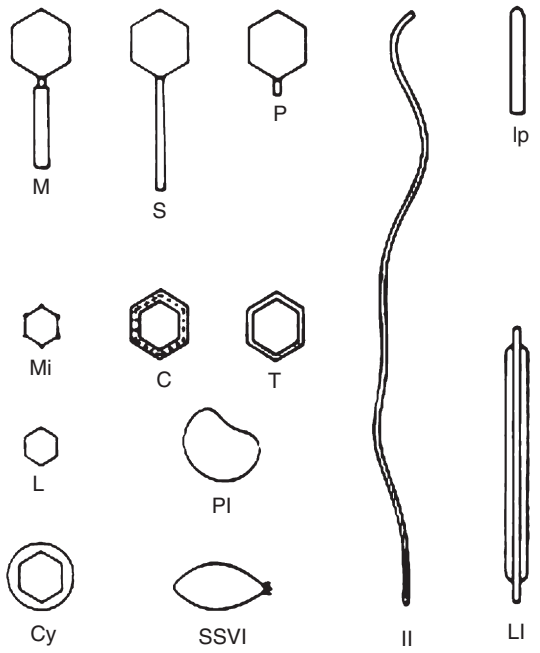


FIGURE 112-3 Various phages.

Obligatorily Lytic Phages and the Development of Molecular Biology

A much better understanding of the interactions between the lytic lifecycle of phages and bacteria began with one-step growth curve experiments. These demonstrated an eclipse period, during which the DNA began replicating and there were no free phages in the cell; a latent period of accumulation of intracellular phages; and a precisely timed lysis process that released the phage to go in search of new hosts. This phage infection cycle is illustrated in Figure 112-4 for coliphage T4, which does a particularly effective job of shutting off all host functions and whose family is very widespread in nature and in therapeutic phage preparations for enteric bacteria.

In 1943, an event occurred that had a major impact on the orientation of phage research in the United States and much of western Europe, strongly shifting the emphasis from practical applications to basic science. Physicist-turned–phage biologist Max Delbruck met with Alfred Hershey and Salvador Luria to form the "Phage Group" and establish the long-time annual phage course and meeting at Cold Spring Harbor, Long Island. A major element of the success of phages as model systems for working out fundamental biological principles at the molecular level was that Delbruck persuaded most U.S. phage biologists to focus on one bacterial host (*E. coli* B) and seven of its highly lytic phages, arbitrarily named types T1 through T7. Fortuitously, T2, T4, and T6 are quite similar to one another, defining a family of myoviridae now called the T-even phages, which were key in demonstrating that DNA is the genetic material, that viruses can encode enzymes, that gene expression is mediated through special "messenger RNA," that the genetic code is triplet in nature, and other fundamental concepts. The negative side of this focus on a few phages growing on one host under rich laboratory conditions was that there was very little study or awareness of the ranges, roles, and properties of bacteriophages in the natural environment or of potential applications. On the positive side, most of the strongly lytic phages selected for therapeutic applications targeting enteric phages have turned out to belong to one or another of these three very well-studied families of phages (as confirmed by sequencing data as well as morphologic details), which is very useful as we work to assure their safety and to understand the physiologic properties involved.

The temperate phages generally encode repressors to turn off most of their own genes when they are in the temperate pro-phage state, integrases to let them insert themselves into the DNA of

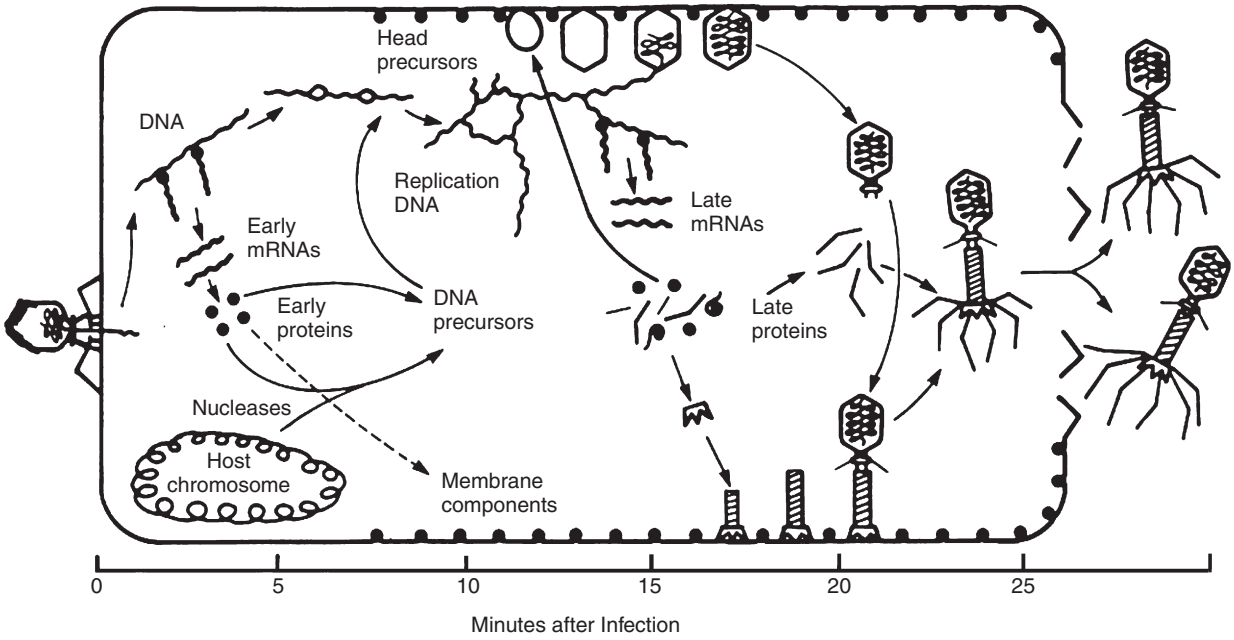


FIGURE 112-4 Bacteriophage intracellular growth cycle. Noteworthy features: both nucleolytic action on host chromosome and new phage enzymes furnish DNA precursors; replicating DNA is much longer than virion DNA; a number of phage-coded proteins become associated with the host membrane to alter host functions and to facilitate phage assembly and maturation.

their hosts, and excision enzymes to cut their DNA back out to enter a lytic cycle. Obligately lytic phages generally have more extensive mechanisms for shutting off the host, often involving nucleases and transcription factors, as well as a variety of small proteins made under the control of strong promoters very early in infection to re-direct cellular metabolism; T4, for example, encodes at least 50 such proteins.

PHAGE INTERACTIONS IN THE BODY

A number of early experiments involving phage injection into animals led to widespread belief that phage therapy could not succeed because the phages were too rapidly cleared by the immune system. Early experiments in rabbits, rats, and mice showed rapid disappearance of phage from the blood and organs, but long-term survival in the spleen.[24,25] However, these experiments were done in the absence of host bacteria in which the phage could multiply and were carried out by the unnatural mode of intravenous injection, exposing the phage almost immediately to the reticuloendothelial system. Many later studies made it clear that phages are seen in the mammalian circulatory system for prolonged periods when they are entering it from some sort of reservoir in other tissues, and the host is dealing with infection by a bacterium in which they can replicate —precisely the sort of situation seen in phage therapy as currently practiced.

This pattern is particularly clear in research published in 1943 by noted Harvard bacteriologist René Dubos[26] (Figure 112-5). Dubos et al[26] injected mice intracerebrally with a dose of a smooth *Shigella dysenteriae* strain that was sufficient to kill more than 95% of the mice in 2 to 5 days and treated them with intraperitoneal injection of a mixture of phages that had been isolated from New York City sewage, grown in the same bacteria, and purified only by sterile filtration. With no treatment or when treated with filtrates of bacterial cultures or with heat-killed phage, only 3 of 84 mice (3.6%) survived; in contrast, 46 of 64 (72%) of the mice given 10^7 to 10^9 phages survived. Pharmacokinetic studies on the mice showed that when phages were given to uninfected mice, they appeared in the bloodstream almost immediately, but the levels started to drop within hours and very few were seen in the brain, as shown in Figure 112-5. However, in infected animals, brain levels of viable phage appropriate to those bacteria soon far exceeded blood levels; around 10^7 to 10^9 phages/g were often seen between 8 and 114 hours after administration, with the level dropping between 75 and 138 hours after phage addition. After the first 18 hours, blood levels were far lower than brain levels, but phages were still present in blood at 10^4 to 10^5 phages/mL in those animals in which the brain levels were still high.

Equally well-controlled experiments performedby Henry Morton and Enrique Perez-Otero from 1943 to 1945 at the University of Pennsylvania supported those of Dubos et al[26] and further showed the lack of any protection when phages with inappropriate host specificities were used. These results clearly established that (1) the phages themselves were responsible, not something in the lysate that just stimulated normal immune mechanisms; (2) phages could rapidly find and multiply in foci of infection anywhere in the body, including crossing the blood–brain barrier; and (3) phages could be maintained in the circulation as long as there was a privileged reservoir of infection where phages were continually being produced. A final review authorized by the Council on Pharmacy and Chemistry discussed the major advantages of phages, such as their ability to replicate into problem areas and treat localized infections that are relatively inaccessible via the circulatory system, and the fact that their high specificity greatly aided in reducing later resistance problems.[27] The review also emphasized that most of the earlier phage research had been so poorly conceived and/or carried out that it offered no proof either for or against the promise of phages as antibiotics; therefore, the negative conclusions of the earlier American Medical Association reviews were neither unexpected nor very relevant to the potential for eventual success.

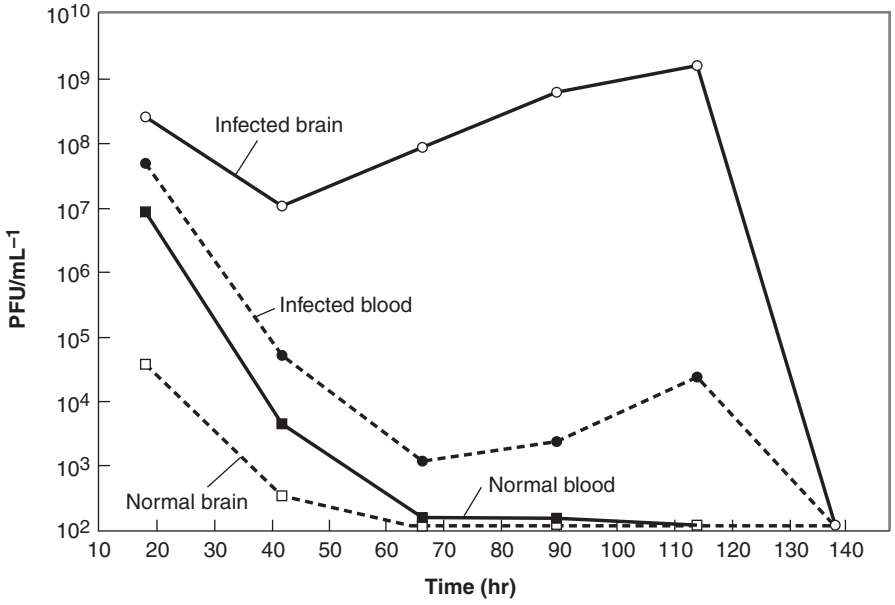


FIGURE 112-5 This figure, based on the data in the 1943 mouse studies of Dubos et al,[26] provides significant insight into why phage therapy works well even in treating infections that antibiotics cannot treat. When the mice were injected intraperitoneally with 10^9 phage, they quickly appeared in the bloodstream and some even crossed the blood–brain barrier, but they were rapidly cleared. However, when the mice were also injected intracerebrally with *Shigella dysenteriae*, the host for these phages, 46 of 64 of the mice survived (compared with 3 of 84 in the absence of appropriate viable phage), and the brain level of phage climbed to over 10^9/g. Once the bacteria cleared, the level of phage dropped below detection limits.

The context of these studies sheds enlightening insights into the historical course of phage therapy in the United States.[28] In 1942, both *The Lancet* and the *British Medical Journal* published editorials about the apparently successful use of antidysentery phages by the Soviet military in the Middle and Far East. By November 1942, the U.S. National Research Council Committee on Medical Research began supporting research possibilities offered by antidysentary phages for dealing with this perpetual scourge of armies (including the previous studies) in top U.S. bacteriology laboratories new to phage work, initially requiring them to keep the results secret. This promising work ended in 1944, when the end of World War II made penicillin generally available. The military secrecy, the end of the war emergency funding, the rapid rise in antibiotic availability and their broad-spectra "wonder-drug" status, and Max Delbruck's success in persuading the phage community to shift its focus to basic molecular research involving a few model systems, all contributed to the fact that there was little U.S. follow-up to these interesting and successful results. Although the results were published in major journals, few people even knew about them, or about highly successful ongoing human applications, until they were recently rediscovered by Thomas Häusler.[2]

Penicillin works only against gram-positive bacteria, so it cannot treat typhoid fever, and early phage efforts against typhoid had very mixed success. It was then found that the major pathogenic strains of *Salmonella typhi* all carried one particular antigen, named Vi (for "virulence"). In 1936, a pair of Canadians identified a number of phages specific against the Vi antigen; these are still used as "typing phages" in rapidly identifying and following outbreaks. In the late 1930s and early 1940s, physicians at the Los Angeles County Hospital used phage treatments to help deal with repeated serious outbreaks of typhoid that were killing one in five of those afflicted.[29] Walter Ward tested the Vi-specific phages against mouse typhus and found that the death rate fell to 6% versus 93% in controls.[29] When these phages were then used to treat patients with typhoid, only 3 of 56 treated patients died compared with the 20% mortality for the other treatments available at the time.[30] Most impressively, this study reported that the patients who received phage therapy rapidly changed from being largely comatose to full of vigor, with renewed appetite, in 24 to 48 hours. In 1948 to 1949, near Montreal, Desranleau treated nearly 100 patients with dysentery by giving them a cocktail of six different Vi-specific phages, and the death rate dropped from 20% to 2%.[30a] By then, however, chloramphenicol had been shown to work well against typhoid, and it was much easier for pharmaceutical companies to deal with, so that seems to have been the end of phage clinical trials in the Western hemisphere.

The high specificity of phages still plays a strong role in the phage typing sets used for detecting and following problem strains of such bacteria as *Shigella, Salmonella,* and *E. coli,* but phage therapy itself is only beginning to stage a comeback.

CLINICAL APPLICATION

The growing understanding of phage biology has the potential to facilitate more rational thinking about the therapeutic process and the selection of therapeutic phages. However, there was generally little interaction between those who were so effectively using phages as tools to understand molecular biology and those working on phage ecology and therapeutic applications. Many in the latter group were spurred on by a concern about the rising incidence of nosocomial infections and of bacteria resistance against most or all known antibiotics, as well as by the fact that phages are far more effective than antibiotics in areas of the body where circulation is poor and does not disrupt normal flora. This strong sense of the potential importance of phages was particularly seen in Poland, France, Switzerland, and the former Soviet Union, where use of

therapeutic phages never died out and where there has been ongoing research and clinical experience. In France, Dr. Jean-François Vieu led the therapeutic phage efforts until his retirement 15 years ago. He worked in the Service des Entérobactéries of the Pasteur Institute in Paris and, for example, prepared *Pseudomonas* phages on a case-by-case basis for patients. His experience there is discussed in two articles.[31,32] In Vevey, Switzerland, the small pharmaceutical firm Saphal made "Coliphagine," "Intestiphagine," "Pyophagine," and "Staphagine" in drinkable and injectable forms, salves, and sprays into the 1960s.[28] The owner, Harrmann Glauser, had been encouraged and trained by d'Hérelle's old colleague Paul Hauduroy, who had become a professor of microbiology at the University of Lausanne during the second World War. These phage preparations were officially approved and were paid for by insurance.

Phage therapy was used extensively in many parts of eastern Europe as a regular part of clinical practice, and companies in Russia now make phages for this purpose. However, most of the research and much of the phage preparation came under the direction of key centers in Tbilisi, Georgia, and Wroclaw, Poland. In both cases, the close interactions between research scientists and physicians played an important role in the high degree of success obtained, just as was the case for d'Hérelle's early work.

Clinical Research at the Institute of Immunology and Experimental Medicine, Polish Academy of Sciences

Some of the most detailed publications documenting phage therapy are from the group led by Stefan Slopek, a long-time director of the Wroclaw Institute of Immunology and Experimental Medicine, as well as his successors there. Slopek's initial series of papers described work completed in 1981-1986 with 550 patients in 10 Polish medical centers.[33-35] The patients ranged in age from 1 week to 86 years and venues included the Wroclaw Medical Academy Institute of Surgery Cardiosurgery Clinic, Children's Surgery Clinic and Orthopedic Clinic, the Institute of Internal Diseases Nephrology Clinic, and the Clinic of Pulmonary Diseases. In 518 cases, phage use followed unsuccessful treatment with all available methods, including antibiotics. The major categories of infections included long-persisting suppurative fistulas and abscesses, septicemia, respiratory tract suppurative infections, pneumonia, and purulent peritonitis. In a final summary article, the results were carefully analyzed with regard to such factors as nature and severity of the infection and monoinfection versus infection with multiple bacteria.[35] Rates of success ranged from 75% to 100% (92% overall), as measured by marked improvement in relevant physical condition, wound healing, and disappearance of titratable bacteria; 84% of subjects demonstrated full elimination of the suppurative process and healing of local wounds. Infants and children did particularly well. Not surprisingly, the poorest results occurred in elderly patients and those in the final stages of extended serious illnesses.

Appropriate individual highly-virulent phages were selected from their extensive collection. In the first study alone, 259 different phages were tested (116 for *Staphylococcus*, 42 for *Klebsiella*, 11 for *Proteus*, 39 for *Escherichia*, 30 for *Shigella*, 20 for *Pseudomonas*, and 1 for *Salmonella*); 40% of them were selected to be used directly for therapy. All of the treatments were conducted in research mode, with the phage prepared at the institute by standard methods and tested for sterility. Treatment generally involved 10 mL of sterile phage lysate given orally half an hour before each meal, with gastric juices neutralized by ingesting (basic) Vichy water, baking soda, or gelatin. In addition, phage-soaked compresses were generally applied three times a day where dictated by localized infection. Treatment ran for 1.5 to 14 weeks (mean, 5.3 weeks). For intestinal problems, short treatment sufficed, whereas long-term use was necessary for such problems as pneumonia with pleural fistula and pyogenic arthritis. Bacterial levels and phage sensitivity were continually monitored, and the phage(s) were changed if the bacteria lost their sensitivity. Therapy was generally continued for 2 weeks beyond the last positive test result for the bacteria. Few side effects were observed; those that were seen seemed to be directly associated with the therapeutic process.[33]

Various methods of administration were successfully used, including oral, aerosols, and infusion, either rectally or in surgical wounds. Intravenous administration was not recommended for fear of possible toxic shock from bacterial debris in the lysates.[33] However, it was clear that the phages readily entered the body from the digestive tract and multiplied internally wherever appropriate bacteria were present, as measured by their presence in blood and urine as well as by therapeutic effects.[36] This interesting and rather unexpected finding has been replicated in many studies and systems.[37-40]

Detailed notes were kept throughout on each patient. The final evaluating therapist also filled out a special inquiry form that was sent to the Polish Academy of Science research team along with the notes. The Computer Center at Wroclaw Technical University carried out extensive analyses of the data. These researchers used the categories established in the World Health Organization's (1977) *International Classification of Diseases* in assessing results. They also looked at the effects of age, severity of initial condition, type(s) of bacteria involved, length of treatment, and other concomitant treatments. After Slopek's retirement, Dr. Beatta Weber-Dabrowska carried on with the treatment work, publishing a summary in English of the results for the next 16 patients.[41] In 1998, immunologist A. Górski took over as Institute director and revived a strong focus on phage work, with special emphasis on the immunologic consequences of phage treatment. These researchers are also now working with the basic phage group of Dr. M. Lobocka in Warsaw to sequence and further characterize key phages—an important step in eventually making them available to the outside world.

Clinical Research at the Bacteriophage Institute, Tbilisi

Particularly extensive efforts for phage therapy were carried out over many decades by scientists at the Bacteriophage Institute in Tbilisi, Georgia, working closely with local physicians. Phage therapy is an accepted component of the general standard of care in Georgia, used extensively in pediatric, burn, and surgical hospital settings. Phage preparation was carried out on an enormous scale before the breakup of the Soviet Union, employing 700 people in the factory and several hundred more in the research arm of the Institute, making 2 tons of phage products weekly to ship throughout the former Soviet Union. They were available both over the counter and through physicians; 80% went to the military for wound and burn infections and for preventing debilitating gastrointestinal epidemics. In hospitals, they were used to treat both primary and nosocomial infections, alone or in conjunction with other antimicrobials. The International Science and Technology Centers program, set up jointly by the United States, Europe, and Japan to give constructive opportunities to scientists formerly working with Soviet military projects, is now one of the strongest supporters of basic and applied research in this area in Tbilisi.

From the Bacteriophage Institute's inception, the industrial part was run on a self-supporting basis, whereas its scientific branch was government supported. The Institute carried out the extensive studies needed for approval by the Ministry of Health in Moscow

of each new strain, therapeutic cocktail, and means of delivery. This careful study of the host range, lytic spectrum, cross resistance, and other fundamental properties of the phages being used was a major factor in the reported successes of their phage therapy work, as were their methods for selecting highly virulent phages from among the many available against any given host. Where necessary, new cocktails were prepared with broader host ranges. The depth and extent of the work involved are impressive. For example, in 1983 to 1985, the Institute's Laboratory of Morphology and Biology of Bacteriophages carried out studies of growth, biochemical features, and phage sensitivity on 2038 strains of *Staphylococcus,* 1128 of *Streptococcus,* 328 of *Proteus,* 373 of *P. aeruginosa,* and 622 of *Clostridium* received from clinics and hospitals in towns across the former Soviet Union. New broader acting phage strains were isolated and were included in a reformulation of their extensively used Pyophage preparation. A good deal of work went into developing the documentation for Ministry of Health approval of specialized new delivery systems, such as a spray for use in respiratory tract infections, in treating the incision area before surgery, and in sanitation of hospital problem areas. An enteric-coated pill was also developed, using phage strains that could survive the drying process, and accounted for the bulk of the shipments to other parts of the former Soviet Union. Much work focused on combating nosocomial infections, in which multidrug-resistant organisms have become a particularly lethal problem. An exciting new product was licensed in 2000 by the Georgian Ministry of Health. PhagoBioDerm is a biodegradable, nontoxic polymer composite that allows the sustained release of the Pyophage cocktail of phages.[42,43] One study on PhagoBioDerm involved 107 patients with ulcers that had failed to respond to conventional therapy—systemic antibiotics, antibiotic-containing ointments, and various phlebotonic and vascular protecting agents. The ulcers were treated with PhagoBioDerm alone or in combination with other interventions during 1999 and 2000. The wounds or ulcers healed completely in 70% of the 96 patients for whom there was follow-up data. In the 22 cases for which complete microbiological analyses were available, healing was associated with the concomitant elimination or very marked reduction of the pathogenic bacteria in the ulcers. A newly formulated version of PhagoBioDerm should soon be on the market; it is much less expensive to produce and has other advantages.

Staphylococcus Aureus Infections, Whether or Not Methicillin-Resistant

Methicillin-resistant *S. Aureus* (MRSA) is a particular concern given its reduced susceptibility to antibiotic treatment, wide prevalence in hospital-acquired infections and in the community, and potentially lethal and otherwise serious consequences. These pathogens are targeted by the anti-*S. aureus* activity of phage preparations such as Pyophage (which include potent anti-*Staphylococcus* phages of the broad-spectrum Sb1-staph phage K family; Kutter EM, unpublished results). Here as elsewhere, there is no cross resistance between phages and antibiotics. Furthermore, very little development of resistance to this family of phages has been observed, presumably implying that the still unidentified primary receptor is a molecule of significant importance to the bacteria. Thus, so far as phages are concerned, MRSA is simply another strain of *Staphylococcus*. Treatment of MRSA using phages can be accomplished by local application for local infections or, if necessary, with substantially more caution, more systemic dosing such as intraperitoneally for systemic infections.[44] The use of phage treatment for local infections, including particularly those due to *Staphylococcus*, has the distinction of being one of only two phage therapy strategies that were deemed to be convincingly efficacious by the Eaton and Bayne-Jones report in 1934,[45-47] and an otherwise phage therapy skeptical publication.[48] The first human phage therapy publication reported on treatment of *S. aureus* skin infections.[6,49,50] Phage preparations for systemic application were developed at the Eliava Institute during the 1980s, including safety studies in human volunteers without adverse effects. Phages were particularly effective in infants and in immune-compromised patients, and for infusion into the urethra in cases of pelvic inflammatory disease. The preparation subsequently was used to treat 653 patients.[6] Historically, questions have been raised as to whether the apparent efficacy documented in these classic articles was due to the phage itself giving rise to bacterial lysis in situ. It was suggested that the debris in the phage lysate, stimulating the host immune system, could be a major factor in bacterial clearance.[6] See Sulakvelidze and Barrow[51] and Kutter et al[5] for discussion of what is known as Staph Phage Lysate or simply SPL, produced by Delmont Laboratories. This product is marketed as a veterinary vaccine conferring resistance to staph through immune stimulation by its staphylococcal phage induced bacterial lysis products, which is advertised as the major active ingredient. It also contains viable phages, often at approximately 10^8 plaque forming units (PFU)/mL (Kutter EM, unpublished data; Kuhl SJ, unpublished data), a level as high as the total phage in Pyophage as determined by direct fluorescent microscopic count.[51a] These staph phage lysates initially were produced for human as well as animal use against chronic infections.[6] However, in 1994, they were limited by the FDA to animal use pending further human efficacy trials, for which no funding has yet been found; no questions have been raised as to their safety.

Phage use to prevent *Staphylococcus* infections has been both proposed and employed. Phages have been used for disinfection in Georgia to sanitize operating rooms and medical equipment and prevent nosocomial infections.[49] A complementary approach proposed by the company Novolytics is to use "an aqueous suspension to treat nasal carriage of MRSA, thus significantly reducing the incidence of MRSA transmission" (see www.novolytics.co.uk/technology.html, see also Mann[51b]). O'Flaherty et al[51c] described removal of *S. aureus* via experimental hand washing with a phage-containing Ringers solution. Approximately 100-fold reductions in bacterial densities were observed after washing with a solution containing 10^8 phages/mL versus the phage-less control solution. Leszczynski et al[51d] described the use of oral phage therapy for targeting MRSA in a nurse who was a carrier. This individual had MRSA colonized in her GI tract and also had a urinary tract infection. The result was complete elimination of culturable MRSA. In an earlier publication, the same group argued that MRSA treatment using phages could be economically preferable to MRSA treatment using antibiotics[52]; in contrast, see the discussion in Abdul-Hassan, et al.[53] Jikia et al[53a] described phage treatment of MRSA infecting radiation burns. Slopek et al[35] reported 92.4% positive cases for phage treatment of 550 single- and mixed-etiology infections involving *S. aureus*. Slopek et al[34] specifically used phage treatment for suppurative staphylococcal infections, with a reported 93% "effective" rate "based on case history and data contained in a special questionnaire," while also using this treatment of various kinds of *Staphylococcus* infections in children (95.5% positive results for the 90 children treated).

Urogenital Tract Infections

Phages have been applied to treat various infections of the urogenital systems either systemically, via direct injection into the bladder

or via topical application. Phage treatment of urogenital tract infections could potentially be complimented by current naturopathic protocols involving alkalinization of the urine with citrates and minerals. Eaton and Bayne-Jones[45-47] in their 1934 report were convinced of the efficacious use of phage therapy against cystitis. Letwiewicz et al[54] described phage application rectally to target *Enterococcus faecalis* infection of the prostate, with substantial success in eliminating the target bacteria. In this case, the phages were presumed to be taken up through the rectal wall. Letarov et al[55] noted that rectal phage suppositories are available on the Russian market. Slopek et al[35] reported 92.9% positive results for phage treatment of 42 "diseases of the genitourinary tract." Chanishvili's and Sharp's[56] book has chapters on "Phage Therapy in Urology" and "Phage Therapy in Gynecology." They summarize the results there as follows: "In cases of acute cystitis a therapeutic effect was observed within 4–5 hours of the first administration and resulted in relief of pain, a decrease in the frequency of urination and a normalization of the composition of the urine. Full recovery was achieved within 1–3 days in all 13 cases (100%) however treatment of chronic forms of cystitis was less successful, with only a moderate improvement observed."[56] Supported by a 3-year grant from the International Science and Technology Centers, the Eliava Institute developed a new phage cocktail specifically targeted against a large pool of bacteria from prostatitis and urinary tract infections. At the 2009 Evergreen International Phage Biology Meeting, Alavidze reported on its production and on very successful preliminary trials involving over 100 patients. A Western-style double-blind, placebo-controlled trial involving addition of this phage to the standard treatment at one of the major clinics in Tbilisi is currently in the planning stage.[56a]

Gastrointestinal Infections

From the beginning, acute diarrheal infections were a major and very successful part of phage therapy practice, as discussed previously in "Phage Interactions in the Body", and the major clinical trial currently under way involves work by Nestlé in Bangladesh to stem the death toll caused by infant diarrhea (see "Introduction"). However, most GI problems, such as irritable bowel syndrome, diverticulitis, and Crohn's disease, may involve long-term chronic infections and immune system challenges. Although there is no body of literature to build on from Tbilisi or from Poland on the latter application, this would appear to be an area well worth exploration.

Respiratory Tract Infections

Respiratory infections can be differentiated into numerous types; however, phage therapy is limited in efficacy to those with a bacterial etiology. Weber-Dabrowska et al[57] reported successful treatment of pneumonia in six cancer patients. Similarly, Slopek et al[58] reported 86.7% positive results for phage treatment in 180 "diseases of the respiratory system" (see also Slopek et al[33]). The first case studies of phages used to treat people for chronic infections of *S. aureus* and *P. aeruginosa* in Tbilisi were recently published; these studies used Pyophage and a fully sequenced *S. aureus* phage delivered by standard cystic fibrosis nebulizers.[59,60] The latter study included a detailed description of the successful treatment of *P. aeruginosa* infection in the lungs of a 7-year-old patient (using Pyophage) along with treatment of a *S. aureus* co-infection in the same patient using phage Sb-1. The company previously known as Biocontrol reported an interest in expanding its anti-*Pseudomonas* phage therapy efforts to include treatment of children with cystic fibrosis.[61] Success in treating infections in animal models of cystic fibrosis associated infection was also reported by Debarbieux et al[62] and Carmody et al[63] in addition to the exploration of using nebulization as a phage delivery strategy. Phage treatments of lung infections, however, can also be used effectively, in at least some circumstances from systemic circulation, as animal models have shown.[63]

Ear Infections

Chronic otitis externa, known less formally as swimmer's ear, is often caused by a *P. aeruginosa* ear infection that resists antibiotic treatment. Otitis media is often caused by *Streptococcus pneumoniae*, and is the leading cause of physician visits from children. The company, Biocontrol (recently acquired by Targeted Genetics of Seattle to form a new joint company, AmpliPhi Biosciences) has been developing anti-*P. aeruginosa* phages targeting otitis externa, after publishing similar studies on dogs.[64,65] In 2009, they published the results of their double-blinded phase 1/2a (safety and small-number efficacy) trial in human patients with this condition.[66] Increases in phage numbers in situ, microbiological improvements (reductions in bacterial presence), and reduction in disease symptoms in the phage-treated cohort, but not the phage-negative controls, were observed. No side effects were seen. Complete bacterial eradication was not observed, but the extent of success was particularly notable considering that only a single phage dose was administered. Weber-Dabrowska et al[57] also reported phage therapy success in treated purulent otitis media, and Slopek et al[58] reported 93.8% positive results for phage treatment of 16 cases of conjunctivitis, blepharoconjunctivitis, and otitis media.

TOXICOLOGY

From a clinical standpoint, all indications are that phages are very safe. This feature is not surprising, given that humans are exposed to phages from birth. Bergh et al[67] reported that nonpolluted water contains about 10^8 phages/mL. Phages are normally found in the GI tract, skin, urine, and mouth, where they are harbored in saliva and dental plaque.[68-70] They have also been shown to be unintentional contaminants of sera and therefore of commercially available vaccines,[71-74] which were given dispensation to be sold despite this discovery, because of the general consensus that phages are safe for humans.

Extensive preclinical animal testing was required for approving new phage formulations in the former Soviet Union, but few of these studies were published. For example, Bogovazova et al[75,76] evaluated the safety and efficacy of *Klebsiella* phages produced by the Russian company Immunopreparat. Pharmacokinetic and toxicologic studies using intramuscular, intraperitoneal, or intravenous administration of phages were carried out in mice and guinea pigs. The researchers found no signs of acute toxicity or histologic changes, even using a dose 3500-fold higher than the projected human dose. They then evaluated the safety and efficacy of the phages in treating 109 patients. The phage preparation was reported to be nontoxic to humans and to be effective in treating *Klebsiella* infections, as manifested by marked clinical improvements and bacterial clearance in the phage-treated patients.

Occasional mild side effects such as liver pain and fever reported in the early days of Western phage therapy may have been due to bacterial byproducts in preparations used intravenously.[77-79] Concerned about this possibility, the Polish group does not administer their phages intravenously. The same is true for almost all of the therapeutic work carried out in Tbilisi, and perhaps helps to explain the virtually total lack of significant problems in both places; their many years of experience, careful attention to detail,

and supportive infrastructure are presumably also important factors. Because phages readily enter the bloodstream after infusion in or near wounds and other sites of localized infection and travel to sites of infection throughout the body,[80] there generally seems to be no reason for undergoing the extra risks of intravenous administration.

Drug Interactions

No negative effects on the efficacy or safety of other drugs have been reported anywhere as a result of phage administration. No systematic studies have been carried out in this regard, but phages are so specific in their actions that it is hard to determine where such interactions might occur. In contrast, at least some antibiotics can interfere with phage treatment of localized infections by killing off the most accessible of the bacteria in which the phages need to multiply as they work their way deeper into the lesion; this would be a particular problem in cases in which the phages can still attach and infect but cannot complete their replication cycle. Georgian physicians generally believe that antibiotics should never be used topically for wounds and deep-seated infections, because the decrease in antibiotic concentration below the surface provides a strong selection for antibiotic resistance; this problem does not occur with phages.

DOSING STRATEGY

Phage cocktails can be designed in two distinctly different ways. The major style currently used in Georgia, Russia, and Poland, termed active treatment, uses a "low" concentration of phages so as to rely on in situ phage replication to achieve a therapeutically relevant concentration of phage. Titers of individual phages are typically approximately 10^6 to 10^7 PFU/mL and in general 5 to 10 mL is used per dose. This approach is preferred particularly when antibiotics fail due to poor circulation or surgical inaccessibility. The other style, passive treatment, ignores the self-replicating nature of phages in favor of a more conventional dosing strategy, in which the infected area is directly accessible and a sufficient number of particles are applied to treat the infection in a single dose.[81]

CONCLUSION

Phages have many potential advantages:

- They are self-replicating but also self-limiting, because they multiply only in the presence of sensitive bacteria.
- They can be targeted much more specifically than most antibiotics to the problem bacteria, causing far less of the bacterial imbalance or "dysbiosis" that are major problems with antibiotics, often leading to serious secondary infections involving relatively resistant bacteria that can increase hospitalization time, expense, and mortality (see Chapters 10 and 27). Particular resultant problems are *Pseudomonads*, which are especially difficult to treat, and *Clostridium difficile*, the cause of serious diarrhea and membranous colitis.[82]
- Phages can often be targeted to receptors on the bacterial surface that are involved in pathogenesis, so any resistant mutants are less problematic.
- No serious side effects have been reported for phage therapy.
- Phage therapy could be particularly useful for people with allergies to antibiotics.
- Appropriately selected phages can easily be used prophylactically to help prevent bacterial disease at times of exposure or to sanitize hospitals and help protect against hospital-acquired (nosocomial) infections.
- Especially for external applications, phages can be prepared fairly inexpensively and locally, facilitating their potential applications to underserved populations.
- Phages can be used either independently or in conjunction with other antibiotics to help reduce the development of bacterial resistance.

The time has come to look more carefully at the potential of phage therapy for future practice, both by strongly supporting new research and by scrutinizing the research already available, such as the very interesting human antityphoid phage research carried out in this country in the 1940s,[30] as well as the extensive earlier work in France, the United States,Georgia, Poland, and Russia.[4,5]

With the enormous possibilities and decreasing costs of genomic analysis, it is now possible to perform genomic sequencing of the phages included in cocktails to ascertain more about the phage families involved and exclude phages from temperate families, because they are likely to carry or acquire genes related to pathogenicity or toxin production. This is now standard procedure for therapeutic phages being developed in the West. Such modern techniques are beginning to be applied to some of the Georgian phage preparations with help from grants from the International Science and Technology Centers and Civilian Research and Development Foundation programs, both of which were set up to support civilian applications of science formerly funded by the Soviet military. This is an important step in considering the importation of such phages for topical use in the Western world.

Although it seems premature to broadly introduce injectable phage preparations in the West without further extensive research, their carefully implemented use in external applications and for a variety of agricultural purposes could potentially help reduce the emergence of antibiotic-resistant strains and deal with problems we have difficulty handling today. Furthermore, compassionate use of appropriate phages seems warranted in cases in which bacteria resistant to all available antibiotics are causing life-threatening illness. Phages are especially useful in dealing with recalcitrant nosocomial infections, in which large numbers of particularly vulnerable people are being exposed to the same strains of bacteria in a closed hospital setting. In these cases especially, the environment as well as the patients can be effectively treated with phage preparations.

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CHAPTER 113

Phosphatidylserine

Parris M. Kidd, BSc, PhD

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INTRODUCTION

Phosphatidylserine (PS) is a phospholipid nutrient that occurs naturally in all cells; it is an orthomolecule according to Linus Pauling's definition.[1] PS is most highly concentrated in brain cells, and as a dietary supplement its clinical benefits are most apparent in brain-related functions, including cognition, mood, and stress management.[2-6]

PS is fundamentally important for life. It is an essential building block for the cell membrane system that manages most life processes.[6] Cell membranes are thin, continuous structures composed mainly of phospholipids (a lipid bilayer), into which are inserted myriad catalytic proteins. PS is an essential phospholipid for the membrane system, helping to create the physical–chemical milieu appropriate for optimal protein activity.[2,7]

The PS molecule has a characteristic layout (Figure 113-1)—a head piece, a middle piece, and two tail pieces ("tails").[2,7] The head piece contains serine attached to a phosphoryl group, has a net negative charge, and is positioned on the membrane's inner (cytoplasmic) surface.[7] The middle piece is a 3-carbon glyceryl sequence. The two tail pieces are constructed from fatty acids, extend deep into the membrane, and help maintain the semi-fluid membrane interior that the proteins require for their catalytic activity.[2]

Biochemically, PS is not a single molecule but a family of molecules.[2,8] The head and middle pieces are standard, but each of the two tail groups can be constructed from many different fatty acids. Thus, there are as many PS molecules as there are fatty acid permutations. Further, all cells carry enzymes ("acylases") that can detach one fatty acid tail and substitute it with another, depending on the need for membrane fluidity.[8] In the brain's highly active gray matter, the PS molecules on average carry more of the highly fluidizing ω-3 fatty acids; in contrast, PS in the white matter has less ω-3 and more saturated and mono-unsaturated (ω-9) fatty acid tails.[8]

PHYSIOLOGIC ROLES

The presence of PS in cell membranes enables the brain's electrical activity, the blood's clotting properties, bone matrix formation, and the selective removal of dying cells from the tissues.[2,7] All these processes are based in cell membrane structure and function. At the cell membrane level, activities specifically linked to PS include[8-12]:

- Energetics: Adenosine triphosphate (ATP) production by the mitochondria relies on phosphatidylethanolamine in their membranes, generated exclusively from PS.[8]
- Membrane/cell stabilization: PS binds with structural proteins to stabilize the cell's outer membrane and overall cell shape.[9]
- Signal transduction: The conversion of external signals to internal cell transformations, which often requires protein kinase C, a PS-dependent protein.[10]
- Secretion: The presence of PS enables membrane vesicles within the cell to fuse with the outer cell membrane and release their contents.[11]
- Apoptosis: A cell that is dying allows its PS to "flip" to the outer (external) face of the cell membrane. This serves as a "suicide" signal for immune cells to recycle that cell.[12]

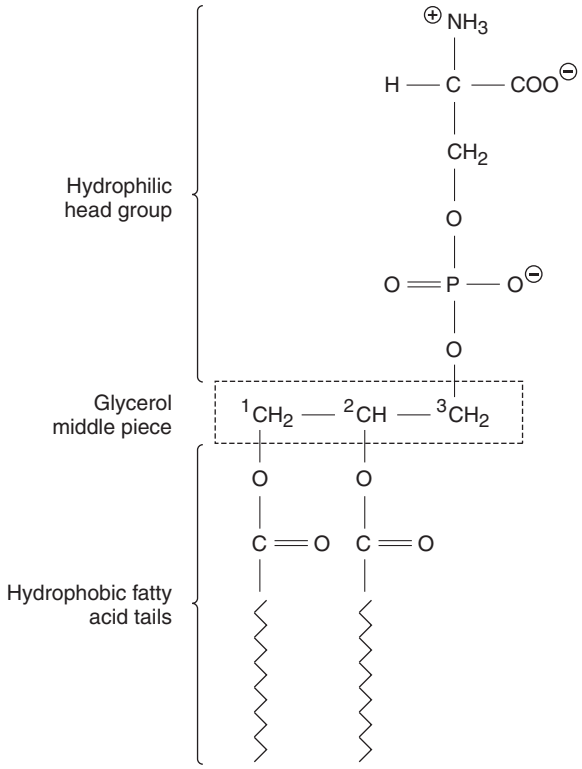


FIGURE 113-1 Phosphatidylserine.

PHARMACOLOGY

The pharmacology of PS is consonant with its diverse actions in cell membranes.[2,13,14] In animal studies, PS enhanced the activities of at least nine major transmitter systems (reviewed in Kidd[2]). In animal and human studies, PS enhanced stress management via the hypothalamic-pituitary-adrenal (HPA) axis,[14] as well as the diurnal hormone secretory rhythms of the pituitary gland.[15]

Other animal findings indicated PS has an overall trophic (restorative) effect in the brain. Feeding PS to aging rats significantly slowed the usual age-related decline of forebrain cholinergic synapses[16] and of nerve cells and their dendritic densities in the hippocampus.[17,18] Also in aging rats, PS by mouth significantly slowed the age-associated decline of receptors for nerve growth factor, a protein factor that stimulates brain circuit maintenance and renewal.[18]

Consistent with its importance for mitochondrial function, PS supports brain energetics. A single-photon emission computed tomographic imaging study of dementia patients found that orally administered PS improved energy production and utilization throughout the brain.[19]

CLINICAL APPLICATIONS

The primary clinical application of PS is to correct impaired mental functioning in the middle-aged and elderly. In multiple randomized, double-blind, placebo-controlled trials, PS consistently improved memory, learning, word recall, and other cognitive functions.[2-5,20-28] In one such trial conducted with healthy subjects at the earliest stage of measurable cognitive decline (age-associated memory impairment), PS seemingly reversed the decline in the subgroup that was afflicted worst at the outset.[3]

Against full-blown Alzheimer's disease, the benefits of PS typically included improvement in activities of daily living, verbal expression, and sociability,[2,5,20,21,23] as well as mild improvements in memory and concentration.[2,4,5] In the largest controlled trial,[5] 425 elderly Alzheimer patients (aged 65 to 93 years) received either PS (300 mg/day) or a placebo for 6 months.[5] The PS group showed improvements in memory, learning, withdrawal, apathy, and "adaptability to the environment" that were highly statistically significant (P <0.01) compared with the placebo group.

In May 2003, PS acquired elite status as a brain nutrient. The U.S. Food and Drug Administration granted two "qualified health claims" that allowed that PS may (1) reduce the risk of dementia in the elderly, and (2) reduce the risk of cognitive dysfunction in the elderly.[29]

PS also can improve mood and anxiety.[2,30-32] In a small double-blind trial in women with major depression, PS (300 mg/day vs placebo for 30 days) significantly improved the symptoms of depression and anxiety along with cognition, irritability, and sociability.[30] PS (200 mg/day, 30 days) again significantly improved depression in another small controlled trial with elderly women.[31] In a double-blind trial in elderly men with cognition problems, PS significantly lessened the risk of developing the "winter blues."[32] An early clinical study suggested PS could partially revitalize the aging HPA axis in aging humans.[33]

PS also improved the ability of young, healthy subjects to cope with stress, whether physical or psychological. PS alleviated students' perceived stress from timed mental arithmetic testing (300 mg/day for 30 days).[34] Another double-blind trial had healthy subjects making an unrehearsed job application speech and doing complex mental arithmetic.[35] In this trial, subjects who received a phospholipid complex with 400 mg PS and 500 mg phosphatidic acid showed significantly less distress and significantly lowered stress hormone elevations of adrenocorticotropic hormone and cortisol compared with placebo.

In the physical arena, PS improved golfers' driving accuracy (at just 200 mg/day for 42 days)[36] and other physical performances in cycling, running, and weight training.[37] Physical and mental challenges often raise blood cortisol, and PS can blunt this cortisol response, albeit at relatively high doses (400 to 800 mg/day).[35,37]

The PS originally used in clinical studies came from cow brains ("bovine cortex PS," "BC-PS"), but "mad cow disease" made this source untenable, and soy became the new source. Unlike BC-PS, initially all soy PS totally lacked ω-3 docosahexaenoic acid (DHA) in its tails.[38] However, this soy PS without DHA showed clinical benefits in a number of double-blind trials.[6,31,32,34-36]

Recently PS carrying DHA and eicosapentaenoic acid (EPA) ("PS ω-3") has become available as a dietary supplement. In a randomized, double-blind, placebo-controlled trial on children with attention deficit hyperactivity disorder, consumption of a PS ω-3 providing PS 300 mg/day, ω-3 EPA 156 mg/day, and ω-3 DHA 95 mg/day for 3 months improved visual sustained attention.[38] The PS ω-3 group experienced significantly more benefit than another group that received matching EPA and DHA allowances from fish oil triglycerides.

In a 2010 double-blind trial on non-demented elderly with memory complaints, another PS ω-3 preparation (PS 300 mg/day, EPA 20 mg/day, DHA 60 mg/day) significantly improved verbal immediate recall.[39]

DOSAGE

The standard dosage recommendation for PS is 100 mg taken with meals one to three times daily.

TOXICOLOGY AND DRUG INTERACTIONS

After more than 16 years of use as a dietary supplement, PS has no evidence of drug interactions or adverse effects at dosages up to 800 mg/day.[2,35,37]

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CHAPTER 114

Piper methysticum (Kava)

Michael T. Murray, ND

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Piper methysticum (family: Piperaceae)
Common name: kava

GENERAL DESCRIPTION

Kava is a hardy, slow-growing perennial that generally resembles other members of the pepper family. It is an attractive shrub and can attain heights of more than 9 ft. The plant does not have many leaves, but those it does have are thin, single, heart-shaped, alternate, petiolate, 4 to 10 inches long, and sometimes wider than they are long. Although *Piper methysticum* does flower, it is incapable of self-reproduction; its propagation is vegetative and now due solely to human effort.[1,2]

For medicinal purposes, it is the rootstock that is used. The rootstock is knotty, thick, and sometimes tuberous with holes or cracks created by partial destruction of the parenchyma. In other words, the rootstock is often somewhat pithy. From the main rootstock, there are extensions of lateral roots up to 9 ft long.[1,2]

CHEMICAL COMPOSITION

Analysis of the composition of the dried kava rootstock indicates that it contains approximately 43% starch, 12% water, 3.2% simple sugars, 3.6% proteins, 3.2% minerals (primarily potassium), and 15% kavalactones (Table 114-1).[1,2]

On the basis of detailed analysis of the active ingredients of kava, a laborious process over the past 120 years, many experts now believe that the pharmacologic activities of kava are due mostly, if not entirely, to the presence of compounds known as kavalactones (also referred to as kava α-pyrones). Although the kavalactones are the primary active components, other components appear to contribute to the sedative and anxiolytic activities of kava, as one study found the sedative activity of a crude preparation to be more effective than the isolated kavalactones (Figure 114-1).[3] The kavalactone content of the root can vary between 3% and 20%.

HISTORY AND FOLK USE

Oceania, the Pacific island communities of Micronesia, Melanesia, and Polynesia, is one of the few geographic areas of the world that did not have alcoholic beverages before European contact in the eighteenth century. However, these islanders did possess a "magical" drink used in ceremonies and celebrations because of its calming effect and ability to promote sociability. The drink, also called kava, is still used today in this region of the world, where the people are often referred to as the happiest and friendliest in the world.

The origins of kava use are not known as it predates written history in Oceania.[1,2] It was first described for the Western world by Captain James Cook in the account of his voyage to the South Seas in 1768.

Many myths and legends surround the early use of kava. The plant itself probably originated in the New Guinea/Indonesia area and was spread from island to island by early Polynesian explorers in canoes, along with other plants. Each culture has its own story on the origins of kava. For example, in Samoa, a story is told about the origins of kava and sugar cane. The story tells that a Samoan girl went to Fiji where she married a great chief. After some time, she returned to Samoa, but before doing so, she noticed two plants growing on a hill. She saw a rat chewing on one of the plants and noticed that the rat seemed to go to sleep. She concluded that the plant

TABLE 114-1 **Kavalactones**

COMPOUND	R	R'	R''	R'''	C5-6	C7-8
Kavain					—	=
7,8-Dihydrokavain					—	—
5,6-Dihydrokavain					—	=
Yangonin	OCH_3				=	=
5,6,7,8-Tetrahydroyangonin	OCH_3				—	—
Methysticin	O-CH_2-O				—	=
Dihydromethysticin	O-CH_2-O				—	=
5,6-Dihydromethysticin	O-CH_2-O				=	=
5,6-Dihydroyangonin	OCH_3				—	=
7,8-Dihydroyangonin	OCH_3				—	=
10-Methoxy-yangonin	OCH_3		OCH_3		=	=
11-Methoxy-yangonin	OCH_3	OCH_3			=	=
11-Hydroxy-yangonin	OCH_3	HO			=	=
Hydroxykavain				OH	—	=
11-Methoxy-12-hydroxy dehydrokavain	OH	OCH_3			=	=

Single dashes represent a single bond, and double dashes represent a double bond.

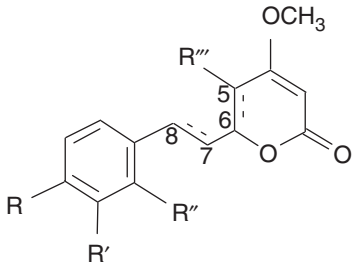


FIGURE 114-1 Kavalactones.

was a comforting food. She decided she would take this plant, sugar cane, back to Samoa, but then she noticed that the rat awoke and began to chew the root of another plant, kava. The animal that had been weak and shy became bold, strong, and more energetic. She decided that she would take both plants back with her to plant in Samoa. The plants grew very well in Samoa, and soon a chief from a neighboring island exchanged two laying hens for roots of the two plants. Hence, the Samoans take credit for the spread of both sugar cane and kava.

In Tonga, a legend is told about a great chief named Loau who lived on the island of Euaiki. He went to visit his servant Feva'anga, who wanted to give a feast in honor of the chief, but it was a time of great famine. In desperation, he and his wife killed and cooked their only daughter to be served to the chief. However, Loau recognized the human flesh in the food when it was served and would not eat it. He instructed Feva'anga to plant the food in the ground and to bring him the plant that would spring forth. On receiving the mature plant, Loau instructed that a drink be prepared from it and consumed with due ceremony.

The Kava Ceremony

Regardless of exactly how kava originated, it has been used in ceremonies by the Oceanic people for thousands of years. There are three basic kava ceremonies: the full ceremonial enacted on every formal occasion; the one performed at the meeting of village elders, chiefs, and nobles and for visiting chiefs and dignitaries; and the less formal kava circle common on social occasions.[1,2]

The first step of any kava ceremony was the preparation of the beverage. The following description of the classic process was written in 1777 by Georg Forster, a young naturalist on James Cook's second Pacific voyage:

> *[Kava] is made in the most disgustful manner that can be imagined, from the juice contained in the roots of a species of pepper-tree. This root is cut small, and the pieces chewed by several people, who spit the macerated mass into a bowl, where some water (milk) of coconuts is poured upon it. They then strain it through a quantity of fibres of coconuts, squeezing the chips, till all their juices mix with the coconut-milk; and the whole liquor is decanted into another bowl. They swallow this nauseous stuff as fast as possible; and some old topers value themselves on being able to empty a great number of bowls.*

As this traditional method of preparation became frowned upon or made illegal by colonial governments and missionaries, more "sanitary" methods of preparation, involving grinding or grating, took its place in many parts of Oceania.

The full kava ceremony, reserved for very highly honored guests, involves leading all the guests to a platform. The ceremony begins with the arrival of a group of young men dressed in ceremonial attire and carrying a bowl of the kava drink and necessary utensils. The bowl is placed between the kava preparers and the visitors. The kava is poured in a cup by a specially selected individual who then turns and faces the visitor and delivers the beverage to the chief guest. The guest is instructed to hold the cup with both hands and drink from it. If the whole cup is drained without stopping, everyone says "a maca" (pronounced "a matha," meaning "it is empty") and claps three times with cupped hands. The cupbearer then returns to the kava bowl and proceeds to serve the person next in rank or importance.

Important people who visit Fiji and other islands of Oceania still participate in the kava ceremonies. For example, during a 1992 presidential campaign visit to Hawaii, Hillary Clinton participated in a kava ceremony conducted by the Samoan community on O'ahu.

The Effects of Drinking Kava

Kava drinkers relate a pleasant sense of tranquility and sociability upon consumption. Subjective reports given by scientists who have sampled kava themselves are relatively abundant. One of the first scientific studies of kava was performed by the noted pharmacologist Louis Lewin in 1886. A later description written in 1927 is as follows[1]:

When the mixture is not too strong, the subject attains a state of happy unconcern, well-being and contentment, free of physical or psychological excitement. At the beginning, conversation comes in a gentle, easy flow and hearing and sight are honed, becoming able to perceive subtle shades of sound and vision. Kava soothes temperaments. The drinker never becomes angry, unpleasant, quarrelsome or noisy, as happens with alcohol. Both natives and whites consider kava as a means of easing moral discomfort. The drinker remains master of his consciousness and his reason. When consumption is excessive, however, the limbs become tired, the muscles seem no longer to respond to the orders and control of the mind, walking becomes slow and unsteady and the drinker looks partially inebriated. He feels the need to lie down. He is overcome by somnolence and finally drifts off to sleep.

A later description was provided by researcher R.J. Gregory, who wrote the following from his own experience:[1]

Kava seizes one's mind. This is not a literal seizure, but something does change in the processes by which information enters, is retrieved, or leads to actions as a result. Thinking is certainly affected by the kava experience, but not in the same ways as are found from caffeine, nicotine, alcohol, or marijuana. I would personally characterize the changes I experienced as going from lineal processing of information to a greater sense of "being" and contentment with being. Memory seemed to be enhanced, whereas restriction of data inputs was strongly desired, especially with regard to disturbances of light, movements, noise and so on. Peace and quiet were very important to maintain the inner sense of serenity. My senses seemed to be unusually sharpened, so that even whispers seemed to be loud while loud noises were extremely unpleasant.

Drinking about half a coconut shell (100 to 150 mL) of certain varieties of kava is enough to put most people into a deep, dreamless sleep within 30 minutes. Unlike alcohol and other sedatives, kava does not produce a morning hangover. The kava drinker awakens having fully recovered normal physical and mental capacities.

PHARMACOLOGY

Many of the first comprehensive studies on the activities of kavalactones were conducted by a team of scientists from the Freiburg University Institute of Pharmacology in Germany, led by Hans J. Meyer, during the 1950s and 1960s.[3] This research determined that kavalactones exhibit sedative, analgesic, anticonvulsant, and muscle-relaxing effects in laboratory animals. These studies seemed to confirm earlier empirical and subjective observations. Later studies utilized better-defined kava extracts.

Isolated Kavalactones Compared with Crude Extracts

Some evidence suggests that the whole complex of kavalactones and other compounds naturally found in kava produce greater pharmacologic activity. In addition, studies showed that kavalactones are more rapidly absorbed when given orally as an extract of the root rather than as the isolated kavalactones. The bioavailability of lactones, as measured by peak plasma concentrations, is up to three to five times higher from the extract than when given as isolated substances.[3] Further evidence that kava root extracts are superior to isolated kavalactones was offered by an animal study that showed that although isolated kavalactones were well absorbed by the brain, crude kava preparations produced brain concentrations of lactones 2 to 20 times higher.[4] This evidence suggests that crude extracts standardized for kavalactone content may offer the greatest therapeutic benefit.

Several clinical trials featured a kava extract standardized to contain 70% kavalactones. However, this high percentage of kavalactones might be sacrificing some of the other constituents that may contribute to the pharmacology of kava. More important than the actual percentage of kavalactones is the total dosage of the kavalactones and the assurance that the full range of kavalactones and other important constituents are present.

Sedative Effects

Numerous studies confirmed and/or elaborated on the sedative effects of kava. Most notable were the studies that demonstrated that kavalactones exert many of their effects through nontraditional mechanisms. For example, most sedative drugs, including the benzodiazepines (e.g., diazepam, triazolam, clorazepate dipotassium) work by binding to specific receptors (benzodiazepine or γ-aminobutyric acid [GABA] receptors) in the brain, leading to the neurochemical changes (potentiation of GABA effects) that promote sedation. Studies in animals showed that the kavalactones do not bind to benzodiazepine or GABA receptors.[5] Instead, the kavalactones are thought to somehow modify receptor domains rather than interact specifically with receptor binding sites. In addition, other studies indicated that the kavalactones appear to act primarily on the limbic system, the ancient part of the brain that affects all other brain activities and is the principal seat of the emotions.[6] It is thought that kava may also promote sleep by altering the way in which the limbic system modulates emotional processes. It appears that many of the laboratory models of identifying how a substance works to promote a calming effect are simply not sophisticated enough to evaluate the physiologic effects of kava.

Analgesic Effects

In another example of the unusual pharmacologic qualities of kava, a study designed to evaluate its pain-relieving effects could not demonstrate any binding to opiate receptors.[7] The significance of this finding was that the study used experimental models in which nonopiate analgesics like aspirin and other nonsteroidal antiinflammatory drugs were ineffective. In addition, it was determined that the sedative or muscle-relaxing effects were not responsible for the pain-relieving effects. These findings indicate that kava reduces pain in a manner unlike morphine, aspirin, or any other pain reliever.

Anxiolytic Effects

An interesting difference of kava from other anxiolytics is that unlike the drugs, kava does not lose effectiveness with time. Kavalactones, even when administered in large doses, demonstrated no loss of effectiveness in animal studies.[8] This is another example of the unusual qualities of kava.

Antiischemia Effects

Another important pharmacologic activity of kava is its ability to protect against brain damage due to ischemia.[9] This effect was demonstrated in two animal models of focal cerebral ischemia. The effectiveness of the kavalactones was due to their ability to limit the infarct area as well as to provide a mild anticonvulsant effect. Kava extract may prove useful in the recovery from a stroke.

CLINICAL APPLICATIONS

The primary clinical application of kava is in the treatment of anxiety. This application is well-supported by clinical research.[10]

However, the medicinal use of kava is shrouded in uncertainty due to reports of hepatoxicity (discussed in the "Toxicology" section).

Early clinical trials used D,L-kavain, a purified kavalactone, at a dosage of 400 mg/day. For example, in one double-blind, placebo-controlled study of 84 patients with anxiety symptoms, kavain was shown to improve vigilance, memory, and reaction time.[11] In another double-blind study, kavain was compared with oxazepam (a drug similar to diazepam [Valium]) in 38 patients.[12] Both substances caused progressive improvements in two different anxiety scores (Anxiety Status Inventory and the Self-rating Anxiety Scale) over a 4-week period. However, although oxazepam and similar drugs are addictive and cause side effects, kavain appeared to be free of these complications.

In one of the early studies with kava extracts, a 70% kavalactone extract was shown to exhibit significant therapeutic benefit in patients with anxiety.[13] The study was double-blind; 29 patients were assigned to receive 100 mg of the kava extract three times a day and 29 other patients received a placebo. Therapeutic effectiveness was assessed using several standard psychological assessments, including the Hamilton Anxiety Scale (HAMA). The results of this 4-week study indicated that individuals taking the kava extract had a statistically significant reduction in symptoms of anxiety, including feelings of nervousness, and somatic complaints, such as heart palpitations, chest pains, headache, dizziness, and feelings of gastric irritation. No side effects were reported with the kava extract.

Studies also compared the effects of a kava extract standardized to contain 30% kavalactones with buspirone and opipramol. In the double-blind study, 129 patients with generalized anxiety disorder were given either 400 mg kava (30% kavalactones), 10 mg buspirone, or 100 mg opipramol daily for 8 weeks. Detailed analysis showed that no significant differences were observed regarding all efficacy and safety measures. About 75% of patients were classified as responders (50% reduction of the HAMA score) in each treatment group, and about 60% achieved full remission.[14]

Kava was also shown to be particularly effective in relieving anxiety in perimenopausal and post-menopausal women.[15-17] In one double-blind study, two groups of 20 women with menopause-related symptoms were treated for 8 weeks with the 70% kavalactone extract (100 mg three times daily) or placebo.[18] The measured variable was once again the HAMA. The group receiving the kava extract demonstrated significant improvement at the end of the very first week of treatment. Scores continued to improve over the course of the 8-week study. In addition to symptoms of stress and anxiety, a number of other symptoms also improved. Most notably there was an overall improvement in subjective well-being, mood, and general symptoms of menopause, including hot flashes. As with previous studies, no side effects were noted.

Additional studies showed that unlike benzodiazepines, alcohol, and other drugs, kava extract was not associated with depressed mental function or impairment in driving or the operation of heavy equipment.[19,20] In one of these studies, 12 healthy volunteers were tested in a double-blind crossover manner to assess the effects of oxazepam (placebo on days 1 to 3, 15 mg on the day before testing, 75 mg on the morning of the experiment), the extract of kava standardized at 70% kavalactones (200 mg three times daily for 5 days), and a placebo on behavior and event-related potentials (ERP) in electroencephalographic readings on a recognition memory task. The subjects' task was to identify within a list of visually presented words those that were shown for the first time and those that were being repeated. Consistent with other benzodiazepines, oxazepam inhibited the recognition of both new and old words as noted by ERP. In contrast, kava allowed a slightly greater recognition rate and a larger ERP difference between old and new words. The results of this study once again demonstrated the unusual effects of kava. In this case, it improved anxiety, but unlike standard anxiolytics, kava actually improved mental function and, at the recommended levels, did not promote sedation. Another study indicated that kava helped improve reflex vagal control of heart rate in generalized anxiety disorder patients.[21]

In 2009, the first documented human clinical trial assessing the anxiolytic and antidepressant efficacy of an aqueous extract of kava was published.[22] The World Health Organization (WHO) suggested the investigation of aqueous kava extracts as a way to reduce the risk of hepatotoxicity with kava preparations (discussed in the "Toxicology" section). The Kava Anxiety Depression Spectrum Study was a 3-week, placebo-controlled, double-blind crossover trial that recruited 60 adult participants with 1 month or more of elevated generalized anxiety. The kava preparation produced significant anxiolytic and antidepressant activity and raised no hepatoxicity or safety concerns at the dose and duration studied. Specifically, kava reduced participants' HAMA scores in the first controlled phase by −9.9 versus −0.8 for placebo and in the second controlled phase by −10.3 versus +3.3. Pooled analyses also revealed highly significant relative reductions in anxiety and depression scale scores.

DOSAGE

In clinical studies using pure kavalactones or kava extracts standardized for kavalactones, the dosage was based on the level of kavalactones. Because the kavalactone content of the root varies between 3% and 20%, preparations standardized for kavalactone content are preferred to crude preparations. A standard bowl of traditionally prepared kava drink contains approximately 250 mg of kavalactones, and in Oceania, several bowls may be consumed at one sitting. Dosages are as follows:

- Anxiolytic dosage: 45 to 80 mg of kavalactones three times a day
- Sedative dosage: 180 to 250 mg of kavalactones 1 hour before retiring

SIDE EFFECTS AND TOXICOLOGY

In November 2001, German health authorities announced that 24 cases of liver disease (including hepatitis, liver failure, and cirrhosis) associated with the use of kava had been reported in Germany; of the affected persons, one died and three required a liver transplant. As a result, in December 2001, the U.S. Food and Drug Administration began advising consumers of the potential risk of severe liver injury associated with the use of kava-containing dietary supplements. Kava was subsequently withdrawn from the market in the European Union, United Kingdom, and Canada. In 2007, Germany reevaluated the data and allowed kava back on the market.

In the initial report, the true nature of kava-induced liver damage was clouded by the fact that in 18 of the cases, conventional prescription or over-the-counter pharmaceutical drugs with known or potential liver toxicity were also being used. Proponents of kava quickly argued that it was entirely possible that the use of kava by these individuals was a coincidence rather than the cause of the liver problems, due to excessive dosage or some other factor. As of 2007, of the approximately 100 cases of hepatoxicity that were reported worldwide, causality deemed to be "probable" occurred in only 14 cases.[23] Two drug monitoring studies, including a total of 7078 patients taking 120 to 150 mg kava extract per day, did not

find a single case of kava-induced hepatotoxicity. Nonetheless, as of 2010, the hepatoxicity of kava cannot be ruled out.

The existing data are complex, but it looks like the major factor in any kava-induced hepatoxocity was the use of aerial parts, such as stems and leaves as well as stem peelings.[24] It turns out that once the demand for kava skyrocketed, there was not enough kava root to fill the demand. Suppliers then knowingly or unknowingly bought the leaves and peelings of kava. Up until that event, the only parts of the kava plant that were traditionally used throughout its 3000 year history were the roots; never the peelings or the leaves. According to a WHO report, German pharmaceutical industries preferred to buy kava stem peelings to extract kavalactones to make kava drugs; kava stem peelings were sold at almost one tenth of the price of kava roots.[25] In addition, dosage might also have been a factor in some of the cases of hepatoxicity. A survey of 400 German medical practices showed that 78% of the kava prescriptions that were written before 2001 significantly exceeded the recommended intake.[26] Nonetheless, there were reports of hepatitis in patients using kava at dosages equal to or only slightly higher than recommended levels, indicating other factors beyond dosage.[27] Flavokawain B, a chalcone from kava root, was identified as a potent hepatocellular toxin.[28]

Measures suggested to address the hepatoxicity issue include: (1) use of a noble kava cultivar such as Borogu, which is at least 5 years old at time of harvest, (2) use of peeled and dried rhizomes and roots, (3) dosage recommendation of less than or equal to 250 mg kavalactones per day (for medicinal use), and (4) a Pan Pacific quality control system enforced by strict policing.[24] Another important step may be determination of flavokawain B. It should be mentioned that although it has been suggested that traditional aqueous extracts should be used over ethanolic or acetonic extracts, the toxicity is linked to the kava plant itself, with a possibly low quality of the used kava cultivar or kava plant part rather than the method of extraction or solvent.[29]

High daily dosages of kava consumed over a prolonged period (a few months to a year) are associated with a number of side effects beyond liver damage, including the development of "kava dermopathy"—a condition of the skin characterized by a peculiar generalized scaly eruption known as kani.[30] The skin becomes dry and covered with scales, especially the palms of the hands, soles of the feet, forearms, the back, and shins. It was thought at one time that kava dermopathy might be due to interference with niacin. However, in a double-blind, placebo-controlled study, niacinamide (100 mg/day) demonstrated no therapeutic effect.[31] It appears that the only effective treatment for kava dermopathy is reduction or cessation of kava consumption. No cases of kava dermopathy have been reported in persons taking standardized kava extracts at recommended levels.

Other reported adverse effects of extremely high doses of kava (e.g., more than 310 g/week) for prolonged periods are as follows[32]:

- Biochemical abnormalities (low levels of serum albumin, protein, urea, and bilirubin)
- Elevated liver enzymes
- Presence of blood in the urine
- Increased red blood cell volume
- Decreased platelet and lymphocyte counts
- Shortness of breath

At this time, kava is not recommended for use by anyone who has any liver problems or who is a regular consumer of alcohol. Use of kava for more than 4 weeks requires close monitoring of liver enzymes (once every 4 to 6 weeks). Patients should be instructed to discontinue use of kava if symptoms of jaundice (e.g., dark urine, yellowing of the eyes) occur. Nonspecific symptoms of liver disease include nausea, vomiting, light-colored stools, unusual tiredness, weakness, stomach or abdominal pain, and loss of appetite.

Kava is not recommended for use by pregnant or breastfeeding women.

DRUG INTERACTIONS

Kava may potentiate the effects of benzodiazepines, barbiturates, and prescription sedatives. Kava also inhibits a number of the cytochrome P450 enzymes that play a role in the breakdown of many medications.[33] Therefore, it has the potential to interact with a wide range of medications. There is evidence that kava interferes with dopamine or other drugs used in the treatment of Parkinson's disease; therefore, until this issue is resolved, kava extract should not be used by patients with Parkinson's disease.[30]

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CHAPTER 115

Prebiotics, Synbiotics, and Colonic Foods

Jason Hawrelak, ND, BNat(Hons), PhD

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INTRODUCTION

A prebiotic is defined as "a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon."[1] For food ingredients to be classified as prebiotics, they must:

1. Neither be digested nor absorbed in the stomach or small intestine.[2]
2. Act as a selective food source for one or a limited number of potentially beneficial commensal bacteria in the large intestine.[2]
3. Change the colonic microflora ecosystem towards a healthier composition.[2]
4. Induce luminal or systemic changes that improve the health of the host.[3]

Most emphasis at this stage has been on finding and studying food sources that are used by lactic acid-producing bacteria. This is due to the health-promoting properties of these organisms.[2] The best known lactic acid-producing bacteria belong to the genera *Lactobacillus* and *Bifidobacterium*.

Not all food ingredients that make it to the colon undigested will be prebiotics. Only compounds that are selectively consumed by beneficial members of the microflora, while being ignored by potentially pathogenic ones, can truly be termed prebiotics. When prebiotics reach the colon, they are preferentially utilized by those organisms that have the capacity to hydrolyse their bonds. The metabolism of the prebiotic results in the increased growth and activity of the beneficial organism(s), often at the expense of other components of the microflora.[4] Food ingredients that make it to the colon undigested, but lack selectivity of fermentation are termed "colonic foods" and are discussed in more depth at the end of this chapter.

There are numerous compounds with the potential to be termed prebiotics. Table 115-1 lists these compounds and the type of microorganisms whose growth they promote. However, the best-researched prebiotics are fructooligosaccharides (FOSs), galactooligosaccharides (GOSs), and lactulose.

FRUCTOOLIGOSACCHARIDES

Description

FOSs are linear or branched chains of fructose and glucose molecules.[9] The number of fructose units contained in the compound determines the name of the FOS. Oligofructose is generally composed of between 2 and 7 units, whereas inulin is composed of up to 60.[10] FOSs are found in varying percentages in foods and have been discovered in over 36,000 plant species, where they function primarily as storage carbohydrates.[11] FOSs are found in many common vegetables, including asparagus, onion, leek, garlic, artichoke, Jerusalem artichoke, and chicory root. However, it is from the chicory root *(Cichorium intybus)* that most of the commercially produced inulin and oligofructose is manufactured. Short-chain fructans, such as oligofructose, are produced from inulin through a process of partial enzymatic hydrolysis.[9]

Commercial Forms

There are two ways in which FOS can be consumed, in supplements and in foods.

TABLE 115-1 **Potential Prebiotics and Their Target Organisms**

PREBIOTIC COMPOUND	FOOD SOURCES	TARGETED MICROORGANISMS
β-glucooligomers	Oats	*Lactobacillus* spp.
Fructooligosaccharides	See Table 115-2	*Bifidobacterium* spp.
Galactooligosaccharides	Cow's milk; yogurt; human milk	*Bifidobacterium* spp.
Galactosyl lactose	Human milk	*Bifidobacterium* spp.
Lactitol	None known	*Lactobacillus* spp.; *Bifidobacterium* spp.
Lactosucrose	None	*Bifidobacterium* spp.
Lactulose	UHT milk	*Lactobacillus* spp.; *Bifidobacterium* spp.
Polydextrose	None known	*Lactobacillus* spp.; *Bifidobacterium* spp.
Raffinose	Legumes; beets	*Lactobacillus* spp.; *Bifidobacterium* spp.
Xylooligosaccharides	Oats	*Bifidobacterium* spp.

UHT = Ultra-high-temperature.
Prebiotic substances and the organisms whose growth they promote.[5-8]

Fructooligosaccharides Supplements

The most commonly employed method to purify and concentrate FOS for supplement use is via a hot water extraction of fresh chicory roots. This process results in inulin (also known as Raftiline, a large-chain FOS) as the end product. Some manufacturers utilize enzymatic hydrolysis to produce oligofructose (also known as Raftilose, a medium-chain FOS) from inulin,[10] although other manufacturers synthesize FOS from sucrose using the fungal enzyme fructosyltransferase (from *Aspergillus niger*). This latter process involves chemical synthesis of a new compound (called Neosugar or Actilight, a short-chain FOS) from two other natural compounds (fructose and glucose). The finished compound is similar to naturally obtained FOS, only smaller in size.[9]

FOSs are resistant to digestion in the upper gastrointestinal tract (GIT) because of the β-configuration of the bonds between the fructose units. Human digestive enzymes are specific in requiring α-linkages; thus, FOSs are classified as nondigestible oligosaccharides.[9]

Food Sources of Fructooligosaccharides

As previously mentioned, FOSs are common food ingredients. Individuals consuming the standard Western diet consume an average of 5.1 g/day of FOS.[12] However, this can easily be increased if foods rich in FOS are consumed on a daily basis. Foods containing FOS are outlined in Table 115-2.

Other FOS-containing foods include honey,[14] beer, Chinese chives, and maple syrup.[15]

There is no particular advantage to the consumption of FOS in supplements compared with FOS-rich foods. As long as the amount of FOS consumed in a food is similar to that used in clinical studies, it will promote identical effects, as all FOSs consumed reach the colon intact, whether ingested in whole foods or in supplements.

TABLE 115-2 **Fructooligosaccharides-Containing Foods**

	FORM	AVERAGE PERCENTAGE OF FRESH WEIGHT
Onion	Raw	4.3%
	Cooked	3.1%
Jerusalem artichoke	Tubers (raw)	18.0%
Rye	Flour (raw)	0.7%
Dandelion	Leaves (raw)	13.5%
	Root (raw)	7.9%
Barley	Raw kernels	0.75%
	Cooked kernels	0.15%
Asparagus	Raw	2.5%
	Boiled	1.7%
Leek	Raw	3.0%
Garlic	Raw	12.9%
Globe artichoke	Boiled	4.4%
Banana	Raw	0.5%
	Dried (raw)	1.5%
Wheat	Bran (raw)	2.5%
	Flour (baked)	2.4%
Chicory	Root (raw)	17.5%
	Roasted (as coffee)	41.7%
Salsify	Root (raw)	4.2%
Burdock	Root (raw)	14.5%
Yacon	Root (raw)	11.0%

The FOS content of some commonly consumed foods.[12,13]

Clinical Applications

The health benefits claimed for FOS mainly stem from their ability to increase numbers of beneficial organisms in the colon, to reduce numbers of potentially pathogenic microorganisms (PPMs), and to stimulate short-chain fatty acid (SCFA) production. These health benefits include:

- Enhanced resistance to enteric pathogens due to colonization resistance provided by the increased growth of lactic acid bacteria, and increased resistance to infections due to the nonspecific stimulation of the immune system[16]
- Modification of carcinogen metabolism[16]
- Enhanced absorption of minerals[16]
- Improved serum lipid parameters[16]
- Improved satiety[17]
- Treatment of atopic eczema and prevention of atopy development[18]
- Increased intestinal mucin production and trophic effects on the colonic epithelium, secondary to the increased production of SCFAs[19]

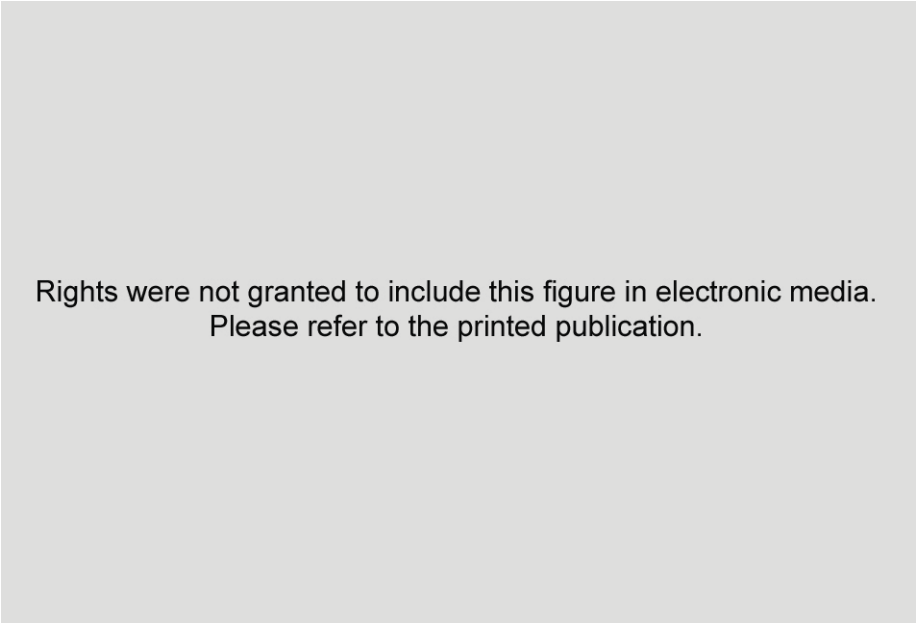


FIGURE 115-1 The prebiotic concept: the effects of sucrose, oligofructose, and inulin on the intestinal ecosystem. Pie diagrams illustrate how the microflora can develop during the feeding of sucrose and the prebiotics, oligofructose and inulin. (From Gibson GR. Dietary modulation of the human gut microflora using prebiotics. Br J Nutr. 1998;80 [suppl 2]:S209-S21, used with permission.)

This review focuses primarily on the ability of FOS to enhance bifidobacterial growth, improve immune response, enhance mineral absorption, possibly treat and prevent atopic diseases, and improve satiety.

Enhanced Growth of Bifidobacteria

In a human trial utilizing oligofructose (8 g/day over a 2-week period), Mitsuoka et al[15] found a 0.9 log unit increase in bifidobacteria numbers with oligofructose consumption (P <0.005). The trial also showed a decrease in enterobacteria numbers.[15]

In an attempt to determine the optimal dose of oligofructose, in terms of maximizing bifidobacteria numbers and minimizing side-effects, Bouhnik et al[20] designed a trial that utilized five different dosage levels. The dosages used were 20, 10, 5, and 2.5 g/day of oligofructose and 0 g/day as the placebo. The trial lasted 7 days. The data indicated that bifidobacteria counts did not change in subjects who received 0 or 2.5 g/day of oligofructose, but that counts in those subjects who ingested 5, 10, and 20 g/day were significantly greater (P <0.05) at day 8 than at baseline. A significant correlation between the ingested dose of oligofructose and fecal bifidobacterial counts was observed at day 8 (P <0.01). In terms of side effects, all groups, including the placebo group, experienced mild abdominal symptoms, such as bloating, excess flatus, borborygmi, or mild abdominal pain. In general, the higher the dose of oligofructose, the more side effects experienced. Bouhnik et al[20] concluded that 10 g/day was well-tolerated and that this dose was probably the optimal dose of oligofructose, since it led to a significant increase in colonic bifidobacteria with minimal side effects.

In a study reported by Gibson et al,[21] both oligofructose and inulin were studied to assess their effects on bifidobacteria levels and the populations of other members of intestinal microflora. Eight subjects participated in the 45-day trial in which they ate controlled diets. For the initial 15 days, all the subjects ate 15 g/day of sucrose. For the middle 15 days, the sucrose was substituted with 15 g of oligofructose. For the final 15 days, four of the participants were given 15 g/day of inulin. A marked effect was noted in bifidobacteria numbers, which increased 0.7 log units on oligofructose (P <0.01) and 0.9 log units on inulin (P <0.001). There was also a significant decrease in bacteroides (P <0.01), clostridia (P <0.05), and fusobacteria (P <0.01) in the oligofructose-fed subjects, whereas gram-positive cocci levels decreased in the inulin-fed group (P <0.001). Inulin administration also increased lactobacilli numbers, although not significantly (P <0.075). In both groups, bifidobacteria became the numerically predominant species in the feces (see Figure 115-1).[21]

Improved Immune Response

Prebiotics, like FOS, have long been suggested to have immune enhancing effects.[22,23] It is, however, only recently that human clinical trials with hard outcomes have been completed. One of the first of these trials investigated the effects of a prebiotic mixture (containing a combination of FOS and GOS) in protecting against infections during the first 6 months of life in formula-fed infants. In this randomized, double-blind, placebo-controlled trial, infants allocated to the prebiotic group experienced significantly fewer episodes of all types of infections combined (P = 0.01) compared with those in the placebo group. There was also a trend for fewer episodes of upper respiratory tract infection (P = 0.07) and fewer infections requiring antibiotic treatment (P = 0.10) in the prebiotic group. Additionally, the cumulative incidence of recurring infection and recurring respiratory tract infection was 3.9% and 2.9% in the prebiotic group versus 13.5% and 9.6% in the placebo group, respectively (P <0.05).[24]

This same infant cohort was followed up over the next 1.5 years. Those infants that received the prebiotic-enhanced formula for the first 6 months of life experienced significantly fewer episodes of physician-diagnosed respiratory tract infections (P <0.01), fever episodes (P <0.00001), and fewer antibiotic prescriptions (P <0.05) compared with those in the placebo group.[25]

In a randomized, placebo-controlled, open-label study, Bruzzese et al[26] also investigated the efficacy of a prebiotic-enhanced infant formula (a combination of GOS and FOS) on infection incidence in infants. The prebiotic-enhanced formula or a standard infant formula was consumed over the initial 12 months of life. During this period, the incidence of gastroenteritis was 59% lower in the prebiotic group ($P = 0.015$). Additionally, the number of children with recurrent upper respiratory tract infections tended to be lower in the prebiotic group (28% vs 45%; $P = 0.06$) and the number of children prescribed multiple antibiotic courses per year was also lower (40% vs 66%; $P = 0.004$).[26]

In a randomized, double-blind, placebo-controlled trial looking at older children (aged 7 to 19 months) attending daycare centers, short-term administration (21 days) of FOS was found to significantly reduce the number of infectious diseases requiring antibiotic treatment ($P < 0.001$), episodes of diarrhea and vomiting ($P < 0.001$), and episodes of fever ($P < 0.05$) compared with controls.[27]

In another randomized, controlled trial investigating the effects of FOS in toddlers (4 to 24 month olds) attending daycare, FOS administration was found to significantly reduce antibiotic use (32% reduction; $P = 0.001$) and daycare absenteeism (61% decrease; $P = 0.025$) compared with those in the control group. There was also a 34% reduction in episodes of fever in combination with any cold symptoms ($P = 0.001$) and a 61% decrease in episodes of fever in association with diarrhea ($P < 0.05$) in the FOS-supplemented group.[28]

Enhanced Mineral Absorption

Studies utilizing animal models demonstrated that microfloral degradation of FOS significantly increased calcium and magnesium absorption.[29-31] Human studies also showed that FOS consumption improved calcium absorption.[32-34] The proposed mechanism by which mineral absorption is enhanced by FOS is via the action of the protonated SCFA. Protonated SCFAs are absorbed across the apical membrane of colonocytes by direct diffusion. Due to the low pK_a values of the SCFA in relation to the intracellular pH, the SCFA dissociates once it enters the cell. This results in the release of a hydrogen ion. The hydrogen ion is subsequently secreted from the cell in return for a cation, which may be a magnesium or calcium ion. The hydrogen ion is then available to protonate another SCFA and enable it to diffuse into the cell.[32] However, other mechanisms may also be involved, such as the decrease in colonic pH, which results in increased solubility of calcium, increased colonic venous blood flow, enlarged colonic villi, and enhanced expression of calbindin-D9k (the active calcium transport route).[35] These effects are more pronounced in the colon, some of which are calcium-specific, explaining why calcium absorption is increased, while there is very little impact on the absorption of other minerals (e.g., iron and zinc).[36]

Improved Bioavailability of Phytoestrogens

An interesting animal (rat) study recently found that concurrent consumption of FOS and the soy isoflavones genistein and daidzein significantly improved the bioavailability of these compounds. The relative absorption of genistein was approximately 20% higher in FOS-fed rats than in controls. In addition, the presence of both phytoestrogens in serum was maintained longer in FOS-fed rats than in controls, suggesting that FOS enhanced colonic absorption of these compounds.[37]

This result may be especially relevant to women after antibiotic therapy, when the metabolism and subsequent absorption of phytoestrogens appears to be impaired.[38] Bifidobacteria were demonstrated to possess β-glucosidase activity, and FOS administration resulted in enhanced β-glucosidase activity in animal models,[39] as well as improved phytoestrogen bioavailability.[40] Therefore, FOS consumption not only aids in the reestablishment of a healthy gut microflora, but its consumption also increases colonic β-glucosidase activity, resulting in enhanced deglycosylation and, thus, increased colonic concentrations of the medicinally active aglycones.

Treatment of Atopic Eczema and Prevention of Atopy Development

A number of studies found an aberrant composition of the GIT microflora in infants who later developed food allergies and atopic eczema.[41-43] More specifically, the development of atopic eczema was correlated with increased colonic concentrations of *Bacteroides* spp., *Clostridia* spp., and *Escherichia coli*, with a decreased concentration of bifidobacteria. This change in microbial composition was theorized to deprive the developing immune system from counter-regulatory signals against T-helper 2 (Th2) mediated responses, and therefore, promote Th2-type immunity.[43] Infantile atopic eczema is characterized by a Th2-dominated immune response, as well as excessive intestinal inflammation and aberrant macromolecular absorption across the intestinal mucosa.[44-46] These latter characteristics may also be caused by the dysbiotic condition. Bacteroides, clostridia, and *E. coli* all have the potential to trigger inflammatory responses in the gut and can release toxins that can impair intestinal permeability, leading to increased exposure to potential antigens.[43] Supplementation with FOS was demonstrated to decrease colonic concentrations of both bacteroides and clostridia, as well as promoting a bifidobacteria-dominated colonic flora.[21] FOS use may thus bring the aberrant intestinal flora back into balance and improve gut barrier function. The promotion of an intestinal flora dominated by gram-positive bacteria may also promote a shift towards Th1 immunity via enhanced production of interleukin-12 and interferon-γ.[47]

No trials appear to have assessed FOS in isolation in the treatment or prevention of atopic eczema. One trial was conducted, however, which assessed the efficacy of a FOS and GOS combination in the prevention of atopic dermatitis in infants.

In a randomized, double-blind, placebo-controlled trial, Moro et al[48] evaluated the effects of a prebiotic-enhanced infant formula on the incidence of atopic dermatitis during the first 6 months of life in formula-fed infants at high risk of atopy development. Atopic dermatitis developed in 23% of infants in the control group compared with 10% in the prebiotic group ($P = 0.014$) over the 6-month intervention period.[48] Subjects in the prebiotic group were also found to have significantly reduced plasma levels of total immunoglobulin (IgE) ($P = 0.007$), IgG2 ($P = 0.029$), and IgG3 ($P = 0.0343$), as well as cow's milk protein-specific IgG1 ($P = 0.015$), suggesting that FOS and GOS supplementation induced an antiallergic antibody profile.[49]

These same infants were followed up over the next 18 months. Those infants that received the prebiotic-enhanced formula for the first 6 months of life were at reduced risk of developing atopic disease over the follow-up period. Infants in the control group experienced a significantly higher rate of atopic disease, such as atopic dermatitis (27.9% vs 13.6%), recurrent wheezing (20.6% vs 7.6%), and allergic urticaria (10.3% vs 1.5%) compared with infants in the prebiotic group (all $P < 0.05$).[25]

Promotion of Satiety

In the wake of some interesting preliminary animal research,[50] a single-blind, crossover, placebo-controlled trial was performed to assess the effects of FOS on satiety and energy intake in humans.

Subjects ingested either 8 g of FOS twice daily (with breakfast and dinner) or a placebo. FOS supplementation was found to significantly increase satiety at breakfast and dinner (both $P = 0.04$), but not lunch. At dinner, FOS supplementation was also found to reduce hunger ($P = 0.04$) and prospective food consumption ($P = 0.05$). Energy intake at breakfast ($P = 0.01$) and lunch ($P = 0.03$) were also found to be significantly reduced after FOS supplementation, resulting in a 5% decrease in total energy intake per day.[17]

A randomized, double-blind, placebo-controlled trial investigated the effects of FOS supplementation in overweight and obese subjects. Over a 12-week period, subjects consumed either a placebo or 21 g/day of FOS. Subjects in the FOS group experienced a mean reduction of 1.03 kg body weight compared with a 0.45 kg increase in weight in the control group ($P = 0.01$). FOS consumption was also associated with a lower area under the curve for ghrelin ($P = 0.004$) and a higher area under the curve for peptide YY ($P = 0.03$), suggesting an upregulation of satiety hormone secretion. These changes coincided with a reduction in self-reported caloric intake ($P \leq 0.05$). Serum glucose concentrations and insulin levels also significantly improved in the FOS group compared with baseline measures (both $P \leq 0.05$).[51]

Dosage

Studies showed a bifidogenic effect in dosages of 4 to 40 g/day of FOS. The optimum dosage in adults, in terms of side-effect profile and increases in bifidobacteria, is considered to be 10 g/day.[20] However, it may be a good idea to start off with a lower dose (e.g., 3 g/day) and slowly increase it to reduce chances of adverse GIT reactions. Dosages of less than 3 g/day in adults are unlikely to cause significant alterations in the GIT microecology. Studies in infants and toddlers generally administered between 1 and 3 g/day of FOS.

Toxicity

FOSs are components of many common foods. There are no genotoxic, carcinogenic, mutagenic, teratogenic, or toxicologic effects associated with the ingestion of any FOS.[16,52] Oligofructose and inulin are officially recognized as natural food ingredients in most European countries and have a self-affirmed "Generally Regarded as Safe" status in the United States.[9]

Recently, a published case study described an instance of anaphylaxis attributed to inulin found in vegetables and processed foods. This was later confirmed with skin-prick testing and blinded food-provocation testing.[53] This allergy does appear to be extremely rare, however, considering the widespread consumption of FOS-containing foods.

The only side effects noted with administration are mild digestive symptoms, such as flatulence, borborygmi, abdominal bloating, and abdominal discomfort. However, these effects are dose-dependent and occur less regularly in smaller doses. Over time, these symptoms will diminish as the intestinal flora adjusts to the greater amount of substrate available.[54] However, some individuals may continue to experience mild abdominal bloating and discomfort even with continued use.

There have been some concerns in the literature regarding the ability of *Klebsiella pneumoniae* to utilize FOS as a growth substrate.[55,56] FOS was shown to stimulate the growth of *K. pneumoniae* in Petri dishes. However, this occurred only when *Klebsiella* was grown in isolation, with no other competing organisms present. In mixed culture experiments, where *Klebsiella* was grown in the presence of many other human GIT microorganisms, this did not occur.[10] In these situations, which more closely resemble the environment of the human GIT (where over 500 species of bacteria compete for available growth substrates),[57] FOS did not stimulate the growth of *Klebsiella*.[9] In addition, no human or animal experiment has ever reported an increase in the *Klebsiella* concentration in the GIT after FOS consumption.

GALACTOOLIGOSACCHARIDES

Description

Galactooligosaccharides (GOSs) are chains of galactose molecules, typically containing between three and eight units, with a glucose molecule at the reducing terminus. Galactose-containing oligosaccharides are found in all mammalian milks.[58] Commercially, they are produced synthetically from lactose using the bacterially derived enzyme β-galactosidase.[59] GOSs are neither broken down nor absorbed in the upper GIT, reaching the colon intact after ingestion.

Commercial Forms

GOSs are available in two main forms: syrup and powder. GOSs are found in significant amounts in human breast milk (up to 1 g/L) and have recently been added to some artificial infant formulas.[60,61]

Clinical Applications

GOSs have a number of clinical applications, including:
- Promotion of bifidobacterial growth
- Treatment of constipation
- Prevention of atopic disease
- Treatment of irritable bowel syndrome
- Increased resistance to infections
- Prevention of gastrointestinal infections
- Improved absorption of calcium

Promotion of Bifidobacterial Growth

In one of the earliest trials to investigate the prebiotic effect of GOS, Ito et al[62] evaluated the effects of 2.5 g/day on the microflora of healthy adults. The concentrations of bifidobacteria increased significantly during GOS ingestion in this open-label study ($P < 0.05$). However, there were no significant changes in levels of other microorganisms, such as lactobacilli, bacteroides, enterococci, *Candida* spp., or enterobacteria. There were significant decreases in the activity of nitroreductase and in fecal concentrations of indole and isovaleric acid during GOS treatment (all $P < 0.05$ compared with baseline).[62]

A later randomized, double-blind, placebo-controlled trial investigated the effects of four different doses of GOS: 2.5, 5, 7.5, and 10 g/day. After 7 days of consumption of 10 g/day, fecal bifidobacteria levels increased 0.4 log units ($P = 0.007$ compared with placebo). In the dose–response phase of the trial, there were no significant differences found between the different GOS doses in their capacity to increase bifidobacteria numbers, i.e., there was a lack of dose response.[63]

A more recent randomized, controlled trial evaluated the effects of 2.6 g/day of GOS on the microflora of healthy elderly subjects. After a 10-week feeding period, fecal bifidobacteria counts increased significantly, as did fecal levels of *Lactobacillus* and *Enterococcus* spp. (both $P < 0.001$ compared with placebo). In contrast, numbers of *Bacteroides* spp., the *Clostridium histolyticum* group, *E. coli*, and *Desulfovibrio* spp. decreased compared with placebo treatment (all $P < 0.001$).[64]

Treatment of Constipation

A number of studies were conducted to evaluate the effects of GOS administration on bowel function. Consuming 9 g/day of GOS was found to increase defecation frequency (from 5.9 to 7.1 movements per week) in elderly subjects over a 2-week treatment period. There was also a trend for easier defecation ($P = 0.07$) during the GOS phase of the trial.[65]

Randomized controlled trials evaluated the laxative effects of GOS in healthy adult subjects with a tendency to constipation. At a daily dose of 5 and 10 g, there were significant improvements in defecation frequency, from 0.92 to 1.07 movements daily ($P < 0.05$) and from 0.85 to 0.97 times per day ($P < 0.05$), respectively.[66]

Prevention of Atopic Disease

No trials appear to have assessed GOS in isolation for the treatment or prevention of atopic eczema. One trial was conducted, however, assessing the efficacy of a GOS and FOS combination in the prevention of atopic dermatitis in infants. This trial is discussed in the FOS section under "Treatment of Atopic Eczema and Prevention of Atopy Development".

Treatment of Irritable Bowel Syndrome

In a randomized, single-blind, placebo-controlled, crossover trial, supplementation of 3.5 g/day of GOS to subjects with irritable bowel syndrome (IBS) was found to significantly improve stool consistency, flatulence scores, bloating scores, and overall IBS symptom scores compared with placebo (all $P < 0.05$) over a 4-week treatment period. Supplementation of 7 g/day resulted in significant improvements in overall IBS symptom scores and a reduction in anxiety levels compared with placebo (both $P < 0.05$). However, there was also a significant increase in bloating scores relative to baseline when subjects were taking the higher dosage ($P < 0.05$).[67]

Increased Resistance to Infections

No human studies appear to have assessed GOS on their own for the improvement of immune function. A number of trials were conducted assessing the efficacy of FOS and GOS combinations, however. These trials are discussed in the FOS section.

Prevention of Gastrointestinal Infections

Animal and in vitro models suggested that GOS supplementation might have a protective effect against a range of gastrointestinal pathogens. GOS was demonstrated to reduce adherence of pathogenic strains of *E. coli* to gastrointestinal cells,[68] inhibit binding of *Vibrio cholerae* toxin to its receptor in the human GIT,[69] and reduce colonization and pathology associated with *Salmonella typhimurium* infection in a murine model.[70]

These preliminary results inspired a recent randomized, double-blind, placebo-controlled trial evaluating the potential of GOS administration to prevent travellers' diarrhea. Subjects ingested 2.6 g GOS once daily, starting 7 days before reaching their holiday destination and continued taking it daily throughout their holiday. Compared with the placebo group, subjects in the GOS group experienced a 40% decrease in the incidence ($P < 0.05$) and a 48% reduction in duration of travellers' diarrhea ($P < 0.05$). Additionally, they had less abdominal pain ($P < 0.05$) and experienced improved quality of life ($P < 0.05$).[71]

Improved Calcium Absorption

Research found supplemental GOS significantly increased calcium absorption in a randomized, double-blind, crossover trial in postmenopausal women. Administration of 20 g/day was found to increase true calcium absorption from 16% during placebo administration to 24% during GOS treatment ($P = 0.04$). This increase in absorption was not accompanied by increases in urinary calcium excretion.[72]

Dosage

A bifidogenic effect was observed in doses of 2.5 to 15 g/day. With no apparent dose response, there appears to be little benefit in dosing higher than the minimum required dose (i.e., 2.5 g/day) for this purpose. For the treatment of IBS, 3.5 g/day seems to be the optimal dose, whereas for the prevention of travellers' diarrhea 2.6 g/day was shown to be effective. To enhance calcium absorption, higher doses may be required (e.g., 20 g/day).

Toxicity

GOSs are found in all mammalian milks. Animal research demonstrated a lack of genotoxic, mutagenic, or toxicologic effects with GOS ingestion.[73] The nontoxic dose level of GOS was found to be over 2000 mg/kg body weight per day in murine models.[74]

All agents in this class are prone to the same range of adverse events—abdominal bloating, excess flatulence, borborygmi, and abdominal discomfort—and GOS is no exception.[63] These effects are, however, dose-dependent and occur less frequently in smaller doses. Additionally, these symptoms tend to diminish over time as the intestinal flora adjusts to the greater amount of substrate available.[54] Accordingly, when prescribing prebiotic agents, doses should initially be small and should be increased slowly over a 2- to 3-week period to minimize adverse gastrointestinal events.

LACTULOSE

Introduction

Lactulose is a semi-synthetic disaccharide composed of the monosaccharides fructose and galactose. It was first synthesized from lactose in 1929 by Montgomery and Hudson.[75] The human digestive system lacks the ability to break down lactulose into its component hexose and pentose moieties. Hence, lactulose is neither catabolized nor absorbed in the small intestine.

Once lactulose reaches the large intestine, it is fermented by the normal intestinal microflora. Fermentation is the process through which the normal intestinal microflora catabolizes carbohydrates to obtain energy for growth and maintenance of cellular functions. The end products of lactulose fermentation include SCFA, lactic acid, hydrogen, and carbon dioxide.[76] In vitro experiments demonstrated that overall SCFA production is increased two- to three-fold by the addition of lactulose, whereas acetate synthesis is increased four- to six-fold.[77]

Within the large intestine, these SCFAs are avidly absorbed by colonocytes and used as a source of energy, either locally or systemically. The production of SCFA also results in the acidification of the colonic contents.[76] Bown et al[78] demonstrated that a daily dose of 30 to 40 g of lactulose decreased the pH of the proximal colon from 6.0 to 4.85.

Commercial Forms

Lactulose is available in two forms, syrup and crystalline powder. Lactulose syrup generally contains between 5% and 67% lactulose (in addition to some lactose and galactose), whereas the crystalline powder is composed of 99% lactulose. The only food source of lactulose thus far identified is ultra-heat treated milk; however, lactulose is present only in insignificant amounts.[5]

Clinical Applications

Lactulose has a wide variety of clinical applications, including:
- Promotion of lactobacilli and bifidobacteria growth
- Decreasing growth of intestinal pathogens
- Constipation
- Prevention of colon cancer
- Liver disease
- Endotoxemia
- Prevention of urinary tract infections (UTIs)
- Enhancing calcium and magnesium absorption

Promotion of Lactobacilli and Bifidobacterial Growth

In one of the original studies utilizing lactulose to change fecal flora, MacGillivray et al[79] assessed the effects of lactulose feeding on infants. All infants were formula-fed and under 4 months old. After a short feeding period of 2 days, the lactulose-containing formula feed produced a preponderance of *Lactobacillus bifidus* (now known as *Bifidobacterium bifidum*) in the stools of 88% of infants. In 66% of the infants, *B. bifidum* dominated the fecal flora in concentrations of greater than 90%. None of these infants had a bifidobacteria-dominated flora at baseline.[79]

Terada et al[80] reported that 3 g/day of lactulose taken over a 2-week period altered intestinal microflora and fecal bacterial metabolism in adults. The study was conducted in eight healthy volunteers. During the intake of lactulose, the number of bifidobacteria increased significantly (P <0.001), as did the lactobacilli population (P <0.05), whereas the number of Bacteroidaceae and clostridia decreased (P <0.05) compared with baseline. Bifidobacteria became the numerically dominant microorganism in the fecal flora after 14-day administration. The fecal metabolites skatole, indole, and phenols were also significantly decreased with lactulose intake (P <0.05). Fecal β-glucuronidase, azoreductase, and nitroreductase activities also decreased significantly (P <0.05) after 14 days of treatment. These latter results indicated decreased metabolism of putrefactive (protein fermenting) organisms of the microflora. The mean fecal pH also decreased from 7.0 to 6.4.[80]

Ballongue et al[81] conducted a double-blind, randomized, placebo-controlled study, assessing the effects of a daily dose of 20 g of lactulose on gastrointestinal microbiota. After a 4-week treatment period, populations of *Bacteroides*, *Clostridium*, coliforms, and *Eubacterium* decreased by 4.1, 2.3, 1.8, and 3.0 log units, respectively. Although *Bifidobacterium*, *Lactobacillus*, and *Streptococcus* increased by 3.0, 1.9, and 1.2 log units (all P <0.01 compared with placebo), the fecal pH also decreased from a baseline of 6.9 to 5.8 by the end of the treatment period (P <0.01). Acetic acid production was increased by 33% and lactic acid production by 30% (P <0.01) via lactulose administration.[81]

Decreased Growth of Potentially Pathogenic Microorganisms

Research suggests that lactulose not only enhances the growth of beneficial members of the GIT microflora, but also inhibits the growth of potential intestinal pathogens. Studies demonstrated that lactulose consumption can decrease colonic concentrations of clostridia, *Bacteroides* spp., and coliforms,[81] as well as eradicating carrier states of *Salmonella* spp.[82] Some preliminary evidence also suggests a possible role for lactulose therapy in the treatment of small intestinal bacterial overgrowth.[83]

The ability of lactulose to increase numbers of lactobacilli and bifidobacteria and to decrease numbers of gram-negative bacteria is believed to be due to two mechanisms. The first is lactulose's ability to act directly as a food source for lactobacilli and bifidobacteria organisms, while being only weakly metabolized by gram-negative organisms.[84] The second mechanism is the change in colonic pH caused by the end products of lactulose metabolism—lactic acid and SCFA. The coupled effect of production of SCFAs and pH decrease was shown to inhibit the growth of gram-negative bacteria. The decreased pH resulting from lactulose administration was shown to increase the total concentration of the undissociated forms of SCFA.[81] These lipophilic acids can penetrate the microbial cell membrane, and at the higher intracellular pH, dissociate to produce hydrogen ions. The hydrogen ions interfere with essential metabolic functions, such as substrate translocation and oxidative phosphorylation, and hence inhibit the growth of gram-negative microbes.[85]

In vitro experiments also demonstrated the ability of lactulose to inhibit the growth of *Candida albicans*. A continuous flow culture was used as a model of the human GIT ecosystem. Within 24 hours of the input of 0.25% lactulose, *C. albicans* numbers were reduced by 97%. The reduction in *Candida* numbers was believed to be caused by the increase in the growth of lactic acid bacteria and the overall decrease in pH.[86]

Constipation

Lactulose is used in conventional medicine mainly for its laxative effects. It works primarily as an osmotic laxative, but the increased production of SCFAs may also play a role.[76,87] Ingestion of lactulose was found to cause statistically significant increases in the frequency, weight, volume, and water content of stools and to produce stools of softer consistency compared with both baseline and placebo.[88]

Prevention of Colon Cancer

Lactulose may protect against the development of colon cancer via a number of different mechanisms. Firstly, lactulose administration was found to decrease the production of secondary bile acids in the intestinal tract (secondary bile acids have been postulated to be promoters of colonic carcinogenesis). This effect was thought to be mediated by the reduction in luminal pH caused by lactulose fermentation.[89]

Secondly, lactulose also has the ability to decrease the metabolism of PPMs. This action appears to be directly related to lactulose's ability to decrease the colonic pH. The low pH suppresses overall metabolism of these organisms, which can be indirectly measured by the decrease in fecal enzymatic activity by these microorganisms. In a human trial, Ballongue et al[81] demonstrated a statistically significant decrease in the specific activity of a number of bacterial enzymes that are believed to be involved in the genesis of colon cancer. Azoreductase activity was lowered by 45%, 7-α-dehydroxylase by 40%, β-glucuronidase by 38%, nitroreductase by 36%, and urease by 27% (all P <0.01). Facultative anaerobes like coliforms and anaerobes like *Clostridium* and *Bacteroides* normally produce β-glucuronidase, 7-α-dehydroxylase, and nitroreductase. The decreased activity of these enzymes correlated with the decreased numbers of bacteroides, clostridia, and coliforms found in this clinical trial after administration of lactulose.[81]

Thirdly, lactulose appears to inhibit the formation of ammonia within the intestinal tract.[90] Ammonia was shown to alter the morphology and intermediary metabolism of intestinal cells, as well as increasing DNA synthesis in, and reducing the life span of mucosal cells.[91] It is also considered to be more toxic to healthy mucosal cells than transformed cells and, thus, it may potentially select for neoplastic growth.[92] Thus, any inhibition of ammonia production should be of benefit in the prevention of colon tumorigenesis.

Additionally, a randomized clinical trial conducted by Roncucci et al[93] demonstrated the ability of lactulose to prevent the growth of resected colorectal polyps. Lactulose administration (20 g/day) reduced the recurrence rates of colonic polyps by 66% (P <0.02) compared with controls.[93]

Liver Disease

Hepatic Encephalopathy. Hepatic encephalopathy is often found as a complication of liver cirrhosis. It is considered the totality of nervous system manifestations of liver failure. Symptoms include tremors, mental confusion, memory loss, and personality changes. The exact cause of hepatic encephalopathy is not known. However, it is commonly believed that an accumulation of neurotoxins (particularly ammonia) in the cerebral circulation is the main causative factor.[94] A number of studies found lactulose to be effective in the management of this condition[95-97] and in its prevention.[98]

Endotoxemia. Endotoxins are lipopolysaccharide constituents of the outer membranes of gram-negative bacteria. Gram-negative bacteria continuously shed components of their outer cell membranes, which results in the release of an enormous quantity of endotoxins. Gram-negative bacteria compose a significant portion of the intestinal microflora (e.g., *Bacteroides* spp., *Fusobacterium* spp., and Enterobacteriaceae)[99,100]; thus, this membrane shedding results in significant quantities of endotoxins being released into the intestinal lumen. In healthy individuals, luminal endotoxin causes minimal systemic effects. However, in individuals with a compromised intestinal barrier or suboptimal liver function, this intestinal endotoxin can have pathologic consequences.[101]

Liehr et al[102] recently demonstrated that lactulose possesses antiendotoxin activity. When rats were fed lactulose over 4 or 8 days before intravenous administration of galactosamine, the liver damage that normally develops was prevented. Because galactosamine-induced liver necrosis and inflammation is mediated by systemic endotoxemia of intestinal origin, the prevention of liver inflammation and necrosis after lactulose consumption suggests an antiendotoxin effect. This effect was most likely mediated by an alteration of the intestinal microecology, which indirectly diminished the intestinal pool of endotoxin. However, the authors also suggested a direct antiendotoxin effect, as intravenous administration of lactulose also preventing galactosamine-induced hepatitis.[102]

This work was followed by a prospective, controlled trial assessing the use of lactulose in endotoxemia secondary to obstructive jaundice. Oral lactulose (30 mL/6 hours) was given to 12 patients for 3 days before surgery, whereas another 12 patients operated as controls. Lactulose administration significantly reduced the incidence of endotoxemia in the portal blood during the operation and in the systemic blood postoperatively (both P <0.05). Interestingly, lactulose appeared to both decrease the luminal pool of endotoxin, as well as directly preventing endotoxin absorption.[103]

Prevention of Urinary Tract Infections

Two human studies demonstrated the efficacy of lactulose therapy in the prevention of UTIs. McCutcheon and Fulton[104] conducted a retrospective study using 45 elderly, long-term hospital patients as subjects. The study found that daily lactulose therapy for 6 months (30 mL lactulose syrup) resulted in a significant reduction in UTIs compared with controls (P <0.025). Sixteen of the seventeen lactulose-treated patients (94%) remained infection free over the 6 months compared with 16 of the 28 control patients (57%) (P <0.005). In addition, there was a significant reduction in the number of antibiotic prescriptions (P <0.05) and in the number of patients who received antibiotics (P <0.005) in the lactulose group.[104]

In the second study, Mack et al enrolled 75 elderly, hospitalized patients in a randomized, placebo-controlled trial. Thirty-eight patients received the placebo and 58 received lactulose therapy. Twelve percent of the lactulose group developed UTIs during follow-up compared with 32% in the control group (P <0.01). Thus, lactulose consumption demonstrated significant protection against the development of UTIs.[105]

Intestinal microflora appears to act as a reservoir for urinary tract pathogens. Microorganisms such as *E. coli, Enterococcus faecalis, E. faecium,* and *K. pneumoniae* are all frequent urinary tract pathogens, and these organisms are also commonly found in the GIT. These organisms can escape the confines of the large bowel, and in susceptible individuals colonize the vagina, periurethral area, and distal urethra. From these areas they can ascend into the bladder. Thus, interventions that can inhibit the growth of these organisms in the GIT should result in decreased numbers of these organisms colonizing the genitourinary tract.[99] This is likely to be the mechanism by which lactulose therapy prevents UTIs. Ingestion of lactulose acidifies the large bowel and significantly increases the production of SCFAs.[78,81] At a low pH, these SCFAs (particularly butyrate) inhibit the growth and metabolism of enterococci and *E. coli*, substantially reducing their overall populations in the large bowel,[99] and thus decreasing the intestinal reservoir of urinary tract pathogens.

Enhanced Calcium and Magnesium Absorption

In a randomized, controlled trial, low-dose lactulose consumption (2 g/day) was found to significantly improve magnesium absorption, and high dose (4 g/day) administration significantly improved both calcium and magnesium absorption in adult males (all P <0.01 compared with placebo). There appeared to be a clear dose-dependent effect, with the higher lactulose dose being more effective than the lower for both magnesium and calcium.[106]

Dosage

Doses as low as 3 g/day were shown to cause beneficial alterations in the intestinal microflora.[80] However, higher doses (e.g., 10 g/day) appeared to produce more substantial changes.[81] As with FOS and GOS, therapy should commence with a lower dose. For the treatment of constipation, the recommended dose is from 15 to 40 g/day,[88,107] although higher dosages have usually been used (approximately 35 g/day) for the management of liver disease.[108]

Toxicity

Therapeutic use of lactulose is considered to be extremely safe, with adverse reactions generally being mild and few. Side effects consist of vomiting, nausea, diarrhea, and abdominal cramping.[109] However, these reactions tend to occur only in single doses of more than 60 g. This appears to be the maximum load of lactulose that the intestinal flora is able to metabolize to SCFAs at one time. When the bacterial fermentation capacity is exceeded, osmotic diarrhea, abdominal cramping, and nausea may result. These symptoms are most likely caused by the interference with net fluid absorption in the colon due to the osmotic effect of malabsorbed and intact sugars.[76] Nonetheless, flatulence, abdominal bloating, and discomfort are common symptoms when lactulose therapy is commenced. Gastrointestinal symptoms, however, diminish as the colonic microflora adapt to the greater amount of fermentable substrate.[110]

SYNBIOTICS

Synbiotics are products that contain both probiotic and prebiotic agents.[111] The combination is supposed to enhance the survival of the probiotic bacteria through the upper GIT, improve implantation of the probiotic in the colon, and have a stimulating effect on the growth and/or activities of both the exogenously provided probiotic strain(s) and the endogenous inhabitants of the bowel.[112] Over the past 5 years, research in this area has been steadily growing.

When considering the therapeutic potential of a product claimed to be a synbiotic, a number of factors should be assessed:

1. Does the product use well-characterized and researched probiotic strains? (See Chapter 116 on Probiotics.)
2. Does the "prebiotic" substance meet the requirements to be truly considered a prebiotic?
3. Has the "prebiotic" been demonstrated to enhance the growth of the exact probiotic strain(s) contained in the product?
4. Are both agents included in therapeutic doses?

Ideally, a synbiotic product should meet all four of these criteria. Many currently on the market do not.

Strain-Specific Synbiotic Combinations

Individual probiotic strains (see Chapter 116 on Probiotics) have variable capacities to utilize different prebiotic substrates. For example, *Bifidobacterium lactis* Bb12 can utilize GOS, lactulose, and FOS, but is unable to use lactitol.[113] *Lactobacillus rhamnosus* GG is unable to use lactulose, lactitol, or FOS.[114,115] Both *L. acidophilus* NCFM and *L. acidophilus* DDS-1 can utilize FOS as a growth substrate.[115]

COLONIC FOODS

Introduction

Colonic foods are defined as "foods entering the colon and serving as substrates for the endogenous colonic bacteria, thus indirectly providing the host with energy, metabolic substrates and essential micronutrients."[3] By definition, colonic foods escape digestion and absorption in the upper GIT to reach the colon intact. Here members of the colonic microflora ferment them to produce SCFAs, hydrogen, methane, and carbon dioxide. Through the production of SCFAs, the ingestion of colonic foods plays a pivotal role in the health of the host.[87]

Colonic foods lack the specificity of fermentation that prebiotics possess. Thus, their ingestion promotes the growth and/or metabolic activity of a number of different bacterial species within the large bowel, including species that are potentially harmful. Colonic foods include resistant starch, plant cell wall polysaccharides (e.g., cellulose), hemicelluloses, pectins, and gums.[3]

Commonly used fibers, such as slippery elm, pectin, psyllium husks, and guar gum should all be considered colonic foods, not prebiotics, as they are utilized by a number of different bacterial species in the bowel. For example, guar gum is metabolized by *Bacteroides* spp. and *Ruminococcus* spp.[116]; pectin is fermented by *Bacteroides* spp., *Bifidobacterium* spp., *Eubacterium* spp., and *Clostridium* spp.[117]; and psyllium husks are fermented solely by *Bacteroides* spp.[116]

Some colonic foods, however, have demonstrated the ability to promote the growth of beneficial species of bacteria, although their effects are not as specific as with prebiotics. Foods and food constituents that promote the growth of beneficial bacteria are listed in Table 115-3.

TABLE 115-3 **Other Foods That May Produce Beneficial Changes in the Intestinal Microflora**

FOOD OR FOOD COMPONENT	TYPE OF STUDY	OBSERVED CHANGES
Brown rice	Human feeding study	Increased numbers of *Bifidobacterium adolescentis* and *Enterococcus faecalis*; decreased counts of bacteroides, *Eubacterium aerofaciens, Escherichia coli,* and *Clostridium* spp.[118]
Carrot	Human feeding study	Increased growth of bifidobacteria[119]
Green tea (300 mg catechins/day–equivalent to 5-6 cups/day)	Human feeding study	Increased numbers of lactobacilli and bifidobacteria; decreased numbers of bacteroides, clostridia, and enterobacteria; decrease in fecal pH; decrease in fecal concentrations of ammonia, sulfide, skatole, indole and cresol; increased production of SCFAs[120]
Larch arabinogalactans	Human feeding study	Increased numbers of lactobacilli; no impact on bifidobacteria, clostridia, or enterobacteria[121]
Oat bran	In vitro	Increased growth of *Lactobacillus rhamnosus, L. plantarum*, and *Lactococcus lactis*[122]
	Rat feeding study	Increased growth of lactobacilli and bifidobacteria; decreased numbers of coliforms[123]
Tea polyphenols	Pig feeding study	Increased numbers of lactobacilli; decreased counts of bacteroides and lecithin positive clostridia; decreased fecal concentrations of ammonia, phenol, cresol, and skatole[124]
	Chicken feeding study	Enhanced growth of lactobacilli; reduced bacteroides numbers[125]
Resistant starch	Human flora-associated rat feeding study	Increased growth of lactobacilli, bifidobacteria, and staphylococci; decreased counts of enterobacteria[126]
Spirulina	Horse-feeding study	Increased growth of lactobacilli[127]

SCFA, short-chain fatty acid.

Drug Interactions

FOSs and GOSs do not appear to interact with any pharmaceuticals. When used in prebiotic dosages, lactulose is also unlikely to elicit any drug interactions. When administered in larger doses for use as a laxative over prolonged periods of time, however, there is a theoretical risk of increased electrolyte loss, which could impact electrolyte balance. These electrolyte alterations could potentiate the risk of more severe electrolyte imbalances, such as hypokalemia, which has been associated with the use of some medications (e.g., corticosteroids, diuretics, and drugs that prolong the QT interval). However, lactulose is less likely to elicit electrolyte disturbances with long-term use than other laxatives because of the capacity of the colonic microflora to adapt to lactulose ingestion, with long-term ingestion resulting in a reduction in lactulose-induced gastrointestinal symptoms and diarrhea.[110,128]

When used in laxative dosages, lactulose was found to significantly increase the relative risk of over anticoagulation in patients taking coumarin anticoagulants, presumably via decreased intestinal absorption.[129]

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CHAPTER 116

Probiotics

Jason Hawrelak, ND, BNat(Hons), PhD

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INTRODUCTION

The term probiotic is derived from the Greek and literally means "for life." It was first coined in 1965 by Lilley and Stillwell to describe substances secreted by one microorganism that stimulate the growth of another.[1] In 1974, Parker modified this definition to "… organisms and substances which contribute to intestinal microbial balance."[2] The current World Health Organization definition of probiotics is "live microorganisms which when administered in adequate amounts confer a health benefit to the host."[3] This definition includes fermented foods such as yogurt, sauerkraut, and kefir, as well as specific supplements containing freeze-dried bacteria. The microorganisms found in these products are usually lactobacilli and bifidobacteria.[4]

Humans have been consuming probiotics for many thousands of years and fermented foods have been, and still are, of great importance to the diets of most of the world's people. Microbial cultures have been used to produce beer, wine, yogurt, tempeh, sauerkraut, olives, cheese, and many other fermented foods.[5] Thus, the symbiotic relationship between humans and probiotic microorganisms has a long history of important nutritional and therapeutic benefits for humans.

Currently, there is renewed interest in the field of fermented foods and probiotics. This interest has been stimulated by the recent explosion of research in this area. This chapter focuses on the health benefits and therapeutic uses of probiotic-containing foods and supplements.

DESCRIPTION

At the turn of the century, Metchnikoff[6] asserted that yogurt was the elixir of life. He theorized that putrefactive bacteria in the large intestine produce toxins that invite disease and shorten life. He believed that eating yogurt would cause lactobacilli to become dominant in the colon and displace the putrefactive bacteria. For years, these claims of healthful effects from fermented foods were considered unscientific folklore. However, a substantial and growing body of scientific evidence has now demonstrated that lactobacilli, bifidobacteria, and fermented foods play a significant role in human health.

The genus *Lactobacillus* is characterized by considerable heterogeneity. Bacteria are classified as lactobacilli if they are gram-positive, nonsporing, and rod-shaped bacteria that produce lactic acid as the major end product of carbohydrate fermentation. Lactobacilli appear to be fairly unique, in that they have been isolated from a number of diverse environments, such as fermented vegetables and dairy foods, as well as the human gastrointestinal tract (GIT) and vagina.[7]

In contrast, bifidobacteria are not found in natural fermentative processes, but are native to the GIT.[8] Bifidobacteria are also gram-positive, nonsporing bacteria; however, they are Y-shaped instead of rod-shaped and their major fermentative end product is acetic acid.[9]

Intestinal colonization by lactobacilli and bifidobacteria begins during the birthing process. Before birth, the GIT of the neonate is completely sterile. During delivery, the newborn is inoculated with microorganisms from the birth canal and the mother's fecal flora, as well as from organisms in the environment. In the first week, the organisms that are best suited to the intestinal environment become established. Initially, there is often a predominance of *Escherichia coli*, enterococci, and streptococci. A diet of breast milk creates a colonic environment that favors the

growth of a simple flora of bifidobacteria and a few other anaerobes. Breast-milk contains many bifidogenic oligosaccharides,[10] as well as living bacteria. Amazingly, breast milk from healthy women can contain up to 10^9 bacteria/L, including various strains of lactobacilli and bifidobacteria.[11-13] In formula-fed infants, the microbiota is more complex (resembling the adult flora), containing far fewer bifidobacteria and more *Bacteroides* spp., clostridia, and anaerobic streptococci. The introduction of solid food to the breast-fed infant causes major changes to the microflora. A rapid rise in the numbers of enterococci and enterobacteria is followed by increases in *Bacteroides* spp., anaerobic streptococci, and clostridia. As the amount of solid food increases in the diet, the bacterial flora of formula-fed and breast-fed infants approaches that of adults.[14-16] Common species of lactobacilli and bifidobacteria found in the infant and adult human GIT are listed in Box 116-1.[11,17-23]

PROPOSED MECHANISMS OF ACTION

The exact mechanisms by which probiotics accomplish their beneficial actions have not been well documented. However, there are several postulated mechanisms that explain many of their favorable effects. One such mechanism is competition for adhesion sites.

Many pathogenic organisms must associate with the GIT epithelium to colonize effectively. However, some strains of bifidobacteria and lactobacilli can adhere to the epithelium and act as "colonization barriers" by preventing pathogens from adhering to the mucosa.[24] This effect was demonstrated with the *Lactobacillus rhamnosus* strain GG and *L. plantarum* 299v. Both of these organisms showed the ability to inhibit attachment of *E. coli* to human colon cells.[25]

Another possible mechanism of action is the modification of the microbial flora through the synthesis of antimicrobial compounds. Many types of lactobacilli and bifidobacteria produce bacteriocins or other antimicrobial compounds. Bacteriocins are defined as "compounds produced by bacteria that have a biologically active protein moiety and a bactericidal action."[26] Other biologically active compounds produced by lactic acid bacteria include hydrogen peroxide, diacetyl, and short-chain fatty acids. The release of these compounds by probiotic organisms results in a beneficial modification of the microflora.[27] However, not all strains of lactobacilli or bifidobacteria produce antimicrobial compounds, and some produce compounds that are fairly nonspecific in their activity, so that beneficial bacteria, as well as pathogenic organisms, may be negatively affected.

It has also been observed that probiotics can stimulate the immune response. This immune response may take the form of increased secretion of immunoglobulin-A (IgA),[28] elevated numbers of natural killer cells, or enhanced phagocytic activity of macrophages.[29] Increased secretion of IgA may decrease numbers of pathogenic organisms in the gut, thus improving the composition of the microflora.[24,30]

Probiotics may also compete for nutrients that would otherwise be utilized by pathogens.[31] This situation occurs with *Clostridium difficile*, a potentially pathogenic organism that is dependent upon monosaccharides for its growth. Probiotic organisms in sufficient numbers can utilize most of the available monosaccharides, which results in the inhibition of *C. difficile*.[32]

BOX 116-1 Common Colonizers of the Human Gastrointestinal Tract Among Lactobacilli and Bifidobacteria

***Lactobacillus* spp.**	***Bifidobacterium* spp.**
reuteri	*adolescentis*
crispatus	*infantis*
acidophilus	*longum*
jensenii	*bifidum*
gasseri	*breve*
plantarum	*catenulatum*
casei	*pseudocatenulatum*
rhamnosus	*angulatum*
paracasei	*ruminantium*
ruminis	*dentium*
salivarius	

Data from references 11, 19-23.

PROBIOTIC CHARACTERISTICS

Probiotic organisms require certain characteristics to enable them to exert maximum therapeutic effects. These qualities are summarized in Table 116-1.

Of these characteristics, there are some that are considered almost essential for a probiotic to have therapeutic effects. These are: (1) gastric acid and bile salt stability; (2) an ability to adhere to the intestinal mucosa; and (3) an ability to colonize the intestinal tract.[34] Unfortunately, many commercially available probiotic supplements and yogurts contain strains that do not

TABLE 116-1 **The Desirable Characteristics of Effective Probiotic Strains**

CHARACTERISTICS	FUNCTIONAL BENEFIT
Human origin	Human origin should translate to ability to survive conditions in the human GIT, as well as the possibility of species-specific health effects.
Gastric acid and bile salt stability	Survival through stomach and small intestine
Adherence to intestinal mucosa	Believed to be essential for immune cell modulation and competitive inhibition of pathogens.
Colonization of intestinal tract	Multiplication in the intestines suggests that daily ingestion may not be needed; immune cell modulation
Safety in food and documented clinical safety	Adverse effects absent or minimal; accurate identification (genus, species, strain)
Production of antimicrobial compounds	Normalization of GIT flora; suppressed growth of pathogens
Antagonism against pathogenic organisms	Prevention of adhesion and toxin production by pathogens
Clinically documented and validated health effects	Clinicians can be confident of therapeutic effects; dose–response data for minimum effective dosage in different formulations is known.

GIT, gastrointestinal tract.
Modified from Mattila-Sandholm T, Salminen S. Up-to-date on probiotics in Europe. Gastroenterol Int. 1998;11(suppl 1):8-16.[33]

exhibit these vital characteristics. If a probiotic strain does not exhibit these characteristics, then it will be nowhere near as effective as those that do.

Probiotics in Use

There are many different microorganisms currently used as probiotics. Table 116-2 lists commonly used probiotic species.

To better understand how bacteria are named and classified, the following discussion may be helpful. Genus is the first name of a bacterium (e.g., *Lactobacillus*). It is somewhat general and refers to a grouping of organisms based on similarity of qualities, such as physical characteristics, metabolic needs, and metabolic end products. Species is a bacterium's second name (e.g., *acidophilus*). It is a much more narrow classification based on shared common characteristics that distinguish them from other species. Strain is an even more specific classification that divides members of the same species into subgroups based on several properties that these bacteria have in common that are distinct from other members of the species (e.g., strain LA5).[37]

Issues in Probiotic Nomenclature

There are some changes in nomenclature, some recent and some fairly antiquated, that should be noted to make better sense of probiotic literature.

- The species *Lactobacillus bulgaricus* is now referred to as *Lactobacillus delbrueckii* ssp. *bulgaricus.*[38]
- *Lactobacillus bifidus* (also known as "bifidus") was renamed *Bifidobacterium bifidum* over 30 years ago, yet the improper nomenclature continues to be widely used.[38]
- Many strains of bacteria that were once classified as *Lactobacillus casei* have been reclassified as strains of *Lactobacillus rhamnosus* (e.g., *L. rhamnosus* GG) or *Lactobacillus paracasei* (e.g., *L. paracasei* Shirota strain).[39]
- Strains of *Lactobacillus sporogenes* have been renamed *Bacillus coagulans* (they are not true lactobacilli because they form spores).[40]
- Bacterial strains that were once classified as *Lactobacillus acidophilus* (often referred to as "acidophilus") have now been divided into six species: *L. acidophilus, L. gasseri, L. amylovorus, L. gallinarum, L. johnsonii* and *L. crispatus.*[39]
- Strains of *Saccharomyces boulardii* are now definitively regarded as a distinct group within the species *Saccharomyces cerevisiae.*[41,42]

Importance of Strain

Strains of bacteria can be likened to different breeds of dogs. All dogs belong to the genus *Canis* and the species *familiaris*. Within this one species there is great diversity in size, shape, strength, and other physical characteristics—ranging from the Irish wolfhound to the chihuahua. A similar division occurs within species of bacteria.

Within each species of bacteria there is a multitude of strains. Some probiotic strains are resilient and strong, able to survive passage through the upper GIT and inhibit pathogenic bacteria, whereas others are weak and cannot survive the upper GIT or kill pathogenic bacteria. It is also important to note that just because one strain of bacteria in a given species has a proven action does not mean that another strain will too, even if they are closely related. Furthermore, actions found in one strain of *L. rhamnosus* cannot be extrapolated to a strain of *L. acidophilus* or *L. plantarum*. Actions and qualities are fundamentally strain specific.[43] Therefore, strains of bacteria within the same species can have significantly different actions, properties, and characteristics.

Unfortunately, this strain specificity is not well known, leading to inaccurate extrapolations from the literature. For example, some supplement manufacturers will quote a study that utilized *L. rhamnosus* strain GG and then say that their probiotic supplement containing a strain of *L. acidophilus* or another strain of *L. rhamnosus* will do the same. This is quite incorrect. Unless proven, one cannot assume that a given strain of *L. acidophilus*, *B. bifidum,* or any other species of lactic acid bacteria will survive transit through the upper GIT, let alone colonize the intestines or have specific therapeutic actions. They might, but unless proven, it is impossible to know. Two recent studies demonstrated this strain specificity.

Two strains of *L. rhamnosus* were utilized in a trial assessing their efficacy in the treatment of viral gastroenteritis. One strain was *L. rhamnosus* strain GG (LGG); the other was a strain found in a supplemental product (Lactophilus). LGG accelerated recovery from diarrhea, whereas the closely related strain did not.[44]

Additional in vitro research using two closely related strains of *B. bifidum* (CIDCA 537 and 5310) found that one strain (CIDCA 5310) inhibited enterocyte invasion by *Salmonella arizonae*, whereas the other had no effect.[45] The results of both these studies demonstrate the principle of strain specificity, that is, different bacterial strains within the same species can have significantly different actions and therapeutic effects.

TABLE 116-2 **Common Probiotic Microorganisms**

***Lactobacillus* Spp.**	***Bifidobacterium* Spp.**	***Bacillus* Spp.**	***Streptococcus* Spp.**	***Enterococcus* Spp.**	***Saccharomyces* Spp.**
acidophilus	*breve*	*coagulans*	*thermophilus*	*faecium*	*cerevisiae*
plantarum	*infantis*				
rhamnosus	*longum*				
paracasei	*bifidum*				
fermentum	*thermophilum*				
reuteri	*adolescentis*				
johnsonii	*animalis*				
brevis	*lactis*				
casei					
lactis					
delbrueckii gasseri					

Organisms that are currently used as probiotics (listed by genus and species).[33,35,36]

Thus, clinicians are urged to utilize well-researched probiotic strains whenever possible. By choosing well-researched strains, one can be assured of getting probiotics that have documented gastric acid and bile tolerance, can adhere to the intestinal mucosa, and can temporarily colonize the intestinal tract, as well as having proven therapeutic actions. This will increase the probability of achieving good clinical outcomes.

COMMERCIAL FORMS

There are two main forms in which probiotic organisms can be ingested—fermented foods and supplements. Fermented foods can be of both dairy and vegetable origin, with the most commonly known of each being yogurt and sauerkraut, respectively. Probiotic supplements consist of freeze-dried (lyophilized) bacteria in powder, capsule, or tablet form. Regardless of the form in which the microorganisms are consumed, for clinical efficacy, products containing probiotic organisms must provide live organisms in sufficient numbers to exert therapeutic effects. Both types of fermented foods and supplements are able to do this. Common probiotic delivery systems are compared in Table 116-3.

Fermented Dairy—Yogurt

The origin of fermented dairy products is somewhat obscure, but their consumption is believed to date back to at least 5000 BC.[46] Sour milks have always been popular throughout Europe, Asia, and Africa as nutritious, long-lasting foodstuffs. Fermented milks were also considered medicine, with ancient physicians like Hippocrates, Galen, and Avicenna advocating their use for the treatment of gastrointestinal ills.[47]

TABLE 116-3 **The Pros and Cons of Different Probiotic Delivery Systems**

DELIVERY SYSTEM	PROS	CONS
Fermented dairy	Affordability and easy availability Ease of incorporation into daily patterns Additional nutritional benefits Enhanced bacterial survival through upper GIT (100× less bacteria can be given per dose)[63] Effective in the upper GIT	Contains dairy proteins and lactose Taste can be issue Not suitable when travelling Not suitable for vegans
Capsules	Ease of administration Contain no binders	Not therapeutic in upper GIT (unless opened or chewed) May contain allergenic excipients Higher cost
Tablets	Ease of administration Effective in the upper GIT	May contain allergenic or otherwise problematic binders and excipients (e.g., gluten) Higher cost
Powders	Effective in the upper GIT Dosages can be easily adjusted Can be incorporated into foods or drinks Contain no binders	

GIT, gastrointestinal tract.

Early in the twentieth century, Nobel prize laureate Elie Metchnikoff popularized the idea that fermented milk products could beneficially alter the microflora of the GIT. He attributed the long life of Bulgarian peasants to their consumption of soured milk, which he believed to arrest the abnormal putrefaction of proteins within the bowel.[6] Metchnikoff later researched the bacteria found in this Bulgarian milk, *Bacillus bulgaricus* (now known as *L. delbrueckii* subspecies *bulgaricus*) and a type of cocci (now known as *Streptococcus thermophilus*).[47] He utilized these cultures in the manufacture of a type of sour milk he launched in Paris at the beginning of the twentieth century.[46]

These same species of bacteria are still used today in the manufacture of commercial yogurts. These two bacterial species (*L. delbrueckii* ssp. *bulgaricus* and *S. thermophilus)* are responsible for the taste, consistency, and smell that we associate with yogurt.[48,49] It is now known, however, that these species lack the ability to survive in the human GIT. Hence, yogurt manufacturers now routinely add additional probiotic species of bacteria to yogurt in an attempt to enhance its therapeutic effects (e.g., *L. acidophilus* and *B. bifidum*).[46]

The therapeutic efficacy of a specific yogurt depends substantially upon the characteristics of the strains of bacteria that it contains, as well as the number of viable bacteria present at the point of consumption. A therapeutic yogurt will contain bacterial strains with the desired characteristics as outlined in Table 116-1, and these strains should be in sufficient numbers to exert therapeutic effects once consumed (i.e., $>10^6$ bacteria/mL of each bacterial strain).[50] Recent market-basket surveys showed that some yogurts do achieve and maintain this level of bacterial viability throughout their shelf-life, and furthermore, these same brands of yogurt often utilize bacterial strains with the desired probiotic characteristics.[51]

A number of studies have attested to the therapeutic efficacy and ability of yogurt and fermented milks to successfully deliver probiotic bacteria to the human GIT.[52-62] Yogurt appears to act as an ideal transport medium for probiotic bacteria, as it has been shown to enhance the survival of bacteria through the upper GIT.[50] One study found that 10^8 bacteria given in a milk-base demonstrated greater fecal recovery after oral administration than 10^{10} organisms given as a freeze-dried powder. Thus, significantly smaller numbers of probiotic bacteria can be given in yogurt than in supplements to achieve similar numbers of viable organisms in the lower GIT.[63]

Fermented Vegetables—Sauerkraut and Kimchi

Fermented plant foods have always been an important component of the human diet, and are still common food items throughout the world, from sauerkraut in Eastern Europe to kimchi in Southeast Asia. Traditionally prepared, both these foods contain large amounts of probiotic bacteria. Strains of *L. plantarum* are involved in the final stages of fermentation in both kimchi and sauerkraut, and they typically reach populations of more than 10^8 bacteria/mL by the end stages of fermentation,[64-67] and thus are present in sufficient quantities to have therapeutic effects when consumed. Additionally, research found that many of the *L. plantarum* strains isolated from fermented foods can survive exposure to gastric acid and bile salts, thereby indicating an ability to survive transit through the upper GIT. These same strains were also able to

adhere to intestinal epithelial cells, thus fulfilling three of the main criteria needed by desirable probiotic organisms.[68] Kimchi and sauerkraut can be used as therapeutic tools in a similar manner to probiotic supplements and yogurts. However, the characteristics of the bacterial strains found in these fermented foods are not known, so therapeutic effects will not be as certain.

Some strains of *L. plantarum* isolated from fermented foods also utilize a mannose-specific mechanism to adhere to human intestinal cells. Many pathogenic bacteria and parasites (e.g., enterotoxigenic *E. coli*, *Shigella* spp., *Vibrio cholerae*, *Salmonella* spp., and *Giardia lamblia*) also utilize a mannose-specific binding mechanism.[69,70] Hence, strains of *L. plantarum* compete directly with these microorganisms for a limited number of binding sites along the human GIT. The consumption of traditionally prepared kimchi and sauerkraut may thus play a role in the prevention and treatment of gastroenteritis caused by these pathogens.

Supplements

The quality of probiotic supplements depends upon two main factors: (1) the characteristics of the strains contained in the supplement; and (2) adequate viability, so that sufficient numbers of bacteria are viable at the point of consumption. Bacterial strains used in probiotic supplements should ideally demonstrate all the characteristics outlined in Table 116-1. Viability at consumption depends upon a number of factors, such as proper manufacturing and the "hardiness" of the strain, as well as packaging and storing the product in the right amount of moisture and at the correct temperature. Many strains of lactobacilli and bifidobacteria do not respond well to freeze-drying (lyophilization), spray drying, or conventional frozen storage, and excessive temperature during packaging or storage can dramatically reduce viability. Typically, unless the product has been shown to be stable, refrigeration is necessary during storage and ideally during transport. Some products may not have to be refrigerated until after the bottle has been opened, however.

Some manufacturers utilize enteric coatings on their tablets and capsules to improve survival through the acidic medium of the stomach. Research suggests that this practice does enhance survival through the upper GIT,[71] although enteric coatings are not necessary if the strain has demonstrated satisfactory tolerance to gastric acid.

Although there are a number of excellent companies providing high-quality probiotic products, it is difficult to sort through all of the manufacturer's claims of superiority. Additionally, market-basket surveys found that some supplements contain potentially pathogenic contaminants,[72] whereas the majority fail to contain the species and quantity of bacteria listed on the label.[73]

Clearly, the clinician needs documentation of strain characteristics, product quality/viability, and microbiological content before prescribing to his or her patients.

CLINICAL APPLICATIONS

The intestinal flora plays a major role in the health of the host.[15,74] The beneficial effects of the intestinal flora include the stimulation of the immune system, synthesis of vitamins (B group and K), enhanced GIT motility and function, improved digestion and nutrient absorption, improvement of gas-induced abdominal distension, inhibition of pathogens (colonization resistance), metabolism of important plant compounds/drugs, and the production of short-chain fatty acids and polyamines.[15,75,76] Due to the important role of lactobacilli and bifidobacteria within the human GIT microflora, and therefore impact on human health, probiotic supplements can be used to promote overall good health. There are, however, several more specific uses for probiotics. These indications and the most appropriate probiotic strains for these conditions are detailed in Table 116-4.

USING THE RIGHT STRAIN

To achieve successful and reproducible clinical outcomes, it is imperative to use the exact probiotic strain that has been proven to have the specific therapeutic action that is desired. For example, *L. rhamnosus* GG was found to prevent viral gastroenteritis[77] and maintain ulcerative colitis in remission.[78] Other strains of *L. rhamnosus* cannot be assumed to act in a similar manner. The clinician who chooses to use the exact strain that had the effects in clinical trials can be confident of similar results. Using another closely related strain may or may not have any effect. Whenever possible, use the exact strain used in research, as other strains, even closely related ones, may not have the same effects. Table 116-4 outlines the most appropriate probiotic strains available for some common health conditions. If it is not possible to prescribe the specific strains delineated in Table 116-4, the best option is to use an alternative bacterial strain that possesses the characteristics outlined in Table 116-2.

DOSAGE

The dosage of probiotic foods and supplements is based solely upon the number of live organisms present in the product. Successful results have been attained in clinical trials using between 10^7 and 10^{11} viable bacteria per day.[129,178,180] Interestingly, it appears that 100 times fewer viable bacteria need to be given in a dairy medium than in a freeze-dried supplement to achieve similar numbers of live bacteria in the lower bowel.[63] Dairy appears to work as an ideal transport medium for the bacteria, enhancing their survival through the upper GIT.[50]

Supplements

Supplements are best consumed with meals to take advantage of the increased alkalinity of the gastric environment (which equates to greater bacterial survival).[181] A dosage of 10^8 bacteria per sitting is often mentioned in the probiotic literature as the minimum quantity of bacteria needed to produce therapeutic effects.[50,181] Additionally, there have been a handful of studies that demonstrated therapeutic effects utilizing 10^7 to 10^8 viable bacteria per dose.[129,178,182] However, most of the successful probiotic research utilized greater than or equal to 10^9 bacteria per dose.

The minimum concentration of probiotic bacteria needed to achieve therapeutic effects appears to be somewhat strain dependent, in that for some strains (e.g., *L. reuteri* MM53) 10^7 bacteria is a sufficient quantity to produce beneficial effects,[178] whereas for other strains, 10^9 viable bacteria is needed (e.g., *L. rhamnosus* GG—if given as lyophilized bacteria).[63] This situation, unfortunately, makes it hard to give firm dosage recommendations, as the minimum effective dosage appears to differ by strain. Thus, it is best practice to ensure that supplements contain bacteria in concentrations greater than or equal to 10^9 bacteria per dose, unless research has demonstrated that the specific strain contained in the supplement is effective in smaller amounts.

Therefore, the dosage of viable bacteria given in supplemental forms should generally be 10^9 to 10^{11} bacteria per dose. If a formulation contains multiple strains, each strain must be present in

TABLE 116-4 **Choosing the Right Strain for Specific Therapeutic Applications**

CONDITION	METHODOLOGY	MOST APPROPRIATE PROBIOTIC STRAIN(S)	RESULTS
Allergic rhinitis	R, DB, PC	*Lactobacillus acidophilus* NCFM and *Bifidobacterium lactis* BI-04	Tendency for fewer subjects to report runny nose in the probiotic group (76% vs 95%; $P = 0.078$) and to report nasal blocking (11% vs 33%; $P = 0.101$); fewer subjects had infiltration of eosinophils into the nasal mucosa (57% vs 95%; $P = 0.013$)[79]
	R, DB, PC	*L. rhamnosus* GG and *L. gasseri* TMC0356	Significant reduction in nasal blockage scores ($P < 0.05$) and reduction in symptom medication scores for nasal blockage ($P < 0.05$)[80]
Antibiotic use	Meta-analysis	*L. rhamnosus* GG	70% reduced risk of developing AAD in children ($P = 0.00003$)[81]
	R, DB, PC	*L. plantarum* 299v	31% reduced risk of developing loose or watery stools ($P = 0.012$); 49% reduced risk of experiencing nausea ($P = 0.0097$)[82]
	R, DB, PC	*L. reuteri* MM53	Reduced incidence of a number of GI symptoms relative to placebo in triple therapy-treated children: epigastric pain (15% vs 45%; $P < 0.04$), abdominal distension (0% vs 25%; $P < 0.04$), disorders of defecation (15% vs 45%; $P < 0.04$), and halitosis (5% vs 35%; $P < 0.04$)[83]
	R, DB, PC	*L. rhamnosus* GG, *L. acidophilus* LA5, and *B. lactis* Bb12	79% reduced risk of developing AAD ($P = 0.035$)[84]
	R, DB, PC	*Saccharomyces cerevisiae* Hansen CBS 5926	71% reduced risk of developing AAD ($P = 0.02$)[85]
Atopic eczema (AE)	Prevention		
	R, DB, PC	*L. paracasei* F-19	Cumulative incidence of eczema was significantly reduced at 13 mo (11% vs 22%; $P < 0.05$)[86]
	R, DB, PC	*L. reuteri* MM53	Incidence of eczema was similar in both groups at 2 y of age; infants in the MM53 group did have less IgE-associated eczema (8% vs 20%; $P = 0.02$) and less skin-prick test reactivity for those infants with allergic mothers (14% vs 31%; $P = 0.02$)[87]
	R, DB, PC	*L. rhamnosus* GG	49% reduced risk of eczema development at 2 y of age ($P = 0.008$); 43% reduced risk of eczema at 4 y of age ($P < 0.05$); 36% reduced risk at 7 y of age[88-90]
	R, DB, PC	*L. rhamnosus* HN001	49% reduced risk of eczema development at 2 y of age ($P = 0.01$)[91]
	Treatment		
	R, DB, PC	*B. lactis* Bb12	Addition of Bb12 to EHWF decreased SCORAD score to 0 vs 13.4 in EHWF only controls ($P = 0.002$) in infants with AE[92]
	R, DB, PC	*L. fermentum* VRI-003	Significantly more probiotic-receiving children had an improvement in SCORAD index compared with placebo controls (92% vs 63%; $P = 0.01$); more children in the probiotic group had mild AE at the end of the study compared with controls (54% vs 30%; $P = 0.066$)[93]
Bacterial gastroenteritis	*Clostridium difficile*		
	R, DB, PC	*L. plantarum* 299v	In antibiotic-treated, critically ill patients, 299v ingestion prevented colonization by *C. difficile* (none vs 19%; $P < 0.05$)[94]
	R, DB, PC	*S. cerevisiae* Hansen CBS 5926	In combination with high-dose vancomycin, supplementation reduced *C. difficile* recurrence (17% vs 50%; $P = 0.05$).[95]
	OL	*L. rhamnosus* GG	27/32 subjects with relapsing *C. difficile* diarrhea were cleared after a single oral administration; the remaining 5 subjects relapsed; 3 of these were re-treated and cured; the other 2 were lost to follow-up[96]
	Vancomycin-resistant enterococci (VRE)		
	R, DB, PC	*L. rhamnosus* GG	All subjects who received LGG were cleared of VRE compared with 8% of controls ($P < 0.001$)[59]
Bacterial vaginosis (BV)	R, DB, PC	*L. rhamnosus* GR-1 and *L. reuteri* RC-14	After a single dose of tinidazole and 4 wks oral treatment, subjects in the probiotic group had a higher rate of BV cure (88% vs 50%; $P = 0.001$); vaginal flora normalized in 75% of probiotic-treated subjects compared with 34% of controls ($P = 0.011$)[97]
	R, OL	*L. rhamnosus* GR-1 and *L. reuteri* RC-14	Intravaginal application of probiotics nightly for 5 d resulted in 90% cure rate by day 30; follow-up at days 6, 15, and 30 showed cure of BV in significantly more probiotic-treated subjects (16, 17, and 18/20, respectively) compared with metronidazole gel (9, 9, and 11/20, respectively; $P = 0.016$ at day 6, $P = 0.002$ at day 15, and $P = 0.056$ at day 30)[98]

TABLE 116-4 **Choosing the Right Strain for Specific Therapeutic Applications—cont'd**

CONDITION	METHODOLOGY	MOST APPROPRIATE PROBIOTIC STRAIN(S)	RESULTS
Bladder cancer	R, DB, PC	*L. paracasei* Shirota	Decreased tumor recurrence in patients with superficial bladder cancer ($P = 0.01$) except in subjects with recurrent multiple tumors [99]
	Animal	*L. rhamnosus* GG	Significantly increased the number of cured mice ($P = 0.006$) in a murine model of bladder cancer[100]
Chemotherapy-induced diarrhea	R, OL	*L. rhamnosus* GG	41% reduced frequency of severe diarrhea in subjects undergoing 5-fluorouracil-based chemotherapy for colorectal cancer ($P = 0.027$); 83% reduction in abdominal discomfort scores ($P = 0.025$); 55% decreased frequency in bowel toxicity-induced dose reductions ($P = 0.0008$)[101]
Chronic fatigue syndrome	R, DB, PC	*L. paracasei* Shirota	Significant decrease in anxiety symptoms compared with controls ($P = 0.01$)[102]
	OL	*L. paracasei* F19, *B. lactis* Bb12, and *L. acidophilus* NCFB 1748	Significant improvement in neurocognitive functioning compared with baseline ($P = 0.04$)[103]
Collagenous colitis	R, DB, PC	*L. acidophilus* LA5 and *B. lactis* Bb12	Compared with baseline, there was a median reduction in weekly bowel frequency (32-23; $P < 0.005$) and a reduction in number of days with liquid stools/wk (from 6-1; $P < 0.005$)[104]
	OL	*Escherichia coli* Nissle 1917	Decrease in stool frequency from 7.6-3.7/day ($P = 0.034$)[105]
Colon cancer—prevention	R, PC	*L. paracasei* Shirota	Decrease in fecal β-glucuronidase activity ($P < 0.05$)[60]
	R, PC	*L. rhamnosus* GG	Decrease in fecal β-glucuronidase ($P < 0.01$), nitroreductase ($P < 0.01$), and glycocholic acid hydrolase ($P < 0.05$) activities compared with baseline; decreased urinary *p*-cresol levels ($P < 0.05$)[58]
	OL	*L. acidophilus* NCFM	Decrease in the activities of fecal bacterial enzymes compared with baseline: β-glucuronidase ($P < 0.001$), nitroreductase ($P < 0.002$), and azoreductase ($P < 0.02$)[106]
Constipation	R, DB, PC	*B. lactis* Bb12	In elderly nursing home residents, defecation frequency improved after Bb12 ingestion ($P = 0.038$), as did the number of days experiencing normal bowel movements ($P = 0.002$)[107]
	R, DB, PC	*E. coli* Nissle 1917	Increase in number of stools/wk (4.9 vs 2.6; $P < 0.001$) and a decrease in occurrence of hard stools (both $P < 0.05$)[108]
	R, DB, PC	*L. paracasei* Shirota	Significant decrease in occurrence of moderate and severe constipation ($P < 0.001$) and in occurrence of hard stools ($P < 0.001$); increase in defecation frequency ($P = 0.004$); improvement in stool consistency ($P < 0.001$)[109]
Crohn's disease	R, OL	*S. cerevisiae* Hansen CBS 5926	In combination with mesalamine, probiotic treatment reduced relapse rate compared with mesalamine alone (6% vs 38%; $P = 0.04$)[110]
Cystic fibrosis	R, SB, PC, CO	*L. rhamnosus* GG	37% decrease in incidence of pulmonary exacerbations in children ($P = 0.003$); 50% reduction in hospital admissions ($P = 0.001$)[111]
Diverticular disease	OL	*E. coli* Nissle 1917	Addition to standard treatment resulted in significant lengthening of remission (2.4 vs 14.1 mo; $P < 0.001$)[112]
Gastrointestinal candidiasis	R, DB, PC	*L. rhamnosus* GG	69% decreased risk of gastrointestinal *Candida* colonization in preterm infants ($P = 0.01$); significantly reduced enteric *Candida* population in infants who were colonized ($P = 0.005$)[113]
Giardia infection	Animal	*L. johnsonii* La1	Ingestion of La1 before *Giardia* inoculation decreased numbers of infected gerbils compared with placebo-treated animals (27% vs 83%; $P = 0.01$); after 14 d, 100% of La1-treated animals were *Giardia*-free vs 57% of controls ($P = 0.02$); prevented parasite-induced mucosal damage[114]
Helicobacter pylori infection	R, DB, C	*L. casei* DN-114	Addition of DN-114 to triple therapy resulted in eradication of *H. pylori* in 92% of subjects vs 85% in controls ($P = 0.0045$)[115]
	R, DB, PC	*L. johnsonii* La1	In asymptomatic children, daily La1 ingestion for 3 wks resulted in *H. pylori* eradication in 15% of subjects vs 1.5% in controls ($P < 0.01$)[116]
	R, DB, PC	*L. reuteri* MM53	Treatment with omeprazole + MM53 eradicated *H. pylori* in 60% of subjects after 30 days compared with none in the placebo + omeprazole group ($P < 0.0001$)[117]
	R, OL	*L. acidophilus* LA5 and *B. lactis* Bb12	4 wks pretreatment with probiotics improved *H. pylori* eradication rates from 71%-85% ($P < 0.05$) after quadruple therapy in subjects in which triple therapy failed[118]

Continued

TABLE 116-4 **Choosing the Right Strain for Specific Therapeutic Applications—cont'd**

CONDITION	METHODOLOGY	MOST APPROPRIATE PROBIOTIC STRAIN(S)	RESULTS
	R, OL	*L. paracasei* Shirota	Addition of Shirota to triple therapy resulted in eradication of *H. pylori* in 94% of subjects vs 76% in controls ($P < 0.05$)[119]
	OL	*L. acidophilus* LA5 and *B. lactis* Bb12	Daily ingestion for 6 wks resulted in decreased *H. pylori* density ($P = 0.006$) and gastritis ($P = 0.015$) on the antrum, as well as decreased urea breath test values compared with baseline ($P < 0.05$)[61]
	OL	*L. acidophilus* NAS	Daily ingestion over a 2-mo period resulted in eradication of *H. pylori* in 43% of subjects[120]
HIV/AIDS-associated diarrhea	DB, PC	*L. rhamnosus* GR-1 and *L. reuteri* RC-14	Increase in CD4 counts observed in probiotic-treated female HIV-infected subjects compared with a decrease in controls ($P < 0.02$); all probiotic-treated subjects were free of diarrhea after 15-d treatment vs 9% of controls[121]
Hypercholesterolemia	R, DB, PC	*L. plantarum* 299v	10% decrease in total cholesterol ($P < 0.05$) and 7% decrease in LDL ($P < 0.05$) compared with baseline after 6 wks[122]
	OL	*Bacillus coagulans ATCC#31284*	32% decrease in total cholesterol over a 3-mo period[123]
Immune enhancement: decreased rates of infection	R, DB, PC	*B. lactis* Bb12	Reduced fever episodes by 34% ($P < 0.001$), diarrhea episodes by 58% ($P < 0.001$), and duration of diarrhea by 37% ($P < 0.001$) in infants[124]
	R, DB, PC	*L. acidophilus* NCFM	Reduced fever incidence by 53% ($P = 0.0085$) and coughing incidence by 41% ($P = 0.027$) in children; use of antibiotics reduced by 68% ($P = 0.0002$); 32% reduction in days absent from childcare ($P = 0.002$)[125]
	R, DB, PC	*L. acidophilus* NCFM & *B. lactis* Bi07	Reduced fever incidence by 73% ($P = 0.0009$), coughing incidence by 62% ($P = 0.005$), and rhinorrhea incidence by 59% ($P = 0.03$) in children; use of antibiotics reduced by 84% ($P < 0.0001$); 28% reduction in days absent from childcare ($P < 0.001$)[125]
	R, DB, PC, CO	*L. fermentum* VRI-003	Over a 4-mo winter period, elite male distance runners taking the probiotic reported less than half the number of days of respiratory symptoms (30 vs 72; $P = 0.00006$) compared with placebo; illness severity was also decreased ($P = 0.06$)[126]
	R, DB, PC	*L. johnsonii* La1	Percentage of days with infections decreased from 15.4 at baseline to 5.7 during probiotic treatment in elderly hospital inpatients ($P = 0.018$); this was significantly greater than the reduction in controls ($P = 0.047$)[127]
	R, DB, PC	*L. reuteri* MM53	Reduced fever episodes by 73% ($P < 0.001$), diarrhea episodes by 94% ($P < 0.001$), duration of diarrhea by 75% ($P < 0.001$), and childcare absences by 67% ($P = 0.015$) in infants[124]
	R, DB, PC	*L. reuteri* MM53	58% reduction in number of subjects reporting sick days in the MM53 group compared with placebo ($P < 0.01$); among shift workers, 33% of those in the placebo group reported sick over the 80-day study period vs none in the MM53 group ($P < 0.005$)[128]
	R, DB, PC	*L. rhamnosus* GG	16% fewer days absent from daycare in children ($P = 0.03$); 19% reduction in antibiotic use for respiratory tract infections ($P = 0.03$)[129]
	R, DB, PC	*L. rhamnosus* GG	34% reduced risk of upper respiratory tract infections in toddlers; 43% reduced risk of respiratory tract infections lasting >3 days; significantly fewer number of days with respiratory tract symptoms (all $P < 0.001$); trend for reduced number of days with GI symptoms ($P = 0.06$)[130]
	R, DB, PC	*L. rhamnosus* GG and *B. lactis* Bb12	56% reduced risk of otitis media in toddlers ($P = 0.014$); 48% reduced risk of antibiotic prescription ($P = 0.015$); 49% reduced risk of recurrent respiratory tract infections ($P = 0.022$)[131]
Infantile colic	R, OL	*L. reuteri* MM53	Significant reduction in daily crying time by day 7 in the MM53 group compared with the simethicone group ($P = 0.005$); improvement continued until day 28, when median crying time was reduced to 51 min/d in the MM53 group vs 145 min/d in controls ($P < 0.001$)[132]
Intestinal dysbiosis	OL	*L. rhamnosus* GG	Significant increases in fecal concentrations of bifidobacteria and lactobacilli (both $P < 0.05$); decrease in lecithinase-negative clostridia concentrations[133]

TABLE 116-4 **Choosing the Right Strain for Specific Therapeutic Applications—cont'd**

CONDITION	METHODOLOGY	MOST APPROPRIATE PROBIOTIC STRAIN(S)	RESULTS
	R, DB, PC	*B. lactis* Bb12	Significant increases in fecal concentrations of bifidobacteria (P <0.001) in preterm infants compared with placebo; decrease in enterobacteria (P = 0.015) and clostridia (P = 0.014)[134]
	R, DB, PC	*B. lactis* HN019	Significant increases in fecal concentrations of bifidobacteria (P <0.0005), lactobacilli (P <0.005), and enterococci (P <0.005) compared with baseline; decrease in coliforms (P <0.005)[135]
	R, DB, PC	*L. johnsonii* La1	Significant increase in fecal bifidobacteria (P <0.01) and lactobacilli (P <0.001) compared with placebo period; decrease in lecithin-positive clostridia (P <0.05)[136]
	R, PC	*L. paracasei* Shirota	Significant increase in fecal bifidobacteria concentrations compared with controls (P <0.05)[60]
IBS	R, DB, PC	*L. acidophilus* strains CUL-60 and CUL-21, *B. lactis* CUL-34, and *B. bifidum* CUL-20	Significant reduction in composite IBS symptom score (P = 0.0217) and improvement in quality of life scores (P = 0.0068) compared with controls[137]
	R, DB, PC, CO	*L. fermentum* VRI-003	Significant reductions in abdominal pain (P = 0.041), constipation (P = 0.045), alternating bowel habit (P = 0.021), flatulence (P = 0.001), and bloating (P = 0.006) scores observed after probiotic treatment, but not after placebo treatment[138]
	R, DB, PC	*L. plantarum* 299v	All subjects in 299v group reported improvement in abdominal pain scores vs 58% of controls (P = 0.012); more 299v-treated subjects rated their overall IBS symptoms as improved (95% vs 15%; P <0.0001)[139]
	R, DB, PC	*L. rhamnosus* GG, *L. rhamnosus* Lc705, *Propionibacterium freudenreichii ssp. shermanii* JS and *B. breve* Bb99	42% reduction in composite IBS symptom score vs 6% in placebo group (P = 0.015); borborygmi reduced compared with controls (P = 0.008)[140]
	R, DB, PC	*L. rhamnosus* GG, *L. rhamnosus* Lc705, *P. freudenreichii ssp. shermanii* JS, and *B. lactis* Bb12	37% reduction in composite IBS symptom score vs 9% in placebo group (P = 0.0083); reduction in abdominal distension (P = 0.023) and pain (P = 0.052) scores compared with controls[141]
	R, DB, PC	VSL#3	Significant reduction in flatulence scores compared with placebo (P = 0.011)[142]
	R, DB, PC	VSL#3	Significant reduction in abdominal bloating scores from baseline in VSL#3 group but not in controls (P = 0.046)[143]
Lactose intolerance	R, SB, CO	*L. acidophilus* LA5	Significantly decreased breath hydrogen values after ingestion of La5-inoculated milk (P <0.05)[144]
	R, SB, CO	*L. acidophilus* NCFM	90% of subjects who were symptomatic after ingestion of uninoculated milk experienced a reduction in symptoms after ingestion of milk inoculated with NCFM; mean symptoms were significantly reduced (P <0.001)[145]
Liver cirrhosis	R, PC	*E. coli* Nissle 1917	Increased fecal concentrations of lactobacilli and bifidobacteria; decreased stool counts of potentially pathogenic bacteria (P <0.001 vs controls); decreased level of endotoxin (P = 0.07) and overall Child-Pugh score (P = 0.07)[146]
	OL	*L. paracasei* Shirota	Significantly improved neutrophil phagocytic capacity compared with baseline (P <0.05)[147]
Nosocomial diarrhea	R, DB, PC	*L. rhamnosus* GG	80% reduced risk of nosocomial diarrhea in infants (P = 0.002)[77]
NSAID use/erosive gastritis	OL	*L. rhamnosus* GG	LGG pretreatment significantly reduced gastric permeability caused by indometacin administration (P = 0.012)[148]
Postpartum obesity	R, DB, PC	*L. rhamnosus* GG and *B. lactis* Bb12	At 12 mo postpartum, central obesity occurred in 25% of probiotic-treated subjects vs 43% in the placebo group; proportion of body fat was also 3.5% lower (P = 0.018)[149]
Prevention of dental caries	R, DB, PC	*L. rhamnosus* GG	49% reduced risk of dental caries in children (P = 0.004)[150]
	R, DB, PC, CO	*B. lactis* Bb12	Significantly decreased salivary levels of *Streptococcus mutans* (P <0.05)[151]
	R, DB, PC	*L. reuteri* MM53	Ingestion of probiotic lozenge significantly decreased oral carriage of *S. mutans* (P <0.05)[152]

Continued

TABLE 116-4 **Choosing the Right Strain for Specific Therapeutic Applications—cont'd**

CONDITION	METHODOLOGY	MOST APPROPRIATE PROBIOTIC STRAIN(S)	RESULTS
Prevention of gestational diabetes	R, DB, PC	*L. rhamnosus* GG and *B. lactis* Bb12	Probiotic combination reduced frequency of gestational diabetes by 62% ($P = 0.003$)[153]
Prevention of traveler's diarrhea (TD)	R, PC	*L. acidophilus* LA5 and *B. lactis* Bb12	Significantly fewer tourists given probiotics developed TD (43% vs 71%; $P < 0.001$)[154]
	R, DB, PC	*L. rhamnosus* GG	Risk of developing TD reduced in LGG group compared with placebo group (3.9 vs 7.4%; $P = 0.05$); 47% reduced risk of developing TD[155]
	R, DB, PC	*S. cerevisiae* Hansen 5926	21% reduction in incidence in 250 mg/d group ($P < 0.007$) and 25% reduction with 500 mg/d ($P < 0.002$) compared with placebo[156]
Radiation-induced diarrhea	R, DB, PC	VSL#3	In subjects undergoing adjuvant postoperative radiation therapy for sigmoid, rectal, or cervical cancer, VSL#3 significantly reduced incidence of radiation-induced diarrhea (52% vs 32%; $P < 0.001$); daily bowel movements were reduced (14.7 vs 5.1; $P < 0.05$); incidence of severe diarrhea was reduced (55% vs 1%; $P < 0.001$)[157]
	R, OL	*L. acidophilus* NCFB-1748	In patients receiving external pelvic radiotherapy for cervical or uterine cancer, diarrhea incidence was significantly reduced (27% vs 90%; $P < 0.01$)[158]
Small intestinal bacterial overgrowth	OL	*L. paracasei* Shirota	64% of subjects had a reversal in their positive early first rise in breath hydrogen after lactulose test results; median time of first rise in breath hydrogen increased from 45 to 75 min ($P = 0.03$); 28% decrease in flatulence scores from baseline ($P = 0.04$)[159]
Ulcerative colitis (UC)	R, DB, C	*E. coli* Nissle 1917	In conjunction with standard IBD therapy (corticosteroids), remission rate ($P = 0.05$) and time to remission was equivalent to mesalazine ($P = 0.009$); duration of remission was also equivalent ($P = 0.017$)[160]
Inducing remission	R, DB, PC	VSL#3	At 6 wks, 33% of VSL#3-treated subjects achieved a >50% decrease in the UC disease activity index vs 10% of controls ($P = 0.001$); at week 12, 43% of subjects in the VSL#3 group were in remission vs 16% of controls ($P < 0.001$)[161]
	R, DB, PC	VSL#3	In conjunction with standard IBD therapy (steroid induction and mesalamine maintenance), remission was achieved in 93% of VSL#3-treated children vs 36% of controls ($P < 0.001$); 21% relapsed within 1 y vs 73% of controls ($P = 0.014$).[162]
Maintaining remission	R, DB, C	*E. coli* Nissle 1917	Equally effective as mesalazine in preventing relapse ($P = 0.003$)[163]
	R, OL	*L. rhamnosus* GG	Equally effective as mesalazine in maintaining clinical remission; significantly more effective than mesalazine in prolonging the relapse-free time ($P < 0.05$)[78]
	OL	*E. coli* Nissle 1917	At 12 mo, the relapse rate was 25% in probiotic-treated teens vs 30% in the mesalazine group[164]
	OL	VSL#3	After 12 mo, 15/20 participants remained in remission, which compares favorably with rates of remission observed during long-term mesalazine therapy.[165]
Preventing pouchitis	R, DB, PC	VSL#3	Remission was maintained at 1 y in 85% of VSL#3-treated patients vs 6% of controls ($P < 0.0001$)[166]
	OL	*L. rhamnosus* GG	Significantly delayed first onset of pouchitis compared with no-treatment controls (cumulative risk at 3 y: 7% vs 29%; $P = 0.011$)[167]
Treating pouchitis	OL	VSL#3	69% of subjects achieved remission after treatment; significant reductions in mean pouchitis disease activity index scores from baseline ($P < 0.01$)[168]
Urinary tract infection (UTI)	R, DB, C	*L. rhamnosus* GR-1 and *L. reuteri* B-54	In women with recurrent UTIs, weekly intravaginal application resulted in a 73% decrease in UTI incidence compared with the previous year (1.6 infections vs 6.0; $P = 0.001$)[169]
Vaginal candidiasis (VC)	R, DB, PC	*L. acidophilus* NAS	In HIV-infected women, weekly intravaginal application of NAS was associated with a 50% reduced risk of VC ($P = 0.09$)[170]
	R, DB, PC	*L. rhamnosus* GR-1 and *L. reuteri* RC-14	After a single dose of fluconazole and 4 wks oral treatment, subjects in the probiotic group had reduced *Candida* colonization (10% vs 39%; $P = 0.014$) and decreased vaginal discharge (10% vs 35%; $P = 0.03$)[171]
	R, PC, CO	*L. acidophilus* LA5	Mean number of infections per 6 mo decreased while taking the probiotic (0.38 vs 2.54; $P = 0.001$); incidence of *Candida* colonization decreased during probiotic treatment (0.84 vs 3.23 per 6 mo; $P = 0.001$)[57]

TABLE 116-4 **Choosing the Right Strain for Specific Therapeutic Applications—cont'd**

CONDITION	METHODOLOGY	MOST APPROPRIATE PROBIOTIC STRAIN(S)	RESULTS
	OL	*L. rhamnosus* GG	Twice daily intravaginal application of LGG resulted in decreased symptoms of VC, as well as less erythema and discharge; 4/5 women who were positive for *Candida* at baseline had negative cultures at the end of 7 d[172]
Vaginal dysbiosis	R, DB, PC	*L. rhamnosus* GR-1 and *L. reuteri* RC-14	60% of postmenopausal women had a reduction in Nugent score by at least 2 grades after oral ingestion of the probiotic vs 16% of controls ($P = 0.0001$); median Nugent score decreased by 3 grades in the probiotic group vs 0 in controls after 14-d treatment ($P = 0.0001$)[173]
	R, PC	*L. rhamnosus* GR-1 and *L. reuteri* RC-14	Ingestion of the probiotic resulted in a significant increase in vaginal lactobacilli ($P = 0.01$), as well as a decrease in vaginal yeasts ($P = 0.01$) and coliform bacteria ($P = 0.001$) populations compared with controls[174]
	OL	*L. rhamnosus* GR-1 and *L. reuteri* RC-14	In women diagnosed with either BV or vaginitis, after antibiotic therapy and 15-d oral probiotic therapy, 92% of subjects had complete lactobacilli vaginal recolonization[175]
Viral gastroenteritis prevention	R, DB, PC	*B. lactis* Bb12 and *Streptococcus thermophilus*	In infants admitted to a long-term medical hospital, probiotic supplementation reduced diarrhea incidence (7 vs 31%; $P = 0.035$) and rotavirus shedding (10 vs 39%; $P = 0.025$)[176]
	R, DB, PC	*L. rhamnosus* GG	In hospitalized children, relative risk of rotavirus gastroenteritis was reduced by 87% ($P = 0.02$)[77]
Treatment	Meta-analysis	*L. rhamnosus* GG	Significantly reduced duration of rotavirus diarrhea by 2.1 d in children ($P = 0.006$); risk of diarrhea lasting >7 d was reduced by 75% ($P = 0.01$)[177]
	R, DB, PC	*L. reuteri* MM53	Duration of diarrhea reduced from 2.5 d in the placebo group to 1.5 d in MM53-treated toddlers ($P = 0.01$)[178]
	R, DB, PC	VSL#3	On day 4 of treatment, 89% of VSL#3-treated children had recovered vs 40% of controls ($P < 0.001$)[179]

AAD = antibiotic-associated diarrhea; C, controlled; CO, crossover; DB, double-blind; EHWF, extensively hydrolyzed whey formula; GI, gastrointestinal: IBD, inflammatory bowel disease; IgE = immunoglobulin-E; IBS, irritable bowel syndrome; LDL, low-density lipoprotein; NSAID, nonsteroidal antiinflammatory drug; OL, open-label; PC, placebo-controlled; R = randomized; SB, single-blind; SCORAD = SCORing Atopic Dermatitis ; VSL#3 = proprietary probiotic mixture.

amounts greater than or equal to 10^9, because dosages of less than 10^9 living bacteria may not produce therapeutic effects.

Yogurts

The minimum dosage of viable bacteria needed in a dairy medium is 10^8 per dose. Therapeutic yogurts contain greater than or equal to 10^6 viable bacteria per milliliter, thus a 100 g serving (approximately 1/2 cup) will provide sufficient probiotic bacteria for therapeutic effects.[181] Unfortunately, many so-called "acidophilus" and/or "bifidus" yogurts do not contain this minimum level.[183] Only yogurt brands that are guaranteed to contain this level of viable bacteria or those that have done so in market-basket surveys should be utilized. A serving of yogurt containing less than 10^8 viable bacteria is unlikely to have any medicinal effects beyond its inherent nutritional content.

A 100 g serving of yogurt contains only 3.1 to 3.5 g of lactose,[184] which is well below the threshold level in individuals with lactose intolerance. Hence, lactose-intolerant individuals should be able to consume the minimum amount of yogurt without ill effects.[185]

Fermented Vegetables

Traditionally prepared fermented vegetables generally contain more than 10^8 living bacteria per gram, thus 10 g is the minimum dosage required.[64,65]

TOXICITY

Lactobacilli have been consumed in large numbers throughout recorded history. The fermentation of foodstuffs is one of the oldest known uses of biotechnology, and even today, fermented foods and beverages constitute 20% to 40% of the human food supply worldwide. Thus, lactobacilli have a long history of safe use.[5]

In 143 human clinical trials, no adverse effects or events were reported by any of the 7526 subjects who participated in these studies.[5] Despite increased use of probiotic supplements worldwide, epidemiologic evidence suggests there has been no corresponding increase in cases of bacteremia or fungemia as a consequence.[186]

There have been a number of cases of fungemia reported in the literature from the oral administration of *Saccharomyces cerevisiae* (also known as *S. boulardii*). These have occurred almost exclusively in immunocompromised or critically ill individuals. Thus, administration of strains of *S. cerevisiae* should be limited to immunocompetent individuals.[187,188]

DRUG INTERACTIONS

Lactobacilli and bifidobacteria are negatively affected by alcohol and antibiotics.[189,190] Although there is no evidence that the organism interferes with the activity of most antibiotics, the metabolism of sulfasalazine, chloramphenicol palmitate, and phthalylsulfathiazole may be affected by some strains of *L. acidophilus*.[191]

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CHAPTER 117

Procyanidolic Oligomers

Michael T. Murray, ND

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GENERAL DESCRIPTION

The proanthocyanidins (also referred to as "procyanidins") are one of the most beneficial groups of plant flavonoids. The most active proanthocyanidins are those bound to other proanthocyanidins. Collectively, mixtures of proanthocyanidin dimers, trimers, tetramers, and larger molecules are referred to as procyanidolic oligomers (PCOs) or oligomeric proanthocyanidins (OPCs).[1,2] Although PCOs exist in many plants as well as red wine, commercially available sources of PCOs include extracts from grape seed skin *(Vitex vinifera)* and the bark of the maritime (Landes) pine.[1,2] This chapter reviews the benefits of PCOs from grape seeds and pine bark interchangeably due to their similar chemical composition and pharmacologic profiles.

CHEMICAL COMPOSITION

Grape seed and pine bark PCO extracts are well defined chemically. Grape seed extracts are available that contain 92% to 95% PCOs, whereas the PCO content of pine bark extracts varies from 80% to 85%. Proanthocyanidin B_2 is shown in Figure 117-1.

HISTORY AND FOLK USE

In 1534, French explorer Jacques Cartier led an expedition up the Saint Lawrence River in what would become North America. Trapped by ice, Cartier and his crew were forced to survive on a ration of salted meat and biscuits. Cartier's crew began to exhibit signs and symptoms of scurvy, the cause of which was unknown at that time. Fortunately for Cartier and the surviving members of his crew, they met a Native American who advised them to make a tea from the bark and needles of pine trees. As a result, Cartier and his men survived.

More than 400 years later, Professor Jacques Masquelier of the University of Bordeaux, France, read the book Cartier wrote detailing his expedition. Intrigued by Cartier's story, Masquelier and others concluded that pine bark must contain some vitamin C as well as bioflavonoids, which can exert vitamin C–like effects.

Masquelier termed the active components of the pine bark pycnogenols.[1,3] This term was used to describe an entire complex of proanthocyanidin complexes found in a variety of plants, including pine bark, grape seeds, lemon tree bark, peanuts, cranberries, and citrus peels. The term pycnogenol has been replaced in the scientific community by the terms proanthocyanidins, OPC, and PCO. In the United States, Pycnogenol is a registered trademark of Horphag Ltd of Guernsey, United Kingdom, and refers to the PCO extracted from the bark of the French maritime pine.

Masquelier patented the method of extracting PCOs from pine bark in France in 1951 and from grape seeds in 1970. The two PCO sources have volleyed back and forth in popularity based largely on which one is receiving research focus and marketing support.

PHARMACOLOGY

Extracts of PCOs demonstrate a wide range of activity as listed in Box 117-1. Pharmacokinetic studies showed that proanthocyanidins and other breakdown products of PCOs from either grape seed extract or maritime pine are detectable in the serum after oral intake.[4,5] Pharmacokinetic studies in humans and animals given C^{14}-labelled PCOs also showed efficient oral absorption.[6,7]

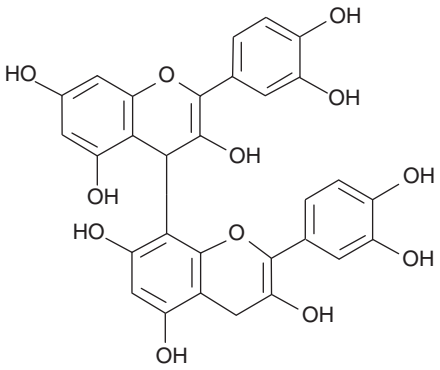


FIGURE 117-1 Proanthocyanidin B_2.

BOX 117-1 Basic Pharmacologic Activity of Proanthocyanidins

- Increase intracellular vitamin C levels
- Decrease capillary permeability and fragility
- Scavenge oxidants and free radicals
- Inhibit destruction of collagen
- Reduce inflammation

Data from references 1 and 2.

Antioxidant and Free Radical Scavenging Activity

Perhaps the most celebrated effects of PCOs in the United States are their potent antioxidant and free radical scavenging activities. The antioxidant and free radical scavenging effects of PCOs were discovered by Masquelier in 1986.[1]

One study evaluated the free radical scavenging activity of PCOs and determined their inhibitory effects on xanthine oxidase (a primary generator of oxygen-derived free radicals) and the lysosomal enzyme system (which governs the release of enzymes that can damage the connective tissue framework acting as a protective sheath around capillary walls).[8] This research, summarized in Box 117-2, provides a detailed explanation of the vascular protective action of PCOs and a strong rationale for their use in vascular disease.

In experimental models, the antioxidant activity of PCOs is much greater (approximately 50 times) than that of vitamin C and vitamin E. PCOs reduce lipid peroxidation[9] and oxidation of low-density lipoprotein (LDL),[10] increase basal levels of α-tocopherol in endothelial cells, protect endothelium from oxidative stress induced by reactive nitrogen species,[11,12] and protect endothelial cells from activated macrophage-induced glutathione depletion.[13] From a cellular perspective, one of the most advantageous features of PCOs' free radical scavenging activity is that, because of their chemical structure, they are incorporated into cell membranes. This physical characteristic, along with their ability to protect against both water- and fat-soluble free radicals, provides significant cellular protection against damage by free radicals.[8]

Protection of Collagen

Collagen, the most abundant protein of the body, is responsible for maintaining the integrity of ground substance as well as the integrity of tendons, ligaments, and cartilage. Collagen is also the support structure of the dermis and blood vessels. PCOs are remarkable in their effects of supporting collagen structures and preventing collagen destruction. They affect collagen metabolism in several ways. They have the unique ability to cross-link collagen fibers, resulting in reinforcement of the natural cross-linking of collagen that forms the so-called collagen matrix of connective tissue.[14,15] They also protect against free radical damage with their potent antioxidant and free radical scavenging action, and they inhibit enzymatic cleavage of collagen by enzymes secreted by leukocytes during inflammation and microbes during infection.[8,16] PCOs also prevent the release and synthesis of compounds that promote inflammation and allergies, such as histamine, serine proteases, prostaglandins, and leukotrienes.[1,2,17,18]

BOX 117-2 Antioxidant and Free Radical Scavenging Activities of Procyanidolic Oligomers

- Trap hydroxyl free radicals
- Trap lipid peroxides and free radicals
- Markedly delay the onset of lipid peroxidation
- Chelate free iron molecules, thereby preventing iron-induced lipid peroxidation
- Inhibit production of free radicals by noncompetitively inhibiting xanthine oxidase
- Inhibit the damaging effects of the enzymes (e.g., hyaluronidase, elastase, collagenase) that can degrade connective tissue structures

Antiinflammatory Activity

In vitro and in vivo studies showed PCOs significantly inhibit cyclooxygenase (COX-1) and COX-2 enzymes as well as the formation of proinflammatory cytokines, interleukin-1β, and tumor necrosis factor-β, as well as histamine release from mast cells.[19-22] When 10 volunteers received a single dose of 300 mg Pycnogenol, within 30 minutes serum samples showed statistically significant inhibition of both COX-1 and COX-2 (P <0.002). Blood samples before and after 5 days administration of 200 mg Pycnogenol to five healthy humans showed similar inhibition.

Cardiovascular Protection

In addition to protecting against oxidative damage to LDL and endothelial cells, PCOs increase erythrocyte membrane fluidity; reduce platelet aggregation; enhance endothelial nitric oxide synthase (eNOS) activity to increase nitric oxide levels; and inhibit angiotensin-I–converting enzyme (ACE).[23-27] PCO extracts were shown to lower blood cholesterol levels and to shrink the size of cholesterol deposits in arteries in animal and human studies.[1,28,29]

PCOs also significantly lower C-reactive protein (CRP), a major risk factor for cardiovascular disease. In a double-blind study, 29 subjects in the Pycnogenol group and 26 patients in the placebo group had CRP levels higher than 3 mg/L at baseline.[21] After 3-month treatment with Pycnogenol, at a dose of 100 mg/day, CRP significantly decreased plasma free radicals to 70.1% of baseline values. Specifically, plasma CRP levels decreased from 3.9 mg/L at baseline to 1.1 mg/L in the Pycnogenol group, whereas the control group had initial values of 3.9 mg/L that decreased to 3.6 mg/L. Fibrinogen levels were found to be lowered to 62.8% of initial values in the Pycnogenol group.

Anticancer Activity

PCOs exert a number of anticancer effects beyond their general antioxidant actions. PCOs were shown to selectively induce apoptosis (programmed cell death) in human breast cancer cells, inhibit cell

proliferation and induce differentiation and apoptosis in leukemia cells, and inhibit nitrosamine activation in lung microsomes.[30-33]

CLINICAL APPLICATIONS

The primary clinical applications of PCOs are in the treatment of the following conditions:

- Antioxidant therapy
- Asthma
- Atherosclerosis, hypertension, metabolic syndrome, and type 2 diabetes
- Attention deficit disorder
- Male infertility
- Osteoarthritis (OA)
- Periodontal disease
- Venous insufficiency and capillary fragility
- Visual function, retinopathy, and macular degeneration

Antioxidant Therapy

PCOs exert broad-spectrum antioxidant activity and are clinically useful in many health conditions because of this action alone. In healthy human subjects, supplementation with PCOs for 6 weeks was shown to considerably improve the plasma oxygen radical absorbance capacity score (ORAC).[28] In one double-blind study, the effect of a standardized formulation of a PCO bound to phosphatidylcholine (Leucoselect-Phytosome) was determined on susceptibility of LDL to oxidation in a group of heavy smokers.[34] Among oxidative indexes, the concentration of thiobarbituric acid reactive substances was significantly reduced in subjects taking the PCO extract, and the lag phase was prolonged compared with the values in subjects taking placebo, as well as with baseline values.

In a double-blind, placebo-controlled study in 101 elderly participants (60 to 85 years), consuming a daily dose of 150 mg of Pycnogenol for 3 months produced significant improvements in several memory-based cognitive assessments and lipid peroxidation products (F2-isoprostanes) relative to the control group.[35]

Asthma

PCOs appear to have an affinity for the lungs, indicating a possible benefit in lung disorders, including asthma. In a double-blind study involving 60 subjects (aged 6 to 18 years old) with mild-to-moderate asthma, patients were given either Pycnogenol (1 mg/lb body weight per day) or placebo for 3 months. Subjects were instructed to record their peak expiratory flow with an Assess Peak Flow Meter each evening. Compared with subjects taking placebo, the group who took Pycnogenol had significantly more improvement in pulmonary function and asthma symptoms. The Pycnogenol group was able to reduce or discontinue their use of rescue inhalers more often than the placebo group. There was also a significant reduction of urinary leukotrienes in the Pycnogenol group. The results of this study demonstrate the efficacy of Pycnogenol as an adjunct in the management of mild-to-moderate childhood asthma. Given the safety of PCOs, higher dosages (e.g., 2 to 3 mg/lb body weight) may produce better results than the lower dosage used in the clinical trial.[36]

Atherosclerosis, Hypertension, Metabolic Syndrome, and Type 2 Diabetes

PCO extracts, although in a supplement form, should be regarded as a necessary food in the prevention and treatment of atherosclerosis, metabolic syndrome, and type 2 diabetes. PCOs are similar to red wine components that are so protective against heart disease.[37] The active components in the wine are thought to be proanthocyanidins. Flavonoid consumption, in general, has an inverse correlation with death due to heart attack.[38] Both Pycnogenol and grape seed extract showed considerable ability to reduce cardiovascular risk factors, especially in patients with type 2 diabetes.[39,40] However, even healthy subjects can take advantage of the beneficial effects of PCOs against cardiovascular risk factors. In one study, when 25 healthy subjects received Pycnogenol (150 mg/day) for 6 weeks, a significant increase in ORAC in plasma was observed throughout the supplementation period (returning to baseline after a 4-week washout period).[28] Pycnogenol also significantly reduced LDL cholesterol levels and increased high-density lipoprotein (HDL) cholesterol levels in plasma of two thirds of the subjects. Although the LDL changes reversed during washout, the HDL increase did not. Like other flavonoid sources, PCO extracts appear to be very helpful in improving endothelial function. Again, this effect may be particularly important in patients with hypertension, metabolic syndrome, and diabetes. In one double-blind study in 58 patients with hypertension who received supplementation with 100 mg PCO over 12 weeks, endothelin-1 concentrations were significantly lower, and concentrations of 6-keto prostaglandin F_{1a} in plasma were significantly higher in the PCO group than in the placebo group. Additionally, the PCOs helped reduce the effective dose of the calcium antagonist nifedipine in a statistically significant manner.[41] In another double-blind study, PCOs from grape seed extract were shown to produce a mild hypotensive effect (–11 mm Hg for both systolic and diastolic readings) in patients with the metabolic syndrome at dosages of 150 and 300 mg/day.[42]

PCOs may prove to be vitally important in preserving renal function in hypertensive patients. One double-blind study evaluated the effects of Pycnogenol as an adjunct to ACE inhibitor ramipril treatment of hypertensive patients presenting with early signs of renal failure. One group of 26 patients was medicated with 10 mg/day ramipril only; a second group of 29 patients took Pycnogenol (150 mg/day) in addition to the ACE inhibitor over 6 months. At trial end, lower systolic and diastolic blood pressures were found in both groups, with a significant further reduction of diastolic pressure in the group given Pycnogenol in addition to ramipril. The study also showed Pycnogenol was effective for improving blood pressure in patients with metabolic syndrome. The study found that taking Pycnogenol as an adjunct to ramipril significantly further lowered systolic and diastolic blood pressures compared with the group taking ramipril alone. Although average blood pressure in the ramipril group was lowered to a borderline high of 128.2/90.2 mm Hg, the values in the group taking Pycnogenol with ramipril reached essentially normal values (122.2/85.3 mm Hg) after 6 months of treatment.

Kidney function improved in both groups as judged by a significant reduction of protein detected in collected urine. With ramipril alone, urinary protein decreased by 22%, and with the addition of Pycnogenol, it decreased by 52.7%. Further, the group taking Pycnogenol had a lower fasting blood glucose level, which was reduced from a high average value of 135.6 mg/dL at baseline to an essentially healthy reference value of 102.3 mg/dL after 6 months of treatment. Pycnogenol also led to a remarkable improvement of blood flow velocity of the kidney arteries. Blood flow velocity in the kidneys significantly increased with ramipril from 17.2 to 23.8 cm/s for systolic and 4.2 to 2.0 cm/s for diastolic; the addition of Pycnogenol was more effective, improving blood flow from 18.2 to 27.2 cm/s for systolic and 4.1 to 9.8 cm/s for diastolic.

Other studies showed that PCOs might lower fasting glucose levels. In a study in type 2 diabetes, patients received, in succession, 50, 100, 200, and 300 mg Pycnogenol in intervals of 3 weeks.[43] Every 3 weeks, fasting and postprandial glucose, endothelin-1, glycosylated hemoglobin (HbA_{1c}), and insulin were analyzed. Fasting blood glucose was lowered dose dependently until a dose of 200 mg Pycnogenol was administered. Increasing the dose from 200 to 300 mg did not further decrease blood glucose. Compared with baseline, 100 to 300 mg of Pycnogenol lowered fasting glucose significantly from 8.64 to 7.54 mmol/L (155 to 135 mg/dL). The maximum decrease of postprandial glucose was observed with 200 mg of Pycnogenol (0.07 ± 2.69 mmol/dL [180 mg/dL]). HbA_{1c} levels decreased continuously from 8.02% to 7.37%. Endothelin-1 decreased significantly after 100 to 300 mg Pycnogenol, from 104 to 91 pg/mL. Stimulation of insulin secretion was excluded as a cause for lower glucose levels because insulin levels were not affected.

These effects were confirmed in a double-blind, placebo-controlled study with 77 patients with type 2 diabetes. After 8 weeks of treatment, the median drop in fasting blood glucose levels in the Pycnogenol group was 1.96 mmol/L (35.28 mg/dL).[44]

PCOs are particularly useful in addressing the microvascular pathology of diabetes. In one study in patients with severe diabetic microangiopathy, 30 patients received oral Pycnogenol (50 mg capsules, 3 times daily, for a total of 150 mg/day for 4 weeks), whereas 30 comparable patients were observed as controls.[45] After 4 weeks, microcirculatory and clinical evaluations showed a progressive decrease in skin flux at rest in the foot (indicating an improvement in the level of microangiopathy), a significant decrease in capillary filtration, and a significant improvement in the venoarteriolar response in all treated subjects. There were no visible effects in controls, except a slight reduction in skin flux at rest in the foot.

PCOs are also very much indicated in the treatment of diabetic retinopathy. Early intervention in diabetic retinopathy led to significant improvements in microcirculation, retinal edema, and visual acuity.[46]

Attention Deficit Disorder

Increased oxidative damage is believed to be a central factor in attention deficit hyperactivity disorder (ADHD), indicating a possible application for PCO therapy. To date, four studies have been conducted in this patient population. In one study, children with ADHD supplementation with PCO (1 mg/kg body weight per day) had an improved reduced glutathione to oxidized glutathione ratio (an indication of improved antioxidant status).[47] A second study confirmed this effect and also showed a reduced urinary catecholamine concentration, leading to less hyperactivity.[48] Another study showed that PCOs reduced the level of oxidized purines represented by 8-oxo-7, 8-dihydroguanine in the urine and also increased total antioxidant status.[49] Finally, 61 children with ADHD supplemented with 1 mg/kg per day Pycnogenol or placebo over 4 weeks showed that 1-month Pycnogenol administration caused a significant reduction of hyperactivity, improved attention and visual-motoric coordination, and improved concentration of children with ADHD.[50] No positive effects were found in the placebo group. Standard questionnaires, the Child Attention Problems teacher rating scale, Conner's Teacher Rating Scale, the Conner's Parent Rating Scale, and a modified Wechsler Intelligence Scale for children were used as assessments. These results point to an option to use Pycnogenol as a nutritional adjunct in children with ADHD.

Male Infertility

Pycnogenol alone[51] and in combination with L-arginine[52] was shown to be helpful in improving sperm quality and function (see Chapter 180, Male Infertility, for more information).

Osteoarthritis

Two double-blind studies were conducted with Pycnogenol in OA. In the first study, Pycnogenol (100 mg) or placebo was given daily for 3 months to 156 patients with osteoarthritis. The global Western Ontario and McMasters University questionnaire for OA score decreased by 56% in the treatment group versus 9.6% in the placebo group. Walking distance in the treadmill test was prolonged from 68 m at the start of the study to 198 m in the Pycnogenol group compared with 65 to 88 m in the placebo group. The use of drugs decreased by 58% in the Pycnogenol group versus 1% in the placebo group. Foot edema decreased in 79% of Pycnogenol-treated patients versus 1% in controls. Similar results were seen in a second study when Pycnogenol was given at a dosage of 100 mg/day.

Periodontal Disease

Given the importance of supporting periodontal collagen structures in periodontal disease, PCOs are an important clinical consideration (see Chapter 199 on Periodontal Disease for more information).

Venous Insufficiency and Capillary Fragility

PCOs are very much indicated for treatment of varicose veins, venous insufficiency, and capillary fragility, because of their ability to:

- Reduce microvascular edema
- Increase the integrity of the venous wall
- Inhibit the breakdown of the compounds composing the ground substance
- Improve the muscular tone of the vein

Numerous double-blind studies with Pycnogenol validated the effectiveness of PCOs in chronic venous insufficiency, including studies showing an ability to decrease venous ulcer size,[53,54] reduce the edema and thrombosis associated with airline travel,[55,56] reduce nighttime claudication, and reduce other signs and symptoms of chronic venous insufficiency and microangiopathy.[57-59]

Visual Function, Retinopathy, and Macular Degeneration

Increased intake of PCO is likely to benefit almost everyone. This suggestion is perhaps best illustrated by research evaluating the effects of grape seed PCOs extract on visual function in healthy subjects.[60,61] In one of the studies, 100 normal volunteers with no retinal disorder received either 200 mg/day of PCOs or placebo for 5 or 6 weeks. The group receiving PCOs demonstrated significant improvement in visual performance in dark and after-glare tests compared with the placebo group. PCO extracts were also shown to be of benefit in treating retinopathies, especially diabetic retinopathy. In one study, 40 patients with diabetes, atherosclerosis, and other vascular diseases involving the retina were randomly treated with placebo or PCO extract (50 mg 3 times daily for 2 months). The results demonstrated a beneficial effect of PCOs on the progression of retinopathy. In patients without any treatment (placebo group), the retinopathy progressively worsened during the trial, and

the visual acuity significantly decreased. In contrast, the PCO-treated patients showed no deterioration of retinal function, and a significant recovery of visual acuity was also obtained. Fluorangiography showed an improvement of retinal vascularization and reduced endothelial permeability and leakage in the PCO group, but not in the placebo-treated patients. Ophthalmoscopy and electroretinography also confirmed the beneficial effects of PCOs. In addition to the PCOs exerting free radical scavenging, anti-inflammatory, and capillary protective activities, it was suggested that PCOs might bind to the blood vessel wall proteins and mucopolysaccharides and produce a capillary "sealing" effect, leading to reductions in capillary permeability and edema formation.[62]

DOSAGE

As antioxidant support, a daily dose of 50 to 100 mg of either the grape seed or pine bark extract is suitable. For comparison, it is now estimated that the average daily intake of total flavonoids in the United States is about 25 mg. An intake greater than 30 mg offers a significant reduction in risk for cardiovascular mortality.[38]

When PCO extracts are being used for therapeutic purposes, the daily dosage should be increased to 150 to 300 mg/day.

TOXICITY

PCO extracts are without known side effects.

DRUG INTERACTIONS

There are no documented drug interactions for the procyanidins.

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CHAPTER 118

Pygeum africanum (Bitter Almond)

Michael T. Murray, ND

Pygeum africanum (family: Rosaceae)
Synonym: *Prunus africanum*
Common names: bitter almond, red stinkwood

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GENERAL DESCRIPTION

Pygeum africanum is an evergreen tree native to Africa that can grow to a height of 120 to 150 ft. It has pendulous branches with thick, oblong, leather-like, mat-colored leaves and creamy white flowers. The fruit (drupe) resembles a cherry when ripe. The dark brown to gray bark of the trunk is the part used for medicinal purposes.

CHEMICAL COMPOSITION

The major active components of the bark are as follows:

- Lipid-soluble pentacyclic triterpenes
- Sterolic triterpenes
- Fatty acids
- Esters of ferulic acid (Figure 118-1)

The pentacyclic triterpenic components are ursolic acid (Figure 118-2), oleanolic acid, crataegolic acid, and their derivatives. The sterolic fraction is composed mainly of β-sitosterol and β-sitosterone (Figure 118-3). The fatty acids range from C12 to C24 and the important ferulic acid esters are those bound to *n*-tetracosanol and *n*-docosanol.[1-4]

HISTORY AND FOLK USE

The powdered bark of *P. africanum* was used by the natives of tropical Africa as a treatment for urinary disorders. It was often given with palm oil or milk. Since about 1970, the bark has been entirely wild-collected, with the major exporters being Cameroon, Madagascar, Equatorial Guinea, and Kenya. Two companies, Groupe Fournier of France and Indena of Italy, produce 86% of the world's bark extract, both for their own products and for the free market. Worldwide exports of dried bark in 2000 were estimated at 1350 to 1525 metric tons per year, down from its peak of 3225 tons in 1997. Bark extracts (6370 to 7225 kg/year) are worth an estimated $4.36 million U.S. dollars per year. However, wild collection of the bark is no longer sustainable. Since 1995, *P. africanum* has been declared an endangered species. Alternatives to wild collection to meet future market demand include conservation practices, enrichment plantings, and small- and large-scale production. Currently, the species is at the beginning of a transition from an exclusively wild-collected species to that of a cultivated medicinal tree.[5]

PHARMACOLOGY

Pharmacologic screening of various extracts prepared with solvents of differing degrees of polarity indicated that the highest activity was found in lipophilic extracts.[1] This finding is interesting in light of pygeum's historical administration in lipophilic media (palm oil or milk). Virtually all of the pharmacologic research featured a pygeum extract standardized to contain 14% triterpenes, including β-sitosterol and 0.5% *n*-docosanol. This extract was extensively studied in both experimental animal studies and clinical trials with humans.

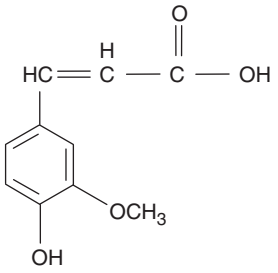


FIGURE 118-1 Ferulic acid.

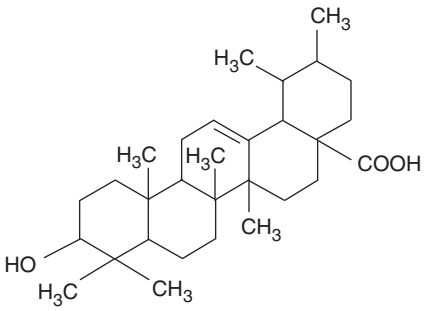


FIGURE 118-2 Ursolic acid.

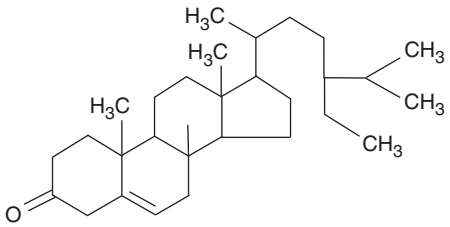


FIGURE 118-3 Beta-sitosterone.

The primary target organ for pygeum's effects in men is the prostate. The three major active components of pygeum appear to exert different, yet complementary, effects in benign prostatic hyperplasia (BPH). In addition, pygeum was shown to enhance the secretions of the prostate and bulbourethral glands, in terms of both quantity and quality.

Ferulic Acid Esters

The esters of ferulic acid act primarily on the endocrine system. Studies in animals showed docosanol reduced levels of luteinizing hormone and testosterone while raising adrenal steroid secretion of both adrenal androgens and corticosteroids.[6,7] Docosanol also significantly lowers serum prolactin levels. This reduction of prolactin is quite significant, because prolactin increases both the uptake of testosterone and the synthesis of dihydrotestosterone within the prostate. The accumulation of testosterone within the prostate and its subsequent conversion to the more potent dihydrotestosterone is thought to be the major contributing factor to the hyperplasia of the prostatic cells observed in BPH.[8] Although traces of docosanol are present in pygeum, the esterification with ferulic acid results in greater bioavailability and activity.[2,4,9]

Ferulic acid esters and the sterol fraction of pygeum exert cholesterol-lowering action systemically as well as within the prostate.[9] Breakdown products of cholesterol were shown to accumulate in prostate tissue affected with either BPH or cancer.[8] These metabolites of cholesterol initiate degeneration of prostatic cells, which can promote prostatic enlargement. Drugs that lower cholesterol levels were shown to have a favorable influence on BPH, preventing the accumulation of cholesterol in prostatic cells and limiting subsequent formation of damaging cholesterol metabolites. The lowering of intraprostatic cholesterol content is an important aspect of the pharmacology of pygeum.

The sterolic fraction is also endowed with competitive action against testosterone accumulation within the prostate. In addition, the sterols of pygeum were also shown to reduce inflammation by preventing the intraprostatic formation of inflammatory prostaglandins.[9,10]

Other Components

Other components of pygeum are also important. For example, the pentacyclic triterpenes exhibit anti-inflammatory effects within the prostatic epithelium and may be responsible for stimulation of the secretory cells of the prostate, seminal vesicles, and bulbourethral glands.[9-11] Finally, the fatty acid components are similar to those of *Serenoa repens* (see Chapter 122) and may exert similar effects as well as improve the oral bioavailability of other components of the lipophilic extract.

CLINICAL APPLICATIONS

Prostate Disorders

The pharmacologic actions of the standardized pygeum extract support its use in prostate disorders, BPH in particular. Adding further support are the results of numerous clinical trials in more than 600 patients.[12-34] These studies consistently demonstrated that pygeum effectively reduces the symptoms and clinical signs of BPH, especially in early cases. However, it must be pointed out that improvement is largely symptomatic, because the reductions in size of the prostate and in residual urine content of the bladder are modest. The results of the clinical trials on pygeum are given in Table 118-1. A discussion of some of the most important aspects of these studies follows.

One of the major findings in evaluating the effectiveness of pygeum in BPH was the high rate of response to placebo. This was well-demonstrated in one of the larger double-blind studies.[30] As in other double-blind studies, pygeum extract was shown to be statistically superior to placebo in reducing the major symptoms of BPH (nocturnal frequency, difficulty in starting micturition, and incomplete emptying of the bladder). However, there was a high percentage of responses to the placebo (Table 118-2). It seems that simply taking a capsule provides relief to many sufferers.

Another study highlighted the importance of double-blind studies that featured both objective and subjective findings. In the study, both patients and physicians rated the placebo and pygeum extract to be effective in improving subjective symptoms, which were daytime frequency, nocturia, weak stream, after-dribbling, hesitation, and interruption of flow.[29] However, urodynamic variables (flow, frequency, and histogram) clearly demonstrated the superiority of pygeum over placebo.

One of the shortcomings of some of the clinical research on pygeum in BPH was the lack, in many of the studies, of objective measures, such as urine flow rate (milliliters per second), residual urine content, and prostate size. Studies that used objective measurements showed some good results. For example, in one open trial, 30 patients with BPH who were given 100 mg/day of the pygeum extract for 75 days demonstrated significant improvements

TABLE 118-1 **Results of the Most Significant Open and Double-Blind Studies of the Last 20 Years on Outpatients Using *Pygeum africanum* for 1 to 3 Months**

STUDY	DOSAGE (MG/DAY)	NO. OF DAYS	NO. OF PATIENTS IN STUDY	PATIENTS SHOWING REDUCTION (%)				
				DYSURIA	NOCTURIA	FREQUENCY	RESIDUAL URINE	PROSTATE VOLUME
Open Trials								
Guillemin[12]	100	30	25	80	80	80	80	NC
Lange and Muret[13]	100	30	25	72	NC	72	NC	NC
Wemeau et al[14]	100	45	27	60	NC	71	NC	NC
Viollet[15]	75	60	20	64	NC	64	NC	NC
Lhez and Leguevague[16]	75	90	52	69	NC	NC	NC	NC
Thomas and Rouffilange[17]	75	50	33	60	57	57	NC	–
Huet[18]	50	30	55	85	85	85	NC	20
Rometti[19]	100	50	25	72	72	72	NC	25
Gallizia and Gallizia[20]	100	60	19	90	85	70	20	NC
Durval[21]	100	90	23	72	72	72	72	NC
Pansadoro and Benincasa[22]	75	90	35	94	94	94	94	–
Double-Blinded Trials								
Maver[24]	100	60	60	77	70	57	23	–
Bongi[25]	75	60	50	88	88	88	88	88
Doremieux et al[26]	100	60	77	85	NC	NC	NC	NC
Del Valio[27]	100	60	30	–	–	48	–	–
Colpi and Farina[28]	150	45	47	–	70	–	76	NC
Donkervoort et al[29]	150	90	20	80	80	80	NC	NC
Dufour et al[30]	100	45	120	–	78	45	65	NC
Legromandi et al[31]	100	45	104	89	89	89	NC	NC
Ranno et al[32]	200	60	39	75	75	75	NC	NC
Frasseto et al[33]	200	60	20	–	–	–	–	–
Bassi et al[34]	200	60	40	70	70	70	70	70

–, Not measured; NC, no change.

TABLE 118-2 **Patients Showing Response to Placebo and Pygeum**

SYMPTOM	PLACEBO GROUP	PYGEUM GROUP
Nocturia	26/52 (50%)	44/56 (78%)
Daytime frequency	16/50 (33%)	27/54 (50%)
Incomplete voiding	14/40 (35%)	21/32 (66%)
Dribbling	15/34 (44%)	13/33 (39%)
Urine flow rate	11/43 (26%)	21/38 (55%)

Data from references 12-22 and 24-34.

in objective parameters: maximum urine flow rate increased from 5.43 to 8.20 mL/s, and the residual urine volume dropped from 76 to 33 mL.[23]

Pygeum may emerge as a significant protector against prostate cancer (PCa), because pygeum extract and its components (e.g., atraric acid and *N*-butylbenzene-sulfonamide) inhibit the transactivation mediated by the ligand-activated human androgen receptor (AR). Inhibition of human AR by androgen ablation therapy and synthetic antiandrogens is the primary goal in treatment of PCa. Both in vitro and in vivo studies showed pygeum components inhibited the nuclear transport of AR and endogenous prostate-specific antigen expression and efficiently repressed the growth of both the androgen-dependent and some types of androgen-independent prostate cancer cells.[35-38] Currently used synthetic AR antagonists bind to the AR, and induce a conformational change that leads to the dissociation of key proteins in the AR, but the antagonist-bound AR is still translocated to the nucleus where it recruits core pressors to block its transcriptional activity. Pygeum components act a little differently, in that they selectively bind to the AR and inhibit the translocation to the nucleus and, in consequence, it functions as an androgen-activated transcription factor. This difference in mechanism may overcome a major shortcoming with antihormone therapy in PCa. Typically, antihormone treatment is effective only for a limited period of about 16 to 24 months, after which PCa becomes androgen independent. Different mechanisms seem to be involved in this process, but AR mutations during PCa progression render therapeutically used antiandrogens into AR agonists. In consequence, those therapeutics then become useless, and even counterproductive, because they can promote PCa progression.

Male Infertility and Impotence

Pygeum may be effective in improving fertility when diminished prostatic secretion plays a significant role in the problem. Pygeum was shown to increase prostatic secretions and improve the

composition of seminal fluid.[39-41] Specifically, pygeum administration to men with decreased prostatic secretion led to higher levels of total seminal fluid plus increases in alkaline phosphatase and protein levels. Pygeum appears to be most effective in cases in which the level of alkaline phosphatase activity is reduced (i.e., less than 400 IU/cm^3), and there is no evidence of inflammation or infection (i.e., absence of white blood cells and immunoglobulin-A [IgA]). The lack of IgA in the semen is a good predictor of clinical success. In one study, the patients with no IgA in the semen demonstrated an alkaline phosphatase increase from 265 to 485 IU/cm^3.[39] In contrast, subjects whose semen contained IgA showed only a modest increase, from 213 to 281 IU/cm^3.

Pygeum extract also showed an ability to improve the capacity to achieve an erection in patients with BPH or prostatitis, as determined by nocturnal penile tumescence in a double-blind clinical trial.[42] BPH and prostatitis are often associated with erectile dysfunction and other sexual disturbances. Presumably by improving the underlying condition, pygeum can improve sexual function.

Pygeum Versus Serenoa

The standardized liposterolic extract of *Serenoa repens* is another popular botanical treatment for BPH (see Chapter 122). In a double-blind study that compared pygeum extract with extract of serenoa, the serenoa extract produced a greater reduction of symptoms and was better tolerated.[43] In addition, the improvement of objective parameters, especially urine flow rate and residual urine content, was better in the clinical studies of serenoa. However, there may be circumstances in which pygeum is more effective than serenoa. For example, serenoa has not been shown to have the effects on prostate secretion that pygeum has, and the anticancer effects of pygeum may be more significant. Although the two extracts have somewhat overlapping mechanisms of actions, they can be used in combination.

DOSAGE

The dosage of the lipophilic extract of *P. africanum* standardized to contain 14% triterpenes including β-sitosterol and 0.5% *n*-docosanol is 100 to 200 mg/day. Typically, the dosage has been divided for twice a day administration; however, results were similar in a double-blind study with 100 mg given once a day and 50 mg twice a day, indicating that taking pygeum once a day is equivalent to using divided doses.[44] The crude herb is not used.

TOXICOLOGY

Tests for acute and long-term toxicity in the rat and mouse showed that the standardized extract of *P. africanum* bark is nontoxic. Raising the dosage from 1 to 6 g/kg in the mouse and from 1 to 8 g/kg in the rat caused no deaths within 48 hours. In long-term toxicity studies, giving the animals from 60 to 600 mg/kg for 11 months did not produce any negative effects.

Pygeum extract also demonstrated no significant toxicity in human clinical trials. The most common side effect is gastrointestinal irritation, resulting in symptoms ranging from nausea to severe stomach pains; however, the presence of these side effects rarely leads to discontinuation of therapy.

DRUG INTERACTIONS

There are no documented drug interactions for *P. africanum*.

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CHAPTER 119

Ruscus aculeatus (Butcher's Broom)

Kathy Abascal, BS, JD, RH(AHG), and Eric L. Yarnell, ND, RH(AHG)

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Ruscus aculeatus (family: Liliaceae)
Common names: butcher's broom, box holly, knee holly, kneeholy, kneeholm, Jew's myrtle, sweet broom, pettigree, Maeusedornwurzelstock (German)

GENERAL DESCRIPTION

Ruscus aculeatus (butcher's broom) is an evergreen shrub native to Mediterranean Europe and Africa.[1] It has rigid leaves that terminate in a single sharp spine. Its berries remain attached to the plant through the winter. The root, the part used medicinally, is thick, typically 2 to 4 inches long, with many woody rootlets growing on its lower surface.

CHEMICAL COMPOSITION

The primary active ingredients of butcher's broom are the steroidal saponins ruscogenin and neoruscogenin (up to 6%). The plant also contains other steroidal sapogenins and saponins (such as ruscin and ruscoside), fatty acids, sterols, flavonoids, coumarins, sparteine, tyramine, and glycolic acid[1-5] (see Figure 119-1).

HISTORY AND FOLK USE

In ancient Greece, butcher's broom was used as a laxative and to treat kidney stones.[6] In Europe, a wine decoction of the root was used as a diuretic to treat urinary obstructions, kidney stones, and gravel. It was also used to regulate menses, ameliorate jaundice, and treat headaches. In South America, the roasted root was made into a beverage for prostate tumors.[7]

PHARMACOLOGY

Anticancer Effect

Butcher's broom saponins have a cytostatic effect on leukemia HL-60 cells in vitro.[8]

Antielastase Effect

Ruscinogens isolated from butcher's broom have a remarkable antielastase effect in vitro.[9]

Antihypoxic Effect

Hypoxia-induced activation of endothelial cells may be a cause of venous disease. A proprietary extract of butcher's broom known as Cyclo 3 Fort dose-dependently protected human endothelial cells from induced hypoxia in vitro.[9]

Antiinflammatory Effect

Butcher's broom extract and its isolated steroidal saponins were antiinflammatory in several animal models.[10] Injected intravenously, it inhibits the permeability increasing effects of bradykinin, leukotriene B4, and histamine in hamster cheek pouch preparations.[11]

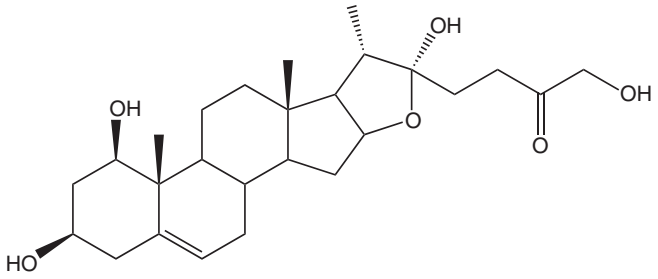


FIGURE 119-1 Ruscogenin.

Antimicrobial Effect

Butcher's broom showed a very low activity against *Candida albicans.*[12]

Fibrinolytic Effect

Thrombosis in chronic venous insufficiency (CVI) is associated with reduced levels of tissue plasminogen activator in varicose veins. In a small study, 20 patients scheduled for vein stripping surgery took butcher's broom (150 mg) and methyl hesperidin chalcone (150 mg) or placebo three times daily for 14 days before surgery.[13] Segments of the great saphenous vein removed from patients in the active group had enhanced levels of tissue plasminogen activator and enhanced fibrinolytic activity compared with placebo.

Lymphatic Flow Effect

Butcher's broom dose dependently enhanced the duration and flow intensity of the lymphatic vessels in dogs.[14] This effect did not change when the calcium channel antagonist nifedipine was injected, indicating that butcher's broom's lymphatic effect does not involve the opening of calcium channels but appears to act directly on peripheral lymphatics.

Vasoconstrictive Effect

Topical administration of butcher's broom extract in a hamster cheek preparation dose dependently inhibited histamine-induced increases in permeability.[15] Research suggested that butcher's broom's vasoconstrictive effect is mediated by calcium and α-1 adrenergic receptors. Heat increases, and cold decreases, butcher's broom's ability to increase the release of norepinephrine from the adrenoreceptors.[15]

CLINICAL APPLICATIONS

There are few clinical studies on the effect of butcher's broom alone. Instead, most of the clinical studies investigated a proprietary combination formula known as Cyclo 3 Fort by Pierre Fabre Medicament of Paris, France, or Phlebodril by Pierre Fabre Pharma GmbH of Freiburg, Germany. These formulas combine butcher's broom with trimethylhesperidin chalcone (a flavonoid precursor) and ascorbic acid. Butcher's broom has action independent of the other compounds in the formula, and some studies indicated that butcher's broom used alone may have a stronger effect. However, other studies indicated that the combination may have a synergistic effect. All discussions of butcher's broom trials in the following therefore include the possibility that it was not butcher's broom by itself that was active.

Butcher's broom is also paired with *Melilotus* spp. (sweet clover) in some topical preparations. There are no studies indicating whether butcher's broom alone would achieve the same results.

Chronic Venous Insufficiency

Butcher's broom is most commonly used to alleviate the symptoms of CVI, including ankle edema, itching, tension, and cramping of the legs. Both animal and clinical studies support its effectiveness in CVI, and the German Commission E approved butcher's broom as an adjunct treatment for this condition.[1] A meta-analysis evaluated 20 placebo-controlled, double-blind studies and 5 randomized trials against a comparator drug along with 6 single-arm studies without a placebo. The review included information on 10,246 subjects. Although data quality varied, Cyclo 3 Fort significantly reduced CVI symptoms compared with placebo.[15a]

Nine of these studies are summarized in Table 119-1.[16-24] All but two were randomized double-blind trials. In one large multicenter trial, 81.6% of treating physicians rated its efficacy as excellent, and the remaining physicians rated it as good.[20] Butcher's broom acts most strongly when circulation is impaired, but some researchers caution that it is less effective when the disease has compromised venous wall receptor activity.[18]

Edema and Varicosities

Butcher's broom shows promise as a treatment for a wide variety of edemas and circulatory disturbances of the venous system. The results of these clinical trials are summarized in Table 119-2.[25-34] These trials were also on combination extracts with butcher's broom as a major component. Many of the studies are small, and some are poorly designed, but the overall picture supports the ability of butcher's broom to reduce swelling and discomfort associated with primary and secondary edema. It has positive effects in pregnancy-related venous insufficiency, varicosities, lymphedema, symptoms of swelling of ankles and breast tenderness in premenstrual syndrome (PMS), edema secondary to calcium channel antagonist therapy of hypertension, and swelling secondary to soft tissue injury.

Hemorrhoids

The German Commission E approved butcher's broom as a treatment for hemorrhoids.[1] In an open-label multicenter study of 124 patients with hemorrhoids, 69% of patients and 75% of the treating physicians rated the butcher's broom combination extract Cyclo 3 Fort as having good or excellent efficacy.[35] Ninety-two percent of physicians rated the treatment as safe and well tolerated. Significant positive effects were observed after 7 days of treatment. Although controlled trials are warranted, butcher's broom may be a useful treatment for patients with hemorrhoids.

Diabetic Retinopathy

Diabetic retinopathy can abruptly cause severe deterioration of vision, and it is estimated that the incidence of retinopathy may be as high as 80% in patients with longstanding, poorly controlled diabetes. In a study of 60 patients with non–insulin-dependent diabetes, butcher's broom compared favorably with troxerutin.[34] Butcher's broom produced a 23% regression of negative changes in the fundus of the eye with no sign of progression. Troxerutin produced a somewhat larger regression (27.8%), but also had a greater (5.8%) progression rate. Butcher's broom also decreased blood glucose and cholesterol levels and significantly increased high-density lipoproteins in this preliminary study.

TABLE 119-1 **Studies on Butcher's Broom in Chronic Vascular Insufficiency (CVI)**

STUDY	NO. OF PARTICIPANTS	TYPE	PRODUCT	FOCUS	RESULT	DURATION
Cappelli et al[16]	40	Double-blind, crossover placebo-controlled, prospective	2 capsules (16.5 mg ruscinogens, 75 mg hesperidin, 50 mg ascorbic acid) 3 times a day	CVI, varicosities	Itching, edema, and paresthesia improved greatly	2 mo with15-d washout and 2 mo crossover
Rudofsky[17]	141 + 20 healthy volunteers	Randomized, double-blind, multicenter	2 capsules (450 mg ruscus extract) 3 times daily for 4 wks, then 2 capsules 2 times daily for 8 wks	CVI	Continuous decrease in foot and ankle volume, decrease in leg swelling, improved venous pumping	2 wks washout followed by 12 wks treatment
Haas et al[18]	20	Placebo-controlled, double-blind	1 capsule (150 mg ruscus, 150 mg methyl hesperidin chalcone) 3 times a day	CVI stage I and II, scheduled for surgery	Significantly increased fibrinolytic activity of removed great saphenous vein	14 d
Kiesewetter et al[19]	30	Random selection, uncontrolled	3 ruscus capsules twice daily for 5 wks, then 2 capsules twice daily; amount of ruscus in capsules not stated	CVI	Reduced circumferences of lower legs and malleoli, subjective complaints; greater rheologic improvement in patients with advanced stages of CVI	5 mo
Beltramino et al[20]	80	Open-label, randomized, multicenter	2 capsules (150 mg ruscus, 150 mg hesperidin methyl chalcone, 100 mg ascorbic acid) daily: control 2 tablets of 500 mg hydroxyethyl rutoside daily	CVI (heavy, tired, swollen or painful legs)	Significant improvement in symptoms, reduction in limb circumference; physicians and patients had a more favorable opinion of ruscus than of rutoside	90 d
Le Devehat et al[21]	60 + 7 healthy volunteers	Randomized, double-blind, placebo-controlled	2 capsules (150 mg ruscus, 150 mg hesperidin methyl chalcone, 100 mg ascorbic acid) daily	CVI; blood samples drawn from foot before and after provoked venous stasis	Improved blood viscosity disturbances caused by venous stasis	4 wks
Seydewitz et al[22]	36	Randomized, double-blind, placebo-controlled	3 capsules (150 mg ruscus, 150 mg trimethyl hesperidin chalcone) daily	Stage IV varicosities with stage I or stage II CVI, scheduled for vein stripping	Increase in enzyme activity in the proximal segment of the vein, distinctly higher incidence of subjective improvement of symptoms	4 wks
Guex JJ et al[23]	917	Observational, multicenter, prospective	150 mg *Ruscus aculeatus* and 100 mg ascorbic acid	CVI (symptoms, ankle swelling)	Significant improvement in quality of life and symptoms	12 wks
Vanscheidt W, et al[24]	148 women	Multicenter, double-blind, randomized, placebo-controlled	36-37 mg butcher's broom extract twice daily	CVI	Significant, positive changes in CVI symptoms	12 wks

Premenstrual Syndrome

Butcher's broom significantly reduced symptoms of breast tenderness in women with diagnosed PMS in a randomized, placebo-controlled, double-blind study of 40 women with PMS of an average duration of 67 months.[32] The amount of butcher's broom administered for 90 days was not stated. Eighty percent of the women in the active group reported a complete resolution of PMS symptoms of mastalgia and breast tension. Unexpectedly, butcher's broom also had a dramatic effect on some of the psychological symptoms associated with PMS (e.g., complete resolution in 85% of the subjects of symptoms such as irritableness, "hair-trigger temper," "temporary alienation"). In vitro research indicated that butcher's broom acts more efficiently in the presence of progesterone; butcher's broom may be most effective during the luteal phase of a woman's menstrual cycle.

TABLE 119-2 **Clinical Studies on Butcher's Broom in Edema and Varicosities**

STUDY	NO. OF PARTICIPANTS	TYPE	PRODUCT	FOCUS	RESULT	LENGTH
Berg[25]	18	Placebo-controlled	Melilot and ruscus cream (4 to 6 g cream/d)	Effect of cream on size of femoral veins in healthy volunteers	Change in size of femoral vein	1 d
Baudet et al [26]	20	Uncontrolled	2 capsules of ruscus extract/day (amount not stated) from wk 21 to 24 of pregnancy	Pregnancy-related symptoms of venolymphatic insufficiency	Improved symptoms based on subjective criteria; "absolute harmlessness" to infant	Women monitored from early pregnancy; infants studied before and after birth
Berg[25]	9	Placebo-controlled	Compression stocking, kinesitherapy, and melilot and ruscus cream (4 to 6 g cream/d)	Pregnant women with painful pregnancy-related varicosity of one limb	Statistically significant reduction in size of femoral vein and pain	Treatment beginning in second trimester
Bohmer[27]	48	Placebo-controlled	4 g ruscus cream (1.6 g ruscus and 1.6 g melilot/100 g) 3 times daily	Sports injuries, patients with sprain or contusions of lower limb or ankle	Increased muscle strength, reduced swelling, decreased temperature, and resolved pain more quickly	14 d
Cluzan et al[28]	57	Placebo-controlled, double-blind	3 capsules (150 mg ruscus, 150 mg hesperidin methylchalcone, 100 mg ascorbic acid) 3 daily plus physiotherapy	Lymphedema after mastectomy	Reduced edema by second month, positive subjective improvement in symptoms	90 d
Cossio et al[29]	12	Uncontrolled	Drinkable ampules; 1st week: 180 mg ruscus and 900 mg hesperidin methyl chalcone per day; wks 2-8: 120 mg ruscus and 600 mg hesperidin methyl chalcone per day	Lymphedema of extremities	Significant improvement in symptoms, reduction of edema in 81% of participants	2 mo
Jager et al[30]	12	Open, uncontrolled	3 capsules (150 mg ruscus, 150 mg hesperidin methyl chalcone, 100 mg ascorbic acid) per day	Primary varicosity of greater saphenous vein	Significant changes in some venous parameters	7 ± 1 d
Weindorf et al[31]	50	Double-blind, placebo-controlled	450 mg ruscus, 450 mg hesperidin, 300 mg ascorbic acid daily	Trunk or branch varicose veins	Venous capacity and improved at rest; expelled blood volume during exercise improved	2 wks
Lagrue et al[32]	11	Open, uncontrolled	3 capsules (150 mg ruscus, 150 mg hesperidin methyl chalcone, 100 mg ascorbic acid) daily	Edema secondary to calcium antagonist treatment of hypertension	4/9 showed complete improvement; 3/9 showed partial improvement; 2/9 showed no change in edema	6-8 wks
Le Devehat et al[33]	25 + 20 healthy controls	Double-blind, placebo-controlled	2 capsules (150 mg ruscus, 150 mg hesperidin methyl chalcone, 100 mg ascorbic acid) daily	Venous insufficiency characterized by varicose veins; blood samples drawn before and after provoked venous stasis	Significant improvement in several microrheologic factors of blood viscosity	Not found
Monteil-Seurin and Ladure[34]	40	Randomized, double-blind, placebo-controlled	2 capsules (150 mg ruscus, 150 mg hesperidin methyl chalcone, 100 mg ascorbic acid) daily	Premenstrual syndrome symptoms for at least 60 months (breast tension, pelvic heaviness, "menstrual psychopathic disorder," ankle edema)	Significantly reduced breast tension, pelvic heaviness, and menstrual "psychopathic disorder"	90 d

Soft Tissue Injuries

In a small study, butcher's broom applied topically reduced swelling and pain caused by soft tissue sports injuries.[25] Several in vitro studies showed that butcher's broom's action is enhanced by heat, suggesting that it may be advantageous to apply heat to the site of the injury when using the herb.

DOSAGE

The dosage of butcher's broom for therapeutic use should be based on the ruscogenin content in the range of 16.5 to 33 mg of ruscogenins two to three times daily. Standardized extracts are preferred for therapeutic use because they allow for more accurate dosages. Recommendations for other forms of butcher's broom are as follows:

Dried rootstalk in capsules, tablets or tea: 500 to 1000 mg three times a day

Tincture (1:5): 2 to 4 mL three times a day

Fluid extract (1:1): 1 to 2 mL three times a day

TOXICOLOGY

Butcher's broom is generally considered very safe. It occasionally causes gastrointestinal distress, and in rare instances, causes lymphatic colitis.[1,37,38] Thus, butcher's broom should probably not be combined with nonsteroidal anti-inflammatory drugs or other drugs linked with lymphatic colitis, and use should be discontinued if negative gastrointestinal symptoms are severe or persist.[37] One author cautioned against the use of butcher's broom in pregnancy based on a lack of proof of safety.[3] Although not definitive, preliminary animal and clinical studies cited previously indicated that butcher's broom does not have negative effects when used during pregnancy.

DRUG INTERACTIONS

In an in vitro study, adenosine, cocaine, phentolamine, prazosin, and verapamil reduced butcher's broom's vasoconstrictive effect.[39] Acetylcholine and rauwolscine potentiated its vasoconstrictive action. No studies have been conducted to determine whether butcher's broom interferes with or affects the action of the aforementioned drugs. One author cautioned against the use of butcher's broom for patients on α-adrenergic antagonistic therapy for benign prostatic hyperplasia or hypertension, or for patients taking monoamine oxidase inhibiting drugs.[3] In vitro, animal, and clinical studies overall did not provide support for this view.

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CHAPTER 120

SAMe (S-Adenosylmethionine)

Michael T. Murray, ND

CHAPTER CONTENTS

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INTRODUCTION

S-Adenosylmethionine (SAMe) is an important physiologic agent formed in the body through combination of the essential amino acid methionine with adenosyl triphosphate (ATP) (Figure 120-1). SAMe was discovered in Italy in 1952. Not surprisingly, most of the research on SAMe has been conducted in the country of its discovery.

Because SAMe is manufactured from methionine, one would think that dietary sources of methionine would provide the same benefits as SAMe. However, high doses of methionine have not been shown to raise levels of SAMe, nor do they provide the same pharmacologic activity as SAMe. High doses of methionine are associated with some degree of toxicity.[1]

Normally the body manufactures all the SAMe it needs from the amino acid methionine. However, a deficiency of methionine, vitamin B_{12}, or folic acid can result in decreased SAMe synthesis. In addition, tissue levels of SAMe are typically low in the elderly and in patients with osteoarthritis, depression, and various liver disorders.

PHARMACOLOGY

SAMe is involved in more than 40 biochemical reactions in the body. It functions closely with folic acid and vitamin B_{12} in "methylation" reactions. Methylation is the process of adding a single carbon unit (a methyl group) to another molecule. SAMe is many times more effective in transferring methyl groups than are other methyl donors. Methylation reactions are critical in the manufacture of many body components, especially brain chemicals, as well as in detoxification reactions.

SAMe is also required in the manufacture of all sulfur-containing compounds in the human body, including glutathione (discussed later) and various sulfur-containing cartilage components.

The beneficial effects of SAMe supplementation are far-reaching owing to this agent's central role in so many metabolic processes.

Available Forms

SAMe has been available commercially in Europe since 1975 and in the United States since 1999. The commercial form of SAMe is a stabilized salt produced under U.S. patents no. 3,954,726 (1976) and no. 4,057,686 (1977).

CLINICAL INDICATIONS

The five principal uses of SAMe are for depression, osteoarthritis, fibromyalgia, liver disorders, and migraine headaches.

Depression

SAMe is necessary in the manufacture of important brain compounds, such as neurotransmitters and phospholipids like phosphatidylcholine and phosphatidylserine. Adding SAMe to the diet of depressed patients raises levels of serotonin, dopamine, and phosphatidylserine and improves binding of neurotransmitters to receptor

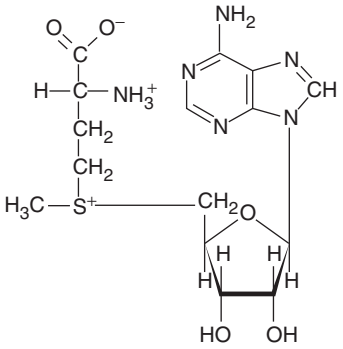


FIGURE 120-1 S-Adenosylmethionine (SAMe).

sites, resulting in increased serotonin and dopamine activity and better brain-cell membrane fluidity, leading to significant clinical improvement.[2-4]

The antidepressant effects of folic acid (see Chapter 142) are mild compared with the effects noted in clinical trials of SAMe. On the basis of results from a number of clinical studies, it appears that SAMe is perhaps the most effective natural antidepressant (although a strong argument could be made for the extract of St. John's wort standardized to contain 0.3% hypericin).[5-11]

Although most of the early studies used injectable SAMe, the later studies have used an oral dose of 400 mg four times daily (1600 mg total) and have demonstrated that SAMe is just as effective given orally as when it is given intravenously.[4,10-15] That is not surprising, because there are no significant differences in the pharmacokinetic parameters of SAMe 1000 mg administered orally or intravenously.[16]

Several studies have compared SAMe with tricyclic antidepressants. Before the rise of selective serotonin reuptake inhibitors (SSRIs), tricyclics were the mainstay pharmaceutical treatment for depression. A 2002 review concluded that "at doses of 200 to 1600 mg/day, SAMe is superior to placebo and is as effective as tricyclic antidepressants in alleviating depression, although some individuals may require higher doses."[10] The reviewers found six of eight placebo-controlled studies, featuring anywhere from 40 to 100 participants, demonstrating that SAMe was superior to placebo; moreover, six of eight comparison studies showed that SAMe was just as effective as tricyclic antidepressants. These studies have shown that SAMe is better tolerated than the tricyclics and has a quicker onset of antidepressant action.[11]

In one study comparing SAMe with desipramine, in addition to determining the clinical response, the blood level of SAMe was determined in both groups. At the end of the 4-week trial, 62% of the patients treated with SAMe and 50% of those treated with desipramine had significantly improved. Regardless of the type of treatment, patients with a 50% decrease in scores on the Hamilton Depression Scale showed a significant rise in plasma SAMe concentration. These results suggest that one of the ways in which tricyclic antidepressant agents exert their antidepressant effects is by raising SAMe levels.[17]

In two separate double-blind studies, SAMe was given orally (1600 mg daily) or intramuscularly (400 mg daily) and compared with 150 mg of imipramine given orally daily. In both studies, the results of SAMe and imipramine treatment did not differ significantly for any efficacy measure. However, significantly fewer adverse events were observed in the patients treated with SAMe. The researchers concluded that the antidepressant efficacy of 1600 mg SAMe orally and 400 mg SAMe intramuscularly is comparable with that of 150 mg of imipramine but that SAMe is significantly better tolerated.[18]

In a double-blind, randomized clinical trial lasting 6 weeks, 73 depressed patients who were unresponsive to SSRI medications alone were given 800 mg of SAMe or placebo twice daily along with their SSRIs.[19] The response and remission rates according to the Hamilton Depression Scale were higher for patients treated with adjunctive SAMe (36.1% and 25.8%, respectively) than adjunctive placebo (17.6% versus 11.7%, respectively). These results indicate that SAMe can be used safely with SSRIs and may have a synergistic effect.

In a study on 20 HIV-seropositive individuals with depression, SAMe as a sole antidepressant medication showed significant effect. There was a significant reduction in acute depressive symptomatology, reaching the defined clinical treatment response threshold of a greater than 50% reduction in symptom scores. The researchers also noted that SAMe had a rapid effect as early as after only 1 week, with progressive decreases in symptom scores throughout the study.[20]

SAMe has also been shown to produce significant effects in other conditions associated with depression, as during the postpartum period and in drug rehabilitation. SAMe's benefits in these conditions are probably due to a combination of its effects on brain chemistry and liver function (discussed later). In the study in postpartum depression, the administration of SAMe (1600 mg/day) was associated with significantly better mood scores compared with placebo.[21] In another study, SAMe (1200 mg/day) was shown to significantly reduce psychological distress (chiefly anxiety and depression) in the detoxification and rehabilitation of opiate abusers.[22]

SAMe may also be helpful in managing the symptomatology of schizophrenia. In one double-blind study, 18 patients with chronic schizophrenia were randomly assigned to receive either SAMe (800 mg) or placebo for 8 weeks. Results indicated some reduction in aggressive behavior and improved quality of life following SAMe administration. Female patients showed improvement of depressive symptoms, whereas male patients showed no change compared with placebo. Blood dopamine levels increased in women, but decreased in men receiving SAMe. Clinical improvement did not correlate with serum SAMe levels. Two patients receiving SAMe exhibited some exacerbation of irritability; therefore, it should be used with caution in these patients.[23]

Detailed clinical evaluations using electroencephalography, event-related potentials, and low-resolution brain electromagnetic tomography have clearly indicated a central nervous system antidepressant action of SAMe.[18]

Osteoarthritis

SAMe has also demonstrated impressive results in the treatment of osteoarthritis.[24-26] A deficiency of SAMe in the joint tissue, just like a deficiency of glucosamine, leads to loss of the gel-like nature and shock-absorbing qualities of cartilage. As a result, osteoarthritis can develop.

In vitro studies have shown that SAMe exerts a number of effects that appear to be highly relevant in the treatment of osteoarthritis. First, the agent has been shown to be very important in the manufacture of cartilage components.[27] This effect has been demonstrated very well in humans. In one double-blind study conducted in Germany, the 14 patients with osteoarthritis of the hands who were given SAMe showed greater cartilage formation on magnetic resonance imaging.[28] These results indicate that SAMe is capable of improving the structure

and function of cartilage in joints affected by osteoarthritis. Second, SAMe has shown some mild pain-relieving and antiinflammatory effects in animal studies.[1] All of these effects combine to produce exceptional clinical benefits.

In double-blind trials, SAMe has demonstrated similar reductions in pain scores and clinical symptoms to those produced by nonsteroidal antiinflammatory drugs (NSAIDs) like ibuprofen, indomethacin, naproxen, nabumetone, celecoxib, and piroxicam. In one double-blind study, SAMe was compared with ibuprofen.[29] The 36 subjects with osteoarthritis of the knee, hip, and/or spine received a daily oral dose of 1200 mg of SAMe or 1200 mg of ibuprofen for 4 weeks. Morning stiffness, pain at rest, pain on motion, crepitation (crackling noise upon movement of a joint), swelling, and limitation of motion of the affected joints were assessed before and after treatment. The total score obtained by evaluating all the individual clinical parameters improved to the same extent in patients treated with SAMe and in those treated with ibuprofen. In two other studies, SAMe was actually shown to produce slightly better results.[30,31]

SAMe has also been compared with naproxen (Naprosyn). In one double-blind study, 20 patients with osteoarthritis of the knee were given either SAMe or naproxen for 6 weeks.[32] During the first week, SAMe was administered at a dose of 400 mg three times daily and afterward at a dose of 400 mg twice daily, whereas the dose of naproxen during the first week was 250 mg three times daily and subsequently 250 mg twice daily. During the first 2 weeks, the patients were allowed to take the drug paracetamol as an additional analgesic if the pain was severe. The patients were examined at the beginning of the study and after 2, 4, and 6 weeks. The parameters tested were pain, crepitation, joint swelling, circumference of joint, extent of motility, and 10-meter walking time. At the end of the sixth week, no statistically significant difference between the two patient groups was found; both groups exhibited a marked improvement on all parameters.

Another double-blind study compared SAMe with both naproxen and placebo in the treatment of osteoarthritis of the hip, knee, spine, and hand. The study involved 33 rheumatologic and orthopedic medical centers and a total of 734 subjects. SAMe administered orally at a dose of 1200 mg daily was shown to exert the same analgesic (pain-relieving) activity as naproxen at a dose of 750 mg daily. However, SAMe was found to be significantly more effective than naproxen, both in terms of physicians' and patients' judgments and in terms of the number of patients with side effects. In fact, SAMe was better tolerated than placebo. A total of 10 patients in the SAMe group and 13 in the placebo group withdrew from the study because of intolerance to the drug.[33] Other double-blind studies have shown SAMe to offer pain-relieving and antiinflammatory benefits similar to those of drugs like indomethacin and piroxicam while also being generally much better tolerated than these potent NSAIDs.[34,35]

Perhaps the most meaningful study of SAMe in the treatment of osteoarthritis was a long-term multicenter open 2-year trial involving 97 patients with osteoarthritis of the knee, hip, and spine.[36] The patients received 600 mg of SAMe daily (equivalent to three tablets of 200 mg each) for the first 2 weeks and thereafter 400 mg daily (equivalent to two tablets of 200 mg each) until the end of the 24th month of treatment. Separate evaluations were made for osteoarthritis of the knee, hip, cervical spine, and dorsal-lumbar spine. The severity of the clinical symptoms (morning stiffness, pain at rest, and pain on movement) was assessed with scoring before the start of the treatment, at the end of the first and second weeks of treatment, and then monthly until the end of the 24-month period. SAMe showed good clinical effectiveness and was well tolerated. Improvement in the clinical symptoms during therapy with SAMe was already evident after the first weeks and continued to the end of treatment. Nonspecific side effects occurred in 20 patients, but in no case did therapy have to be discontinued. Most side effects disappeared during the course of therapy. Moreover, during the last 6 months of treatment, no adverse effect was recorded. Detailed laboratory tests carried out at the start and after 6, 12, 18, and 24 months of treatment showed no pathologic changes. SAMe administration also improved the depressive feelings often associated with osteoarthritis.

One study compared the efficacy and tolerability of SAMe (1200 mg/day) and nabumetone (Relafene, 1000 mg/day) in 134 patients with osteoarthritis of the knee for 8 weeks.[37] An analysis of changes in pain intensity between weeks 0 and 8 found that both SAMe and nabumetone effectively reduced pain intensity from baseline in each group and that the degree of decrease in pain intensity was not significantly different between the groups. The patients' global assessments of disease status, physician's global assessment of response to therapy, and Western Ontario and McMaster Universities Arthritis Index (WOMAC) index scores were not significantly different between the groups.

A randomized double-blind crossover study, comparing SAMe (1200 mg) with celecoxib (Celebrex 200 mg) for 16 weeks to reduce pain associated with osteoarthritis of the knee in 56 subjects showed that SAMe has a slower onset of action but is as effective as celecoxib in the management of symptoms of knee osteoarthritis.[38]

Finally, in the largest study, 20,641 patients with osteoarthritis of the knee, hip, and spine and also with osteoarthritic polyarthritis of the fingers were studied over 8 weeks.[39] The patients were given 400 mg of SAMe three times daily for the first week, 400 mg twice daily for the second week, and 200 mg twice daily from the third week onward. No additional analgesic or antiinflammatory treatment was allowed. The efficacy of SAMe was comparable with results achieved with NSAIDs. Efficacy was described as very good or good in 71% of cases, moderate in 21%, and poor in 9%; tolerance of the agent was assessed as very good or good in 87%, moderate in 8%, and poor in 5%.

What all of these studies indicate is that SAMe appears to offer significant advantages over NSAIDs. The latter drugs are associated with significant risks of toxicity, side effects, and actual promotion of the disease process in osteoarthritis, but SAMe offers similar benefits without risks or side effects.

Fibromyalgia

SAMe has been shown in four double-blind clinical studies to produce excellent benefits in patients suffering from fibromyalgia.[40-43] In two of the studies, injectable SAMe (200 mg daily) was used. During treatment, subjects demonstrated significant reductions in the number of trigger points and painful areas as well as improvements in mood.[40,41]

In one of the studies, oral SAMe (800 mg/day) was compared with a placebo for 6 weeks in 44 patients with fibromyalgia.[42] Tender-point score, muscle strength, disease activity, subjective symptoms, mood parameters, and side effects were evaluated. Patients given SAMe demonstrated improvements in clinical disease activity, pain experienced during the last week, fatigue, morning stiffness, and mood; however, the tender-point score and muscle strength did not differ in the two treatment groups. SAMe was without side effects.

In one of the studies, SAMe was compared with transcutaneous electrical nerve stimulation—a popular treatment for

fibromyalgia—in 30 patients with this disorder.[43] Patients receiving SAMe (200 mg by injection and 400 mg/day orally) experienced significantly greater clinical benefit as shown by a decreased number of tender points, diminished subjective feelings of pain and fatigue, and improved mood. Transcutaneous electrical nerve stimulation offered little benefit for most symptoms, whereas SAMe was deemed "effective in relieving the signs and symptoms of primary fibromyalgia."[43]

Liver Disorders

SAMe has been shown to be beneficial in several liver disorders, including cirrhosis, Gilbert's syndrome, and oral contraceptive–induced liver damage. Its benefits are related to its function as the major methyl donor in the liver as well as its lipotropic activity. One of the leading contributors to impaired liver function is diminished bile flow, or cholestasis. SAMe is beneficial for a variety of liver disorders because of its ability to promote bile flow and relieve cholestasis.[44,45]

One of the key functions of SAMe in the liver is the inactivation of estrogens. Clinical studies have shown that SAMe is useful in protecting the liver from damage and improving liver function in conditions associated with estrogen excess—namely, oral contraceptive use, pregnancy, and premenstrual syndrome.[46-48]

Another key indication for the use of SAMe is in the treatment of Gilbert's syndrome, a common disorder characterized by a chronically elevated serum bilirubin level (1.2 to 3.0 mg/dL). Previously considered rare, this disorder is now known to affect as many as 5% of the general population. The condition is usually without symptoms, although some patients complain of loss of appetite, malaise, and fatigue (typical symptoms of impaired liver function). SAMe at a dosage of 400 mg three times daily has resulted in a significant decrease in serum bilirubin in patients with Gilbert's syndrome.[49]

In addition to these relatively minor disturbances in liver function, SAMe offers benefits in the treatment of more severe liver disorders, including cirrhosis. Its effect in cirrhosis appears to be due to an ability to overcome the SAMe depletion characterized by the disorder. Because SAMe is involved in so many liver processes, the depletion of levels of SAMe within the liver has serious consequences. Supplementation with SAMe in patients with liver cirrhosis not only improves bile flow and clinical signs and symptoms but also promotes membrane function and increases levels of glutathione.[50-53] Glutathione assumes a critical role in detoxification as well as in the defense against a variety of injurious agents by combining directly with these toxic substances to eventually form water-soluble compounds. Because many of the toxic compounds are lipid- (fat-) soluble, conversion to water-soluble compounds results in more efficient excretion via the kidneys. When higher levels of toxic compounds are present or liver function is impaired, higher glutathione levels are required.

One of the greatest risks of chronic liver diseases such as chronic hepatitis is liver cancer. Supplementation with SAMe appears to be strongly indicated in patients with such diseases in the attempt to reduce the risk for liver cancer. Animal studies have shown a significant protective effect of supplemental SAMe against liver cancer in animals exposed to liver carcinogens.[54]

Migraine

SAMe has also been shown to be of benefit in the treatment of migraine headaches. The benefit arises gradually and long-term treatment is required for therapeutic effectiveness.[55]

DOSAGE

In general, the longer SAMe is used, the more beneficial the results. This agent is perfectly suited for long-term use because of its excellent safety profile. Although some studies have used intravenous dosages, there were no significant differences in the pharmacokinetic parameters of SAMe between single- and multiple-dose administration of a standard 1000-mg dose administered orally or intravenously. No evidence of accumulation of SAMe in plasma was found on multiple dosing. The dosage ranges for the various clinical indications are as follows:

- Depression: 400 to 1600 mg daily. Because SAMe can cause nausea and gastrointestinal disturbances in some people, it is recommended that it be started at a dosage of 200 mg twice daily for the first day, increased to 400 mg twice daily on day 3, and finally raised to the full dosage of 800 mg twice daily after 10 days if needed.
- Osteoarthritis: The dosage is best started out as above for depression. After 21 days at a dosage of 1600 mg daily, the maintenance dosage is reduced to 200 mg twice a day.
- Fibromyalgia: 200 to 400 mg two times a day.
- Liver Disorders: 200 to 400 mg two to three times a day.
- Migraine Headaches: 200 to 400 mg two times a day.

TOXICOLOGY

No significant side effects have been reported with oral SAMe other than occasional nausea and gastrointestinal disturbances. However, individuals with bipolar (manic) depression should not take SAMe unless they are under strict medical supervision, because SAMe's antidepressant activity may lead to the manic phase in these individuals; this effect is seen only in some people with bipolar depression.

INTERACTIONS AND CONTRAINDICATIONS

SAMe functions very closely with vitamin B_{12}, folic acid, vitamin B_6, and choline in methylation reactions. Because of SAMe's effects on the liver, it may enhance the elimination of various drugs from the body.[56] The clinical significance of this effect has not been fully determined.

It has been cautioned that SAMe should be avoided in patients with Parkinson's disease. Animal studies indicate that excessive methylation is associated with Parkinson's disease, and SAMe excess has caused Parkinson's disease–like effects in animal studies.[57] In addition, both animal and human studies indicate that increased methylation can cause the depletion of dopamine and block the effects of L-dopa.[53,58,59] This line of research is contradicted, however, by preliminary evidence that SAMe may improve the emotional depression and impaired mental function often associated with this disorder.[50] Nonetheless, it is recommended that patients with Parkinson's disease avoid supplementing with SAMe until more is known.

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CHAPTER 121

Sarsaparilla Species

Michael T. Murray, ND

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Smilax aristolochiifolia (family: Liliaceae)
Synonym: *Smilax medica*
Common name: Mexican sarsaparilla
Smilax chinensis (family: Liliaceae)
Common name: Chinese sarasaparilla
Smilax officinalis (family: Liliaceae)
Synonym: *Smilax regelii*
Common name: Honduras sarsaparilla

GENERAL DESCRIPTION

Sarsaparilla is a tropical American perennial plant. Its long slender root and short thick rhizomes produce a vine that trails on the ground and climbs by means of tendrils growing in pairs from the petioles of the alternate obicular-to-ovate evergreen leaves. The root is the part of the plant used for medicinal purposes.

CHEMICAL COMPOSITION

Sarsaparilla contains 1.8% to 2.4% steroid saponins, including the following:

- Sarsaponin
- Smilasaponin
- Sarsaparilloside and its aglycones, sarsapogenin (Figure 121-1), smilagenin, and pollinastanol

Other constituents are starch, resins, polyphenols (stilbenes, including resveratrol), flavonoids, and a trace of volatile oil.[1-3]

HISTORY AND FOLK USE

Smilax species are distributed widely in tropical and temperate regions throughout the world and have been used in many different cultures for the same conditions—namely gout, arthritis, fevers, digestive disorders, skin disease, and cancer.[1] From a historic perspective, sarsaparilla's medicinal use has been as a tonic and blood purifier. *Tonics* are defined as agents that "permanently exalt the energies of the body at large, without vitally affecting any one organ in particular. In short, tonics tone the whole system. A blood purifier or depurative [is] an agent that cleanses and purifies the system."[4] Sarsaparilla's reputation in this regard probably stems from its importation from the Caribbean and South America to Europe in the sixteenth century for the treatment of syphilis.[5]

Historic Use in the Treatment of Syphilis

Nicholas Monardes, a French physician, published a comprehensive account of sarsaparilla and several other "new" drugs for the treatment of syphilis in 1574. Many Europeans at the time believed that syphilis had come to Europe from the West Indies, with Columbus' sailors. Because there was a general belief that whatever disease was native to a country might be cured by the medicinal herbs grown in that region, it was only natural for sarsaparilla to become a popular remedy. Furthermore, use of the standard treatment for syphilis, mercury, often resulted in greater morbidity and mortality than the disease itself.

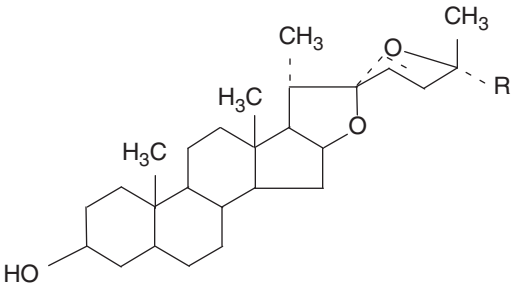


FIGURE 121-1 Sarsasapogenin.

Sarsaparilla was a welcome alternative, but despite initial excitement, Monardes' sarsaparilla cure sank in favor. This was probably because of other aspects of the cure, which involved confinement to a warm room for 30 days, followed by 40 days of abstinence from both wine and sexual intercourse.[5]

However, sarsaparilla continued to be used in the treatment of syphilis. During military operations in Portugal in 1812, a British inspector general of hospitals noted that the Portuguese soldiers suffering from syphilis who used sarsaparilla recovered much faster and more completely than their British counterparts, who were treated with mercury.[5]

Sarsaparilla was also used by the Chinese in the treatment of syphilis. Clinical observations in China show that sarsaparilla was effective, according to blood tests, in about 90% of acute cases and 50% of chronic cases.[1,6]

Although sarsaparilla was clearly more beneficial than mercury in the treatment of syphilis, it was mercury that established itself as the standard treatment for more than 4½ centuries. It has been stated that "the use of mercury in the treatment of syphilis may have been the most colossal hoax ever perpetrated" in the history of medicine.[5] Mercury represented a new kind of medicine, one formulated and prepared in a laboratory using the new techniques of chemistry. It helped prepare the way for the future use of drugs rather than herbal medicines.

PHARMACOLOGY

Various steroidal saponins, polyphenols, and flavonoids from *Smilax* species have shown antiinflammatory and cytotoxic effects against several tumor cell lines.[7-10] Yet, sarsaparilla's mechanism of action is largely unknown. Clinically, it has been shown to be effective in the treatment of psoriasis.[1,11,12] This evidence points to a possible effect on the binding of cholesterol and bacterial toxins in the intestines. Sarsaparilla has also demonstrated hepatoprotective effects[13] and an ability to protect against lead-induced oxidative stress in an animal model.[14]

Endotoxin Binding

Evidence seems to support sarsaparilla as an endotoxin binder. Endotoxins are cell wall constituents of bacteria absorbed from the gut. Normally, the liver plays a vital role by filtering these and other gut-derived compounds before they reach the general circulation. If the amount of endotoxin absorbed is excessive or the liver is not functioning adequately, it can become overwhelmed, and endotoxins then spill into the blood.

If endotoxins are allowed to circulate, activation of the alternate complement system occurs. This system plays a critical role in aggravating inflammatory processes, and activation of complement is responsible for much of the inflammation and cell damage seen in many diseases, including gout, arthritis, and psoriasis. Historically, these conditions have been treated with sarsaparilla.

In further support of sarsaparilla's effect as a binder of endotoxin is its historic use in the treatment of fever, because absorbed endotoxins produce fever. Sarsaparilla also exhibits some antibiotic activity, but this is probably secondary to its endotoxin-binding action.[1]

CLINICAL APPLICATION

Sarsaparilla's medicinal action appears to be a result of its binding of bacterial endotoxins in the gut, which makes them unabsorbable. This action greatly reduces the stress on the liver and other organs and is probably responsible for sarsaparilla's historic use as a tonic and blood purifier. The ability to bind endotoxins is also probably the reason that sarsaparilla is effective in many cases of psoriasis, gout, and arthritis.

Psoriasis

Individuals with psoriasis have been shown to have high levels of circulating endotoxins. Binding of endotoxin in the gut is associated with clinical improvement in these individuals. In a controlled study of 92 patients, an endotoxin-binding saponin (sarsaponin) from sarsaparilla greatly improved the psoriasis in 62% of the patients and resulted in complete clearance in 18%.[12]

DOSAGE

- Dried root: 1 to 4 g or by decoction three times a day
- Liquid extract (1:1): 2 to 4 mL three times a day
- Solid extract (4:1): 250 to 500 mg three times a day

TOXICOLOGY

Although no adverse effects have been reported for sarsaparilla, it is possible that problems can arise if large doses are used over a long time.

DRUG INTERACTIONS

No drug interactions have been reported for sarsaparilla. However, it has been theorized that sarsaparilla may increase the absorption of certain drugs, notably digitalis and bismuth, thereby potentially increasing the chance of drug toxicity.

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CHAPTER 122

Serenoa repens (Saw Palmetto)

Eric L. Yarnell, ND, RH(AHG), and Kathy Abascal, BS, JD, RH(AHG)

Serenoa repens (family: Arecaceae)
Common names: saw palmetto, palmetto scrub, *Sabal serrulata*

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GENERAL DESCRIPTION

Serenoa repens is a small palm tree native to the West Indies and southeastern United States, particularly Florida. The deep red-brown to black fruits, the medicinal parts, are wrinkled and oblong, measuring 0.5 to 1 in. in length with a diameter of 0.5 in. [1]

CHEMICAL COMPOSITION

Saw palmetto berries contain about 1.5% of a fruity-smelling oil containing saturated and unsaturated fatty acids and sterols.[1] About 63% of this oil is composed of free fatty acids, including capric, caprylic, caproic, lauric, palmitic, and oleic acids. The remaining portion is composed of ethyl esters of these fatty acids and sterols, including beta-sitosterol and its glucoside. The lipid-soluble compounds are thought to be the major pharmacologic components. Other components of the berries are proanthocyanidins, carotenes, lipase, tannins, and sugars.

The purified fat-soluble extract, the most researched medicinal product, contains 85% to 95% fatty acids and sterols. It is made up predominantly of a complex mixture of saturated and unsaturated free fatty acids, their methyl- and ethyl-esters (approximately 7%), long-chain alcohols in free and esterified forms, and various free and esterified sterol derivatives.

HISTORY AND FOLK USE

The American Indians, and later eclectic and naturopathic physicians, used saw palmetto berries in the treatment of genitourinary tract disturbances and as a tonic to support the body nutritionally.[2,3] This substance was strongly recommended as a remedy for symptoms of benign prostatic hyperplasia as early as 1919.[4] It was used in men to increase the function of the testicles and relieve irritation in mucous membranes, particularly those of the genitourinary tract and prostate. Saw palmetto has been used in women with disorders of the mammary glands; long-term use was reputed to cause the breasts to enlarge slowly.[2] Many herbalists have regarded saw palmetto as an aphrodisiac.[1]

PHARMACOLOGY

A standardized liposterolic (fat-soluble), saw palmetto berry extract has demonstrated numerous pharmacologic effects relating to its primary clinical application in the treatment of benign prostatic hyperplasia (BPH), a common disorder of the prostate gland. Saw palmetto extract affects BPH through multiple mechanisms, including inhibition of the intraprostatic conversion of testosterone to DHT and of its intracellular binding and transport, antiestrogenic, and receptor site–binding effects.[5-7]

Estrogen may contribute to BPH because it inhibits the hydroxylation and subsequent elimination of DHT. *Serenoa* appears to inhibit the activity of estrogen in the prostate. For example, in a double-blind study of 35 men with BPH, 18 were given the saw palmetto extract at 160 mg twice daily and 17 were given placebo.[5] At the end of the 90-day study, the men receiving the saw palmetto extract had significantly lower cytosol and receptor values for estrogen and progesterone than

the placebo group. The results imply that at least part of the efficacy of the saw palmetto extract is due to its antiestrogenic effect.

There was no change in the number of cytosol androgen receptors, but the number of nuclear androgen receptors was significantly lower in the saw palmetto group (60% of the placebo group tested positive for the nuclear receptor, compared with 10% of the saw palmetto group). These results indicate that the saw palmetto extract probably competitively blocks the translocation of the cytosol androgen receptor to the nucleus.

Preliminary analysis of the extract demonstrates that separate fractions are responsible for the antiandrogenic and antiestrogenic effects. Researchers in this study said, "It cannot be excluded, however, that the primary effect is antiestrogenic and that the inactivation of androgen receptors and progesterone receptors and of the 5-α-reductase activity is secondary to the estrogen receptor blockade."[7]

Serenoa standardized extracts do not affect systemic levels of androgens, follicle-stimulating hormone, or luteinizing hormone in men with BPH.[8] This may help explain the relatively low incidence of adverse effects of this substance in clinical trials. These findings do not, however, rule out localized effects of saw palmetto on androgen or estrogen effects in other tissues of the body.

Various locally produced growth factors also play a role in the pathogenesis of BPH, and liposterolic extracts of *Serenoa* block the ability of one of them, basic fibroblast growth factor, to induce prostatic hyperplasia in vitro.[9] High prolactin levels may also stimulate prostate hyperplasia; *Serenoa* extracts interfere with this process in rats but the drug finasteride does not.[10]

Saw palmetto extracts exert antispasmodic effects on smooth muscle. Rat smooth muscle was originally shown to be inhibited by two *Serenoa* extracts owing to inhibition of calcium ion influx.[11] A later study found that *Serenoa* extract but not pumpkin seed extract, stinging nettle root extract, or β-sitosterol consistently inhibited human α_1-adrenergic receptors in vitro.[12] Whether this effect is relevant clinically is still unknown.

The standardized extract has demonstrated antiedematous effects, and the polysaccharide components have been shown to have immunostimulatory effects.[13,14] *Serenoa* extract and myristoleic acid induced apoptosis and necrosis in an androgen-sensitive human prostate cancer cell line in vitro.[15]

CLINICAL APPLICATIONS

The primary clinical application of saw palmetto berries (specifically the fat-soluble extract) is in the treatment of men with BPH. There is also preliminary evidence that saw palmetto may also help counter male-pattern baldness. On the basis of its pharmacology, this extract may also be of benefit in conditions of androgen excess in women, such as hirsutism and polycystic ovary disease.

Benign Prostatic Hyperplasia

The major symptoms of BPH (increased urinary frequency, nighttime awakening to empty the bladder, and reduced force and caliber of urination; see Chapter 152), have been shown to be significantly improved by saw palmetto extract in more than a dozen double-blind placebo-controlled clinical trials (summarized in Table 122-1).[16-29] At least three meta-analyses have combined data from these and other trials and concluded that, despite some limitations in trial design, *Serenoa* extracts have been shown to reduce symptoms of BPH and increase urine flow in comparison with placebo without affecting prostate volume.[30-33] One of these analyses also concluded that *Serenoa* extracts are as effective as the 5-α-reductase–inhibiting drug finasteride (Proscar), with significantly fewer adverse effects.[34] In the most recent meta-analysis, it was concluded that saw palmetto extracts were not superior to placebo for symptoms of BPH but were just as effective as finasteride and tamsulosin.[33] However, this analysis was strongly affected by a single negative trial involving 225 men with moderate to severe BPH randomized to receive *Serenoa* extract 160 mg twice daily or placebo.[17] After 1 year of treatment, there was no significant difference in the scores on the American Urological Association Symptom Index and the maximal urinary flow rate in men receiving 320 mg per day of the liposterolic *Serenoa* extract or placebo. Secondary outcome measures, including changes in prostate size, residual urinary volume after voiding, quality of life, laboratory values, and the rate of reported adverse effects also did not differ between the two groups. These results may simply indicate that treatment of moderate to severe BPH is likely unresponsive to *Serenoa* therapy. A large negative clinical trial of *Serenoa* in 369 men with mild-to-moderate BPH failed to show a benefit for up to 960 mg/day of standardized extracts compared with the placebo.[33a]

The single largest (n = 1,069) clinical trial of *Serenoa* extract compared 160 mg of *Serenoa* twice daily with finasteride 5 mg daily for 26 weeks.[34] The two agents were equally effective at improving symptoms (by 37%-39% on average) and increasing peak urine flow (by 38%-41% on average). Although finasteride decreased prostate volume and levels of prostate-specific antigen (PSA) significantly, *Serenoa* extract had no such effect. Finasteride caused more sexual side effects than saw palmetto.

In a comparison double-blind trial, 542 men with BPH symptoms were randomly assigned to receive either the α blocker tamsulosin or *Serenoa* extract for 1 year.[35] The two groups showed identical levels of improvement in symptoms. Tamsulosin was more frequently associated with ejaculatory disorders than *Serenoa* extract. In the subset of patients with the most severe BPH in this trial, *Serenoa* extract was actually statistically significantly superior to tamsulosin at relieving symptoms.[36] In a separate double-blind trial involving 329 men with BPH symptoms, tamsulosin combined with placebo was just as effective as tamsulosin combined with *Serenoa* extract at relieving symptoms.[37] Adding *Serenoa* extract to tamsulosin caused no alteration in adverse effects. A 6-month double-blind trial of *Serenoa* extract with 60 men found results very similar to those of the prior two studies, although it also demonstrated an equivalent improvement in maximum flow rate between the groups.[38]

Serenoa may work most effectively in combination with *Urtica urens* root extract. In a long-term study, the efficacy and tolerability of this combination were investigated in a prospective multicenter trial comprising elderly male patients suffering from lower urinary tract symptoms (LUTS) caused by BPH. A total of 257 patients were randomized to treatment with the combination (320 mg of *Serenoa* and 240 mg of *U. urens* extracts per day) or placebo. Following a single-blind placebo run-in phase of 2 weeks, the patients received either the study medication or placebo under double-blind conditions over 24 weeks. Double-blind treatment was followed by an open control period of 24 weeks during which all patients were given the *Serenoa* and *U. urens* combination. Outcome measures for treatment efficacy included the assessment of the patients' LUTS by means of a self-rating questionnaire and a quality-of-life index as well as uroflow and sonographic parameters. Using the International Prostate Symptom Score (I-PSS), patients treated with the *Serenoa* and *U. urens* combination exhibited a substantially higher total score reduction after 24 weeks of double-blind treatment than patients of the placebo group (6 points vs. 4 points; P = 0.003), with a tendency in the same direction after 16 weeks. This applied to obstructive as well as to irritative symptoms and to patients with moderate or severe symptoms at baseline. Patients

TABLE 122-1 **Clinical Studies Demonstrating the Efficacy of *Serenoa repens* Extract***

STUDY	TYPE OF STUDY	NO. OF PATIENTS	LENGTH OF STUDY	RESULTS
Controlled Trials				
Shi et al[16]	Double-blind, placebo-controlled	92	12 weeks	Significant for flow rate
Bent et al[17]	Double-blind, placebo-controlled	225	1 year	Equal to placebo
Willetts et al[18]	Double-blind	91	12 weeks	Equal to placebo
Boccafoschi and Annoscia[19]	Double-blind, placebo-controlled	22	60 days	Significant difference for volume voided, maximum flow, mean flow, dysuria, nocturia
Emili et al[20]	Double-blind, placebo-controlled	30	30 days	Significant difference for number of voided, strangury, maximum and mean urine flow, residual urine
Duvia et al[21]	Controlled	30	30 days	Significant difference for voiding rate vs. *Pygeum africanum*
Tasca et al[22]	Double-blind, placebo-controlled	30	31-90 days	Significant difference for frequency, urine flow measurement
Cukier et al[23]	Double-blind, placebo-controlled	168	60-90 days	Significant difference for dysuria, frequency, residual urine
Champault et al[24]	Double-blind, placebo-controlled	168	60-90 days	Significant difference for objective and subjective parameters
Champault et al[25]	Double-blind, placebo-controlled	110	28 days	Significant difference for dysuria, nocturia, flow measurement, residual urine
Mattei et al[26]	Double-blind	40	3 months	Significant difference for dysuria, nocturia, residual urine
Open Long-Term Trials				
Djavan et al[27]	Open, watchful waiting control	189	2 years	Significant for symptom relief, reduction in surgical rates compared with control
Pytel et al[28]	Open	255	2 years	Significant for symptom relief
Pierre Fabre [29]	Open	154	2 years	Significant for symptom relief

*85% to 95% fatty acids and sterols at a dosage of 320 mg/day.

randomized to placebo showed a marked improvement in LUTS (as measured by the I-PSS) after being switched to the *Serenoa* and *U. urens* combination during the control period.[39]

Chronic Prostatitis

Several recent studies indicate that *S. repens* may have clinical benefit in chronic prostatitis or pelvic pain. One double-blind, randomized trial compared *S. repens* extract alone with a combination of *S. repens*, selenium, and lycopene in men with nonbacterial chronic pelvic pain.[40] After 8 weeks, the two groups had equivalent improvements in symptoms, whereas only the combination product lowered PSA and levels of white blood cell in urine.

One study used a combination of *S. repens* extract 160 mg, *Urtica dioica* root extract 120 mg, quercetin 100 mg, and curcumin 200 mg once daily with the antibiotic prufloxacin 600 mg once daily in men with bacterial prostatitis.[41] One fourth of the 143 subjects were randomly assigned to take prufloxacin alone. Treatment lasted 14 days. One month after treatment, patients in the combination group were dramatically more likely (88% vs. 27%) to be symptom free than the antibiotic-only group.

Male-Pattern Baldness

A combination of 400 mg *S. repens* extract and 100 mg beta-sitosterol daily was found effective for male-pattern baldness in a pilot double-blind placebo-controlled trial.[42] The trial lasted 5 months and involved 19 men with mild to moderate baldness. Sixty percent (6 of 10) of the men in the treatment group were rated as having improved by blinded observers, whereas only 11% (1 of 9) of men in the placebo group were rated as improved. Thirty-three percent (3 of 9) of the men in the placebo group showed deterioration compared with none in the treatment group. There were no major adverse effects, although two men originally entered into the study dropped out because of adverse effects (it is not clear from the study report which group these men had been assigned to).

Dosage

The dosage for the liposterolic extract of saw palmetto berries (containing 85%-95% fatty acids and sterols) is 160 mg twice daily or 320 mg daily; the two regimens have been shown to be equally effective.[43] A similar dosage using fluid extracts and tinctures would require extremely large quantities of alcohol if the liposterolic components were the primary active constituents. The eclectics used comparatively small dosages of saw palmetto in crude extracts effectively for BPH with apparent clinical success. Ellingwood[4] lists a dose as 10 drops to 1 dram of specific *S. repens* (meaning basically a fresh berry tincture). We are unaware of any published clinical study of a crude extract.

Dosages are as follows:

- Crude berries: 10 g twice a day
- Liposterolic extract (standardized at 85% to 95% fatty acids and sterols): 160 mg twice a day or 320 mg once a day

The dosage of fluid extracts or tinctures is typically 3 to 5 mL two to three times per day, although there is a lack of research on this dose form.

TOXICOLOGY

No significant adverse effects have been reported in clinical trials of the saw palmetto berry extract or for saw palmetto berry ingestion; rates of mild adverse effects are no different than those seen with placebo treatment.[44] Mild gastrointestinal upset and erectile dysfunction (in approximately 1% of users in clinical trials)[3] occasionally occur.

DRUG INTERACTIONS

No drug-herb interactions had been reported as of 2011.

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CHAPTER 123

Silybum marianum (Milk Thistle)

Michael T. Murray, ND

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Silybum marianum (family: Compositae)
Synonym: *Carduus marianus*
Common names: milk thistle, marian thistle, St. Mary's thistle

GENERAL DESCRIPTION

Silybum marianum is a stout annual or biennial plant found in dry rocky soils in southern and western Europe and some parts of the United States. The branched stem grows 1 to 3 ft high and bears alternate dark green, shiny leaves with spiny, scalloped edges that are markedly streaked with white along the veins. The solitary flower heads are reddish purple with bracts ending in sharp spines. Flowering season is from June to August. The seeds, fruit, and leaves are used for medicinal purposes.

CHEMICAL COMPOSITION

Silybum marianum contains *silymarin*, a mixture of flavanolignans, consisting chiefly of silybin, silydianin, and silychristine.[1-3] The concentration of silymarin is highest in the fruit, but it is also found in the seeds and leaves. Other flavanolignans contained in *Silybum* include silandrin, silyhermin, silymonin, and neosilyhermin.[1] *Silybin* is the silymarin component with the greatest degree of biological activity (Figure 123-1).

HISTORY AND FOLK USE

Perhaps the most widespread folk use of this plant has been in assisting the nursing mother in the production of milk. It was also used in Germany for curing jaundice and biliary derangements. It is interesting to note that the discovery of the liver-protecting flavanolignans in *S. marianum* was the result not of systemic pharmacologic screening but rather of investigation of *Silybum*'s empiric effects in liver disorders.[1]

PHARMACOLOGY

Currently *S. marianum* extracts (usually standardized to contain 70% silymarin) are widely used in European pharmaceutical preparations for hepatic disorders. Silymarin is one of the most potent liver-protecting substances known.[1-8]

Hepatoprotection Effects

Free Radical Scavenging

Silybum's ability to prevent liver destruction and enhance liver function is due largely to silymarin's inhibition of the factors responsible for hepatic damage—free radicals and leukotrienes—coupled with its ability to stimulate liver protein synthesis. *Silybum* components prevent free radical damage by acting as antioxidants.[1-4] Silymarin is many times more potent in antioxidant activity than vitamin E.

Effects on Hepatic Glutathione

Silymarin prevents the depletion of glutathione (GSH) induced by alcohol and other liver toxins. Even in normal people, silymarin has been shown to raise the basal GSH level in the liver by 35%.

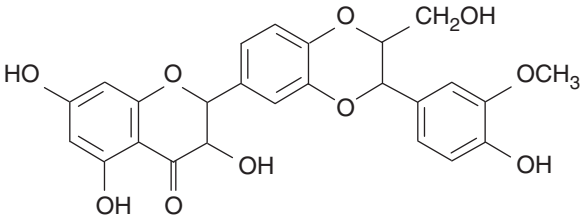


FIGURE 123-1 Silybin.

Protection from Liver-Damaging Chemicals and Drugs

The protective effect of *Silybum* against liver damage has been demonstrated in a number of experimental and clinical studies. Experimental liver damage in animals can be produced by such diverse toxic chemicals as carbon tetrachloride, galactosamine, ethanol, and praseodymium nitrate. Silymarin has been shown to protect the liver from all of these toxins.[1-4,7]

Perhaps the most impressive of silymarin's protective effects is against the severe poisoning by *Amanita phalloides* (the "death cap" or toadstool mushroom), an effect that has long been recognized in folk medicine.[5-7] Ingestion of *A. phalloides* or its toxins causes severe poisoning and, in approximately 30% of victims, death.

Among the experimental models for measuring protection against liver damage, those based on amanitin or phalloidin toxicity are the most important because these two peptides from *A. phalloides* are the most powerful liver-damaging substances known. Silymarin has demonstrated impressive results in these experimental models. When silymarin was administered before amanita toxin poisoning, it was 100% effective in preventing toxicity.[5,7] Even if given 10 minutes after the amanita toxin, it completely counteracted the toxic effects.

In two cases reported in the literature, silymarin prevented death and greatly reduced the amount of liver damage as long as 24 hours after ingestion of *A. phalloides*.[6] This study reported on a husband and wife who ate toxic mushrooms and experienced gastrointestinal symptoms 18 hours later. Despite initial conventional treatment with gastric emptying, intravenous fluids, activated charcoal, and a duodenal tube, both patients' laboratory parameters showed deteriorating liver and renal function. Mild hepatic encephalopathy developed in one of the patients. Treatment with intravenous silybinin at a dose of 20 mg/kg body weight, penicillin, and glucose for 3 days resulted in reversal of both the organ failures and encephalopathy.

Silymarin may also be of great value as an adjunct in patients receiving long-term drug therapy. A very interesting study found that silymarin, in an unusually high dose of 800 mg/day, given to psychiatric patients receiving phenothiazines or butyrophenones resulted in significant protection of the liver as measured by malondialdehyde serum liver enzyme levels.[9] The silymarin did not interfere with the efficacy of the antidepressants.

Stimulation of Hepatic Protein Synthesis

Perhaps the most interesting effect of *Silybum* components on the liver is their ability to stimulate protein synthesis.[4,10,11] This results in an increase in the production of new liver cells to replace the damaged old ones. Sonnenbichler and Zetl[11] have suggested that "silybinin imitates in some way a physiological regulator in animal cells, so that the structure fits into a specific binding site on the polymerase and in such a way causes the observed effects on rRNA synthesis making the drug from *Silybum marianum* indeed interesting for liver therapy." Interestingly, silybinin does not have a stimulatory effect on malignant hepatic tissue.[10]

Antiinflammatory Effects

Leukotrienes, key chemical mediators of inflammation produced by the transfer of oxygen to polyunsaturated fatty acids (a reaction catalyzed by the enzyme lipoxygenase), can also damage the liver. Silymarin has been shown to be a potent inhibitor of this enzyme, thereby inhibiting the formation of damaging leukotrienes.[12]

Silymarin has also been demonstrated to inhibit prostaglandin synthesis during inflammation.[13] Free radical damage to membrane structures due to organic disease or intoxication results in increased release, through lipolysis, of fatty acids. This leads, among other things, to greater prostaglandin and leukotriene synthesis. Silymarin counteracts this deleterious process by suppressing the pathologic decomposition of membrane lipids and inhibiting prostaglandin formation.[13] Leukotrienes and inflammatory prostaglandins are also involved in damage of the liver by toxins, so their neutralization by silybin is another mechanism for its protection of the liver.

Anticancer Effects

Silymarin has shown significant anticancer effects in both in vivo and in vitro cancer models—including skin, breast, lung, colon, bladder, prostate, and kidney carcinomas—as well as adjunctive actions when combined with standard cancer therapies.[14-18] Some of the effects noted include that it:

- Prevents the expression of genes and enzymes pivotal in cancer development
- Modulates imbalance between cell survival and apoptosis through interference with the expression of cell cycle regulators and proteins involved in apoptosis
- Exerts significant antimetastatic effects
- Has a synergistic effect when combined with conventional chemotherapy agents, including growth inhibition, reversal of chemoresistance, apoptosis induction, and reduced chemotherapy side effects in a variety of models

These preliminary studies suggest a clinical application in cancer patients as an adjunct to established therapies so as to prevent or reduce chemotherapy as well as radiotherapy-induced toxicity.[18] Considering the significant problem of serious nephrotoxicity from cisplatin and other chemotherapeutic agents, silybinin may be of great value as an adjunct in the treatment of cancer.

Other Pharmacologic Actions

Silymarin shows antiviral effects against hepatitis C virus cell culture infection, including inhibition of virus entry, RNA and protein expression, and infectious virus production.[19]

In animal studies silymarin has been shown to increase the proliferation of lymphocytes as well as levels of interferon-gamma, interleukin-4 (IL-4), and IL-10 cytokines in a dose-dependent manner.[20] It has also shown a broad range of anticancer effects in various animal models and in vitro studies.[21-23]

Silymarin is a strong inhibitor of cyclic adenosine monophosphate(cAMP) phosphodiesterase, being 13 to 50 times more active than theophylline and 1 to 3 times more active than papaverine.[24] Silymarin has also been shown to prevent the toxic effects of a variety of compounds, such as hemolysis induced by phenylhydrazine, damage from x-irradiation, and brain edema induced by triethyltinsulfate.[25-27] Presumably these effects are related to silymarin's significant membrane-stabilizing and

antioxidant actions. Its action in increasing the osmotic resistance of red blood cells is also quite significant.[28]

Silymarin has also been shown to lower cholesterol levels in animal studies and may block cholesterol synthesis.[29]

In patients with hemochromatosis, silybin adminstration at meals was shown to reduce iron absorption.[30]

CLINICAL APPLICATIONS

Silymarin's primary use is as an aid to the liver, although additional clinical applications are regularly being discovered. This substance can be used to support detoxification reactions or in the treatment of more severe liver disease. In numerous clinical studies, silymarin has been shown to have positive effects in treating several types of liver disease, including the following:[31-48]

- Cirrhosis
- Chronic hepatitis
- Fatty infiltration of the liver (chemical- and alcohol-induced fatty liver)
- Subclinical cholestasis of pregnancy
- Cholangitis and pericholangitis

The therapeutic effect of silymarin in these disorders has been confirmed by histologic, clinical, and laboratory data. Silymarin may also be useful in improving the solubility of the bile in the treatment of gallstones as well as in psoriasis and as a galactogogue.

Chemically Induced Liver Damage

In one of the first extensive double-blind clinical trials investigating silymarin's therapeutic effect in liver disorders, the substance demonstrated impressive results in 129 patients with toxic metabolic liver damage, fatty degeneration of the liver of various origins, or chronic hepatitis who were compared with a control group of 56 patients. The results might have been even more impressive if the study had lasted longer than 35 days.[31]

A follow-up study of patients with liver damage due to alcohol, diabetes viruses, or toxic exposure yielded even more striking results. Patients were monitored for a long time (7 weeks). Not only were clinical findings markedly improved in the silymarin-treated groups, but laboratory and liver biopsy data improved as well. Highly significant results were obtained in bromsulphalein retention as well as in measurements of alanine transaminase (ALT), iron, and cholesterol levels. Biopsy showed remarkable tissue restorative effects. Upon completion of silymarin therapy, restitution of normal cell structure was found even in severely damaged livers. These effects on the tissue level correlated well with improvements in blood chemistry values.[32]

Another study highlighted the benefit of silymarin in individuals exposed to toxic chemicals. In this study, abnormal results of liver function tests (elevated levels of aspartate amino transferase [AST] and ALT activity), and/or abnormal hematologic values (low platelet counts, increased white blood cell counts, and a relative increase of lymphocytes compared with other white blood cells) were observed in 49 of 200 workers exposed to toxic toluene and/or xylene vapors for 5 to 20 years.[43] Thirty of the affected workers were treated with silymarin and the remaining 19 were left without treatment. Under the influence of silymarin, liver function parameters and platelet counts significantly improved. The WBC counts also showed a tendency toward improvement.

Pooled data from case record studies involving 452 patients with *A. phalloides* poisoning show a highly significant difference in mortality in favor of silymarin therapy. The mortality rate for silymarin therapy is 9.8%, compared with 18.3% for standard treatment.[49]

Cirrhosis

As previously described, silymarin is quite effective in treating alcohol-related liver disease. There is a tremendous range in the severity of alcohol-related liver disease, from relatively mild to serious damage, such as cirrhosis. Even in this severe state, silymarin has shown benefit. Perhaps the most significant benefit is in extending the life spans of patients with these disorders.

In one study, 87 patients with cirrhosis (46 with alcoholic-related cirrhosis) received silymarin, whereas 83 patients (45 with alcoholic cirrhosis) received a placebo.[44] The mean observation period was 41 months. In the treatment group, there were 24 deaths, 18 related to liver disease; in the control group, there were 37 deaths, 31 related to liver disease. The 4-year survival rate was 58% in the treatment group compared with 39% in the controls.

Analysis of the results of five trials involving a total of 602 patients with liver cirrhosis demonstrated that, although silymarin produced a statistically insignificant reduction of total mortality by 4.2% in comparison with placebo, it did lead to a statistically significant reduction in liver-related mortality of 7%.[49] Silymarin can also improve immune function in patients with cirrhosis.[45]

Viral Hepatitis

Silymarin is useful in helping to reverse virally induced liver damage. It is effective in both acute and chronic viral hepatitis. In one study of acute viral hepatitis, 29 patients treated with silymarin showed a definite therapeutic influence on the characteristic increased serum levels of bilirubin and liver enzymes compared with a placebo group.[46] The laboratory parameters had regressed more in the silymarin group than in the placebo group by the fifth day of treatment. The number of patients attaining normal liver values after 3 weeks of treatment was significantly higher in the silymarin group than in the placebo group.

In a double-blind study of various causes of acute hepatitis, patients were given either a standard recommended dose of 140 mg of silymarin or a placebo three times daily for 4 weeks. Patients randomized to the silymarin group had quicker resolution of symptoms related to biliary retention: dark urine, jaundice, and scleral icterus. There was a reduction in indirect bilirubin among those assigned to silymarin, but other variables including direct bilirubin, ALT, and AST were not significantly reduced.[50]

In a study of chronic viral hepatitis, silymarin was shown to result in dramatic improvement. Used at a high dose (420 mg) for periods of 3 to 12 months, silymarin resulted in a reversal of liver cell damage (as noted on biopsy), a rise in protein level in the blood, and a lowering of liver enzyme values. Common symptoms of hepatitis (e.g., abdominal discomfort, decreased appetite, and fatigue) were all improved.[47]

Gallstones

Silymarin may help prevent or treat gallstones through its ability to increase the solubility of the bile. In one study, the composition of the bile was assayed in 19 patients with a history of gallstones (4 patients) or removal of the gallbladder due to gallstones (15) before and after silymarin (420 mg/day for 30 days) or placebo. Silymarin treatment led to significant reduction in the biliary cholesterol concentration and bile saturation index.[48]

Psoriasis

Correction of abnormal liver function is indicated in the treatment of psoriasis. Silymarin has been reported to be of value in the treatment of psoriasis; this effect may be due to its ability to inhibit the synthesis of leukotrienes and improved liver function.[51]

The connection between the liver and psoriasis relates to one of the liver's basic tasks, filtering of the blood. Psoriasis has been shown to be linked to high levels of circulating endotoxins, such as those found in the cell walls of gut bacteria. If the liver is overwhelmed by an increased number of endotoxins or chemical toxins or if the liver's functional ability to filter and detoxify is decreased, the psoriasis is aggravated. Another factor in psoriasis is excessive production of leukotrienes. Silymarin has been shown to reduce leukotriene formation by inhibiting lipooxygenase.[12] Therefore, silymarin would inhibit one of the causes of the excessive cellular replication.

Silymarin has other effects of value in patients with psoriasis. Most of them revolve around correcting the abnormal ratio of cAMP to cyclic guanosine monophosphate (cGMP) observed in the skin of patients with psoriasis. The ratio of these two cellular control agents governs cellular replication. In psoriasis, cGMP levels are high relative to cAMP levels. Silymarin works to lower cGMP levels and raise cAMP levels.[24]

Silymarin as a Galactogogue

A micronized form of silymarin has been shown to exert clear galactogogue effects. In a double-blind study in 50 healthy lactating women, micronized silymarin (420 mg/day) increased daily milk production by 86%, compared with 32% for the placebo. Milk quality was unaffected. The galactogogue effect may be the result of increased circulating prolactin levels.[52]

Silybin Bound to Phosphatidylcholine

Given the poor relative bioavailability of silymarin components, methods are being developed to increase their bioavailability to improve clinical effects. One enhanced form of silymarin binds silybin to phosphatidylcholine. Preliminary research indicates that phosphatidylcholine-bound silybin is better absorbed and produces better clinical results than other forms.

Absorption Studies

Several human and animal studies have shown that phosphatidylcholine-bound silybin is better absorbed. In one study, the excretion of silybin, the major component of silymarin, in the bile was evaluated in patients undergoing gallbladder removal (cholecystectomy). A drainage tube, the T-tube, was used to sample the bile. Patients were given either a single oral dose of the silybin-phosphatidylcholine complex or silymarin. The amount of silybin recovered in the bile in free and conjugated form within 48 hours was 11% for the silybin-phosphatidylcholine group and 3% for unmodified silybin group.[53]

One of the significant features of this study is the fact that silymarin has been shown to improve the solubility of the bile. Because more silybin is being delivered to the liver and gallbladder when the phosphatidylcholine-bound silybin is used, this form is ideal for individuals with gallstones or fatty infiltration of the liver, two conditions characterized by decreased bile solubility.

In another study, plasma silybin levels were determined after administration of single oral doses of silybin-phosphatidylcholine complex and a similar amount of silymarin to nine healthy volunteers. Although absorption was rapid with both preparations, the bioavailability of the silybin-phosphatidylcholine complex was much greater than that of silymarin, as indicated by higher plasma silybin levels at all sampling times after intake of the complex. The researchers in this study concluded that complexation with phosphatidylcholine greatly increases the oral bioavailability of silybin, probably by facilitating its passage across the gastrointestinal mucosa.[54]

Clinical Studies

Several clinical studies have shown phosphatidylcholine-bound silybin to be more effective than silymarin. In one study, 8 patients with chronic viral hepatitis (3 with hepatitis B, 3 with both hepatitis B and hepatitis C, and 2 with hepatitis C) were given one capsule of phosphatidylcholine-bound silybin (equivalent to 140 mg silymarin) between meals for 2 months.[55] After treatment, serum malondialdehyde levels (an indicator of lipid peroxidation) decreased by 36%, and the quantitative liver function evaluation as measured by galactose elimination capacity increased by 15%. A statistically significant reduction of liver enzymes was also seen: AST diminished by 17% and ALT rose by 16%.

In another study designed primarily to evaluate the dose-response relationship of phosphatidylcholine-bound silybin, positive effects were again displayed.[56] In this study, patients with chronic hepatitis due to either a virus or alcohol were given different doses for 2 weeks: 20 patients received 80 mg twice daily, 20 received 120 mg twice daily, and 20 received 120 mg three times daily. At all tested doses, phosphatidylcholine-bound silybin produced remarkable and statistically significant decreases in mean serum and total bilirubin levels. When used at the dose of 240 or 360 mg/day, it also resulted in remarkable and statistically significant decreases in the liver enzymes ALT and gamma-glutamyltranspeptidase. These results indicate that even short-term treatment of viral- or alcohol-induced hepatitis with relatively low doses of phosphatidylcholine-bound silybin can be effective; for the best results, however, higher doses are needed.

Treatment with phosphatidylcholine-bound silybin is associated with reduced body iron stores, especially among patients with the advanced fibrosis stage of chronic viral hepatitis.[57]

DOSAGE

The standard dose of milk thistle is based on its silymarin content (70 to 210 mg three times daily). For this reason, standardized extracts are preferred. The best results are achieved at higher dosages—140 to 210 mg of silymarin three times daily.

The dosage for silybin bound to phosphatidylcholine is 120 to 240 mg twice daily.

Alcohol-based extracts are virtually always contraindicated in liver disease because a relatively large amount of alcohol is administered to obtain an adequate dose of silymarin in this form.

TOXICITY

Silymarin preparations are widely used medications in Europe, where a considerable body of evidence points to very low toxicity.[1] When used at high doses for short periods, silymarin given by various routes to mice, rats, rabbits, and dogs has shown no toxic effects. Studies in rats receiving silymarin for protracted periods have also demonstrated a complete lack of toxicity.[1]

Because silymarin possesses choleretic activity, it may produce a looser stool as a result of greater bile flow and secretion. If higher doses are used, it may be appropriate to use bile-sequestering fiber

compounds (e.g., guar gum, pectin, psyllium, oat bran) to prevent mucosal irritation and loose stools. Because of silymarin's lack of toxicity, its long-term use is feasible when necessary.

DRUG INTERACTIONS

Although silymarin components have been shown to interact with drug-metabolizing cytochrome P_{450} enzymes in in vitro studies, the concentrations showing an inhibitory effects are not achieved with normal dosage recommendations.[58] Clinical studies have shown that coadministration of silymarin with drugs metabolized by P_{450} enzymes (e.g., indinavir) causes no adverse interactions.[59,60]

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CHAPTER 124

Soy Isoflavones and Other Constituents

Douglas "Duffy" Mackay, ND

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INTRODUCTION

Over the past two decades soy and its constituents have received considerable attention from both researchers and health practitioners. Epidemiologic data indicating that people from Asian cultures have lower rates of cardiovascular disease and a decreased risk of certain cancers, including cancers of the breast and prostate, sparked an interest in soy as a contributing factor. Although soy constituents—saponins, lignans, phytosterols, protease inhibitors, and phytates—have come under investigation, the constituents that seem to hold the most promise from a therapeutic standpoint are two isoflavones: genistein and daidzein.

The discovery that isoflavones bind to estrogen receptors, which classifies them as phytoestrogens, has led to much investigation into the possibility that isoflavone consumption could improve bone health and relieve hot flashes in menopausal women. Conversely, the phytoestrogenic activity of isoflavones has also raised safety questions about their use in hormone-sensitive cancer patients, and the potential for isoflavones to act as endocrine disruptors.

The health effects of soy and its constituent isoflavones are one of the most thoroughly researched fields in nutritional science. Over 2000 soy-related papers are published annually and more than one half are related to isoflavones.[1] Overall, soy foods are considered a heart-healthy source of protein because of their high content of polyunsaturated fats, fiber, vitamins, and minerals and low content of saturated fat.[2] The data related to specific health benefits of isoflavones—such as supporting bone health, decreasing menopausal hot flashes, improving cognitive function, and reducing the risk of certain types of cancers—are inconsistent. Several factors have been identified that contributed significantly to inconsistent results from early studies. These factors were rarely accounted for during the first 20 years of soy research (Box 124-1) and include individual variability of the human response to soy, differences in the isoflavone composition of different soy preparations, and the lack of analytic methods to assess soy constituents in foods, supplements, and biological fluids and tissues.[3] The design and evaluation of future soy-food and isoflavone research will be guided by these realizations, and will produce higher-quality data to help answer remaining questions about the health benefits and safety considerations of consuming soy and its bioactive constituents.

CHEMICAL COMPOSITION OF SOY

Interest in the constituents of soybeans, particularly soy protein and isoflavones, has catapulted soy to the status of a promising nutrient. Isoflavones remain in soy protein and other soy foods unless the preparation is extracted with alcohol.[4] Commonly consumed soy foods—including soy milk, protein powders, and soy-based infant formula—are considered rich sources of dietary isoflavones.[5] These are believed to be the most biologically active compounds in soy, but this has not been determined with certainty.

The principal isoflavones and most researched soy constituents in soy are genistein (4',5,7-trihydroxyisoflavone) and daidzein (4',7-dihydroxyisoflavone) (Figure 124-1). Glycetein is another isoflavone found in soy, but relatively little is published on its biological activity. In addition to isoflavones, soybeans contain

BOX 124-1 Historic Overview of Soy and Isoflavone Research

Traditional Use
- Eleventh century BC: evidence of soy being consumed as a traditional food in China
- 1760s: Soy's first recorded use in the United States

Evidence of Bioactivity
- 1940s: Breeding problems identified in Australian sheep grazing on red clover
- 1950s: Soy studied as a growth promoter in animal feed
- 1960s: Isoflavones established as phytoestrogens

Clinical Research Initiated
- 1970s: Tofu popularized as a health food in the United States
- 1990s: U.S. National Cancer Institute initiates a multimillion-dollar research program evaluating the anticancer effects of soy

Potential Benefits Explored
- 1990s: Research evaluates soy for hypocholesterolemic and mixed estrogen receptor properties, including potential benefits for postmenopausal hot flashes, bone health, and influence on hormone-sensitive cancers
- 1996: First isoflavone supplement becomes available
- 1999: FDA approves health claim for soy protein and coronary heart disease

New Evidence Emerges
- 2001: Researchers begin to explore impact of soy consumption on cognitive function
- 2002: Hypothesis introduced that individuals who possess equol-producing intestinal bacteria are more likely to benefit from soy-food consumption

Guidelines for Next Generation of Soy Research Established
- 2010: NIH identifies methodologic issues that confound soy and isoflavone study results and interpretation and publishes guidelines for the next generation of soy protein–isoflavone research

Data from Messina M. A brief historical overview of the past two decades of soy and isoflavone research. J Nutr 2010;140:1350S-1354S and Barnes S. The biochemistry, chemistry and physiology of the isoflavones in soybeans and their food products. Lymphat Res Biol 2010;8:89-98.

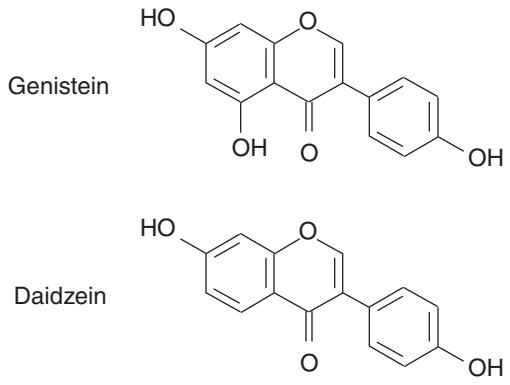


FIGURE 124-1 Structures of genistein and daidzein.

lignans, coumestans, saponins, plant sterols, phytates, and protease inhibitors. The chemical composition, including the isoflavone content, of different soy-food preparations are variable and dependent on soybean strain, growing conditions, harvest time, and processing method (Table 124-1).

TABLE 124-1 Percentage and Ratio of Principle Isoflavones in Common Soy Products

SOY PRODUCT	ISOFLAVONE CONTENT	GENISTEIN:DAIDZEIN
Whole soybeans	0.1%-0.2%	1:1
Soy flour (defatted)	0.07%-0.3%	1:1
Soy germ	5%	1:4
Synthetic genistein	100%	1:0
Soy protein isolate	0.01%-0.3%	1:1
Tofu	0.02%-0.07%	1:0.7
Soy milk	0.001%-0.02%	1:1
Miso (dry)	0.02%-0.09%	1:0.9

Data from Empie MW. Compositional specificity in soy isoflavone supplements. soy/protein/isoflavone research: challenges in designing and evaluating intervention studies. NIH Workshop; Bethesda, Maryland: July 28-29, 2009.

Isoflavones

Classification

Flavonoids are a subgroup of a larger group of plant constituents, the polyphenols. Flavonoids are further differentiated into isoflavonoids, of which isoflavones are a subcategory (Figure 124-2). Isoflavonoids are not as ubiquitous in nature as some of the other flavonoids, such as flavones and flavonols. Approximately 600 isoflavonoids have been identified and further divided into subclasses according to the oxidation level of the central pyran ring. Isoflavones are the most abundant of the subclasses of isoflavonoids.

Absorption, Metabolism, and Excretion

The primary human exposure to isoflavones comes from the diet. Evidence suggests that the absorption and metabolism of isoflavones vary considerably among individuals.[6] Factors that influence the bioavailability and possibly the bioactivity of isoflavones include absorption, metabolism by intestinal bacteria, liver metabolism, and enterohepatic circulation.

The native isoflavones in soy and unfermented soy foods—genistein and daidzein—occur conjugated to sugar moieties as glycosides and are not readily absorbed. After ingestion, isoflavone glycosides are hydrolyzed by intestinal brush border and bacterial glucosidases and released as the absorbable aglycone isoflavones genistein and daidzein. After absorption, the bioactive isoflavones are attached to glucuronic acid and made more water-soluble. It is predominantly the glucuronidated metabolites of isoflavones that circulate in the blood and are excreted in urine.[7] In adults, genistein and daidzein can be further metabolized by bacteria to specific metabolites: equol, O-desmethylangolensis, dihydrogenistein, and p-ethylphenol. Emerging evidence suggests that the biological activity of isoflavones may be dependent, at least in part, on the bacterial conversion of isoflavones to corresponding metabolites such as equol, which is highly variable among individuals. It has been reported that 20% to 30% of Westerners have the intestinal bacteria necessary to metabolize daidzein to equol, whereas in Asian countries the frequency of equol producers is 50% to 60%.[8] The hypothesis that individuals who possess the necessary bacteria to produce equol are more likely to achieve health benefits from soy-food consumption than those who do not is currently being investigated with great interest. Isoflavones attain maximal plasma levels 4 to 8 hours after ingestion and are excreted from the body within 24 hours, mainly in urine and to a lesser extent in feces.[7]

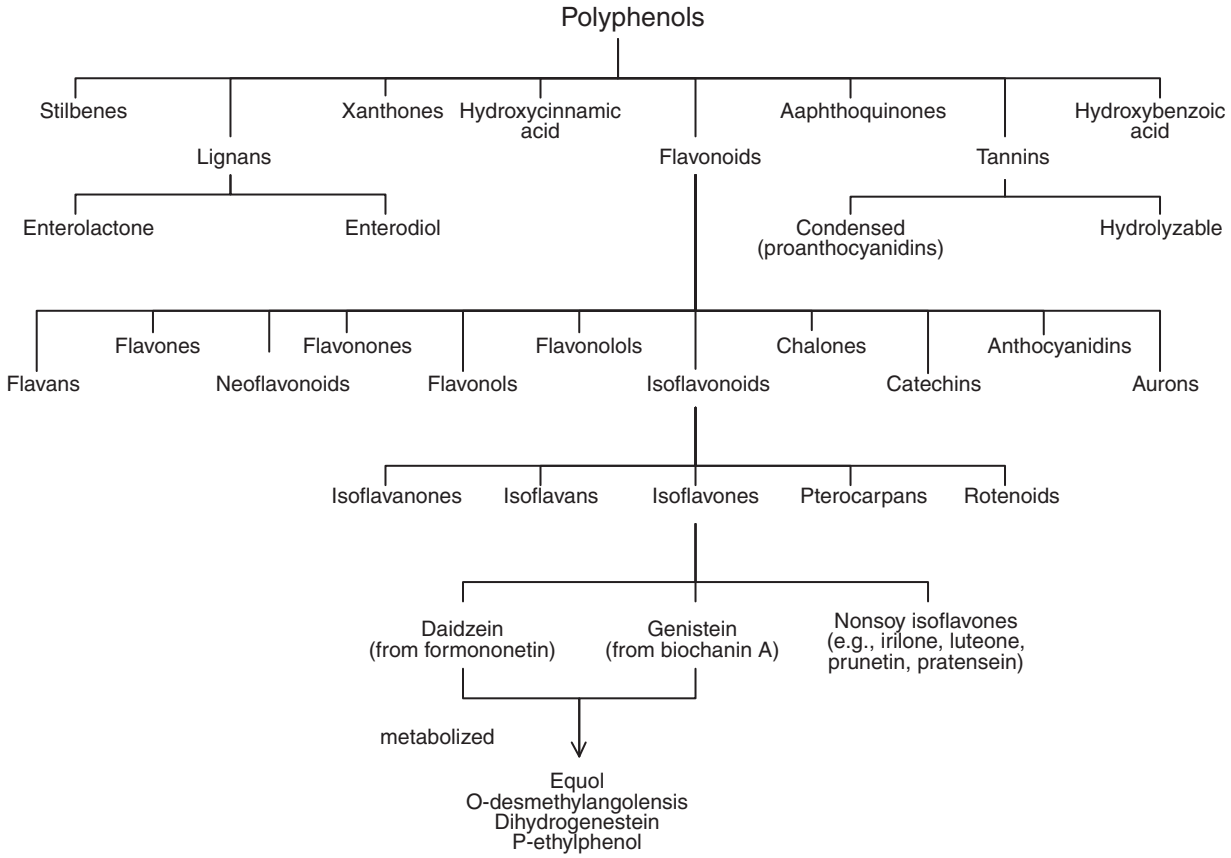


FIGURE 124-2 Polyphenol classification.

Isoflavone aglycones are thought to be more absorbable than their glucoside counterparts because aglycones have greater hydrophobicity and lower molecular weights. However, the relative bioavailability of isoflavone aglycones versus glucosides is debated. One study examined plasma and urinary concentrations of isoflavones and daidzein metabolites in healthy volunteers after ingesting soy milk, glucosidase-treated soy milk, and fermented soy milk. The researchers concluded that in humans, isoflavone aglycones, which are higher in fermented soy foods, were absorbed faster and in greater amounts than glucosides.[9] Another study conducted on healthy male subjects (aged 20 to 40 years) found that urinary excretion of genistein and daidzein was greater after consumption of 112 g of tempeh, a fermented soy product, than after 125 g of unfermented soy pieces.[10] These and other findings[11] seem to indicate that fermentation of soy products increases the bioavailability of the isoflavones. Other studies have reported conflicting results. One study reported the greater bioavailability of glycoside isoflavones, as measured from the area under the curve of plasma appearance and disappearance,[7] whereas other studies have reported no significant difference in absorption between aglycone and glycoside isoflavones.[12,13]

Isoflavone Content of Soy Products

A 2009 National Institutes of Health (NIH) workshop on designing, implementing, and reporting clinical studies of soy interventions has identified product composition and integrity as key challenges to accurately interpreting soy clinical studies.[3] The type and proportion of isoflavones will vary depending on plant genetics, growing and harvesting conditions, storage before and after processing, plant parts used, and processing and extraction method. The typical isoflavone content and genistein:daidzein ratios from different soy foods are listed in Table 124-1. Differences in the isoflavone content of soy products may account for different biological effects and consequently contribute to the heterogeneous results observed among clinical and epidemiologic studies of soy foods.

Soy foods are the primary dietary source of isoflavones and the only foods that provide isoflavones in physiologically relevant amounts. Other plants, such as red clover (*Trifolium pratense*) and kudzu (*Pueraria lobata*), contain isoflavones, but these are generally not consumed via the diet. Traditional Asian diets provide a different isoflavone profile when compared with Western diets. Traditionally, Asians consumed minimally processed and fermented soy foods. Fermented soy foods account for approximately 30% of total soy-food consumption among Asians,[14] which correlates with a higher consumption of isoflavone aglycones. Forms of soy consumed in Asia include boiled soybeans, miso soup with tofu, natto, and soy milk.[15] Americans consume much less soy overall but also more processed soy foods, such as soy flour, textured vegetable protein, and isolated soy protein. Soy foods, including protein powders and soy-based infant formula, are considered rich sources of dietary isoflavones and contain 1 to 4.2 mg isoflavones per gram.[5] Approximately 25% of formula-fed infants consume soy formula, and these infants have isoflavone concentrations that are significantly higher on a body-weight basis than do adults with high soy intake.[16] The impact of early exposure to higher levels of isoflavones remains unclear. However, Asian populations whose isoflavone exposure begins earlier in life and continues throughout life have been the source of epidemiologic data demonstrating a relationship between soy consumption and health benefits.

TABLE 124-2 **Isoflavone Composition of Various Commercially Available Isoflavone Dietary Supplements**

PRODUCT	TOTAL ISOFLAVONES (mg/g)	RATIO OF (DAIDZEIN + GLYCITEIN)/ GENISTEIN	AGLYCONES
Healthy woman	67.77 + 0.52	1.41 + 0.01	9.5%
Soy extract	32.32 + 1.05	2.65 + 0.05	12.1%
Sundown	82.77 + 1.03	1.58 + 0.01	5.5%
Trinovin (red clover)	73.59 + 1.33	1.58 + 0.01	95.6%
Promensil (red clover)	78.15 + 1.61	1.36 + 0.07	99.9%
Kudzu root extract	35.89 + 0.17	6.65 + 0.04	13%

Data from Setchell KD, Brown NM, Desai P, et al. Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements. J Nutr 2001;131:1362S-1375S.

Individuals from Western cultures consume approximately 1 to 2 mg of isoflavones daily,[17] whereas total mean intake of isoflavones among Asian populations ranges from 25 to 50 mg daily.[3] In 1999, the U.S. Food and Drug Administration (FDA) approved a food-labeling health claim for soy protein in the prevention of coronary heart disease,[18] which subsequently led to a significant increase in retail soy-food consumption. Sales of U.S. soy foods increased from $2 billion in 1999 to $4.3 billion in 2005, and the number of soy-food products increased from hundreds to thousands.[5] Soy is also increasingly being used in food processing. Soy flour and soy protein isolates are added to processed meats, meat substitutes, breads, and other processed foods, making these items additional hidden sources of dietary isoflavones. For a comprehensive list of foods and their isoflavones content, the reader is referred to extensive published lists.[19,20] Overall, the combined effect of increased availability of frank soy-food products and hidden isoflavones in processed foods suggests an overall net increase in isoflavone intake among Western populations.

Dietary supplements are an additional source of isoflavones that contribute to an individual's total isoflavone intake. Soy, red clover, and kudzu root are the primary materials used to manufacture isoflavone supplements. These three materials provide differing amounts and types of isoflavones. For example, red clover contains formononetin and biochanin A, which are methoxylated forms of genistein and daidzein. Kudzu contains high levels of daidzein and puerarin, another methoxylated derivative of daidzein (Table 124-2).

Other Soy Constituents

Soy is a source of a variety of bioactive compounds that include protein, lignans, coumestans, saponins, plant sterols, phytates, protease inhibitors, and isoflavones. There are over 100 different phytochemicals present in soy, and much is unknown about the potential interactions that occur among components within soy foods or supplement formulations. The types and amounts of isoflavones and other soy constituents will vary based on the initial source, processing, and storage conditions. Although isoflavones are believed to be the most biologically active compounds in soy, the presence or absence of other potentially active constituents may provide synergistic, additive, or other effects on the physiologic impact of a particular soy product. Common and potentially misleading assumptions in the interpretation of research on the biological actions of soy are that the effects of soy-food consumption reflect the activity of one or a small number of its components and, conversely, that the activity of a purified soy component reflects the effects of eating soy foods.

TABLE 124-3 **Soy Constituents and Their Functions**

CONSTITUENT	FUNCTION
Protease inhibitors (Bowman-Birk inhibitor, Kunitz trypsin inhibitor)	Inhibit oncogene expression Inhibit chemically induced carcinogenesis Implicated in pancreatic hypertrophy (animal studies)
Lignans (enterolactone, enterodiol)	Phytoestrogen effects (agonistic/ antagonistic) Antitumor Antiviral
Phytosterols, beta-sitosterol	Binds cholesterol in the gut
Coumestans (coumestrol)	Phytoestrogen effects (agonistic/ antagonistic)
Saponins	Antioxidant Bind cholesterol and bile acids in the gut Antiviral (human immunodeficiency virus)
Phytates	Antioxidant Chelate metal ions (e.g., iron) Enhance natural killer cell activity
Isoflavones (genistein, daidzein, and their metabolites)	Phytoestrogen effects (agonistic/ antagonistic) Antimutagenic Antioxidant Antiinflammatory Antiproliferative Antihypertensive Angiogenesis inhibition

For a summary of soy constituents and their functions, see Table 124-3; for a detailed review, see Kang et al.[21]

Protease Inhibitors

Researchers have looked with interest at protease inhibitors (PIs) and their potential anticancer and antiinflammatory effects. Soybeans contain several possibly active PIs, including Bowman-Birk inhibitor (BBI), lunasin, and Kunitz trypsin inhibitor (KTI). BBI is particularly effective in suppressing carcinogenesis, and concentrated BBI, known as BBIC, was approved by the FDA as an Investigational New Drug in 1998.[22]

Researchers have questioned the concept that PIs contribute significantly to the anticancer effects of soy. This is partly because raw and cooked soy products are equally effective in reducing cancer incidence even though heating destroys virtually all PI activity.[23] Another point to consider is that PIs are peptides, and ingested PIs (such as BBIC) may not survive digestion and reach target tissues intact. Data suggest that lunasin may be the actual bioactive cancer-preventive agent in BBIC, and that BBI simply protects lunasin when soybeans and other PI foods are eaten by humans.[24]

Lignans

Lignans are capable of exerting a phytoestrogenic effect in humans.[25,26] In addition, they exhibit antitumor and antiviral activity.[27] The presence of lignans in soybeans has been hypothesized to

support beneficial health effects of soy foods while negating potential adverse effects in postmenopausal women by opposing the potential stimulatory effects of isoflavones, particularly genistein, on human breast tissue.[28]

Phytosterols

Phytosterols, such as beta-sitosterol, are found in soy products, although it has not been established that the amounts present in soy foods are sufficient to derive the health benefits associated with phytosterol consumption. Although poorly absorbed, phytosterols bind cholesterol in the gut and, based on this activity, phytosterols are the subject of an FDA-approved health claim for reducing the risk of heart disease.[29] An analysis of 22 randomized trials on isolated soy protein showed an average 3% reduction in low-density-lipoprotein (LDL) cholesterol.[2] The phytosterol content of isolated soy protein is significantly reduced compared with soy food, which suggests that the LDL-lowering activity of soy protein is not related to its phytosterol content.

Coumestans

The phytoestrogen coumestrol and other coumestan isoflavonoids have been found by some researchers in significant quantities in soy foods of all types.[19] On the other hand, Adlercreutz and Mazur[25] report the presence of coumestans only in soy sprouts.

Saponins

Saponins are found in many plants, including soybeans. They appear to have anticancer properties by virtue of their antioxidant and antimutagenic properties.[30] They are also known to reduce plasma and LDL cholesterol levels by affecting intestinal cholesterol absorption.[31] It has been suggested that saponins found in soybeans have important synergistic functions and may contribute to the LDL-lowering effect of soy protein.[32]

Phytates

Although phytic acid (inositol hexaphosphate) has been implicated in blocking the absorption of minerals, the phytate content of plants, including soy, seems to be responsible for some of the anticancer properties of vegetable-based foods. Phytic acid is a highly charged antioxidant, capable of scavenging hydroxyl radicals and chelating metal ions such as the prooxidant iron. Graf and Eaton[33] reported the iron-chelating ability of phytate to be more important than the activity of fiber in the dietary prevention of colon cancer. Vucenik et al[34] reported antitumor effects of phytic acid both in vitro and in animal models.

PHARMACOLOGY

Soy constituents have been shown to have estrogenic,[4] antiestrogenic,[4] antiviral,[35] anticarcinogenic,[36–38] bacteriocidal, and antifungal[39] effects. Isoflavones have demonstrated selective estrogen-receptor modulating,[40] antimutagenic,[37] antioxidant,[41,42] mild antiinflammatory,[43] antihypertensive,[43] and antiproliferative effects.[38,44]

Hormonal Effects in Infants

Soy formula is an infant food made from soy protein and other soy components; it is fed to millions of infants worldwide as a supplement or replacement for human milk or cow's milk. Soy formula has been shown to be comparable with milk-based formulas in supporting infant growth and development.[45] The potential for estrogenic effects to occur in infants fed with soy formula has raised the possibility of long-term safety considerations.

In the United States and Canada, approximately 25% of formula-fed infants are fed soy-based formulas.[5] The range of total isoflavone content in soy formula has been reported to be 10 to 47 mg/L.[46,47] Genistein is the predominant isoflavone found in soy formula (about 58% to 67%), followed by daidzein (about 29% to 34%) and glycetein (about 5% to 8%).[48] Infants fed soy formula also have higher blood levels of genistein and daidzein compared with other populations, with relatively high levels among vegan and Asian infants also consuming a traditional diet high in soy foods.[48] Data from the United States show that the concentrations of total genistein in blood samples from infants fed soy formula were higher than the maximum total genistein concentrations available for any other population. The average blood levels of total genistein in the soy formula-fed infants were approximately 160 times higher than the mean levels of total genistein in omnivorous adults in the United States, and a similar pattern was observed for urinary concentrations of genistein and daidzein.[49]

Adverse effects of phytoestrogens on the development and reproductive capacity of livestock, wildlife, and experimental animals have been reported.[50] Historically, there have been relatively few studies of children fed soy formula, and data are insufficient to judge if soy feeding results in adverse health consequences. The Arkansas Children's Nutrition Center is conducting a prospective longitudinal study comparing the growth, development, and health of breastfed children with those of children fed soy- and milk-based formulas from birth through age 6. After the first 5 years of the study, all of the children were found to be growing and developing within normal limits; there were no indications of adverse effects in the soy-fed children.[45] In 2009, the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction convened an expert panel to evaluate soy formula. This panel reviewed and evaluated all available data on soy formula and concluded that there is minimal concern for adverse developmental effects in infants fed soy infant formula.[48]

Millions of Asians have consumed large quantities of soy foods for hundreds of years without any apparent health risk and seemingly with health benefits. Long-term human studies of children fed soy formula and conclusions from the 2009 National Toxicology Program expert review panel collectively suggest that soy formula supports normal growth and is not associated with any adverse health effects.[45,48] Healthy dietary choices during the early phases of life positively influence long-term health. Therefore, additional studies are needed to affirm the safety of soy-based formulas and to assess the potential beneficial effects of consuming phytoestrogens in the form of soy isoflavones early in life.

Hormonal Effects in Adults

Much of the interest in the biological activity of isoflavones relates to their structural similarity to estrogens. In the 1960s it was discovered that isoflavones had a weak binding affinity for estrogen receptor alpha. It was later determined that isoflavones had mixed estrogen receptor agonist-antagonist properties and that isoflavones preferentially bind to estrogen receptor beta,[51] which has led some researchers to classify isoflavones as natural selective estrogen receptor modulators.[40] The binding of isoflavones to mammalian estrogen receptors is approximately 100 times weaker than the binding affinity of physiologic estrogens. However, this can be offset by higher circulating levels of isoflavones.[52]

After ingestion, isoflavone glycosides are converted by gut bacteria in the intestines to compounds with molecular weights and

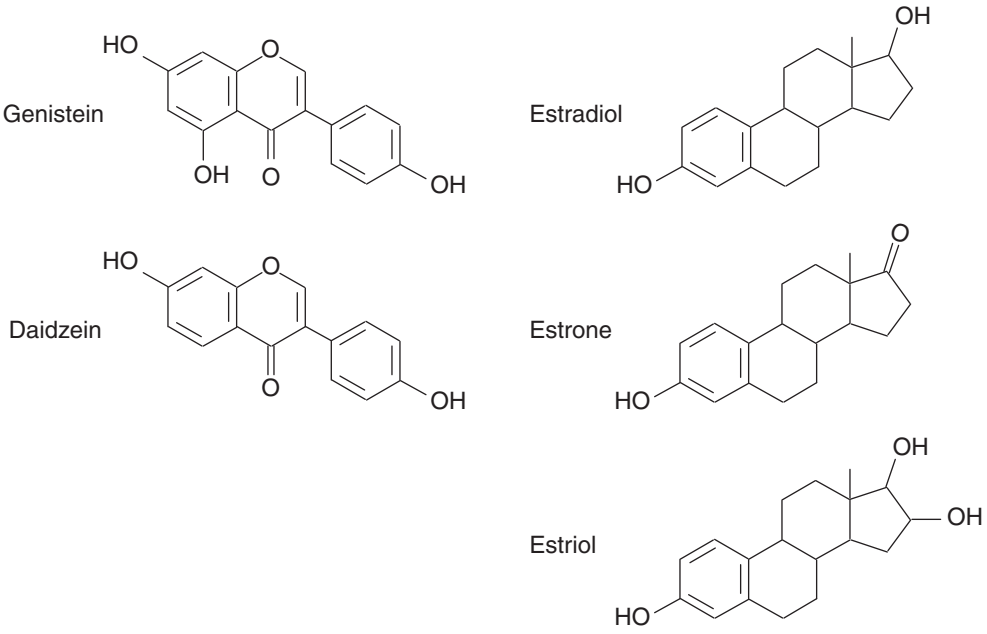


FIGURE 124-3 Structure of soy isoflavones compared with estrogens.

structures similar to those of steroid hormones (Figure 124-3). The pattern of isoflavone and lignan excretion in the urine is similar to that seen with endogenous estrogens.[53] Hormonal effects of isoflavones have been evaluated in several human clinical trials with equivocal results. Overall, isoflavones appear to have a modest hormonal effect in women, but the clinical implications of these modest hormonal changes remain to be determined.

A study of premenopausal women found that 60 g of soy protein, providing 45 mg of isoflavones daily, resulted in the suppression of midcycle surges of follicle-stimulating hormone (FSH) and luteinizing hormone (LH).[54] Plasma concentrations of estradiol rose during the follicular phase in the soy group, and cholesterol values decreased by 9.6%. The researchers noted that a similar effect occurs in women given tamoxifen (Nolvadex). There were no significant differences in estradiol levels between the soy and control groups at midcycle or during the luteal phase.[54] Studies have also reported soy protein isolate to have a stimulatory effect on breast tissue in premenopausal women, which is characterized by increased breast secretions, epithelial cell hyperplasia, and elevations of serum estradiol.[55] A meta-analysis of data from 8 randomized controlled trials comprising 1287 women compared isoflavones with placebo for 6 months to 3 years; it suggested no overall effect of isoflavones on breast density in all women combined or in postmenopausal women. There was a modest increase in mammographic breast density in premenopausal women, but it remains to be determined if these small effects are clinically relevant.[56] A study in which postmenopausal women received soy supplementation found a small estrogenic effect on vaginal cytology. However, no difference between soy-supplemented subjects and controls with regard to serum levels of FSH, LH, sex hormone–binding globulin (SHBG), endogenous estradiol, or body weight was observed.[57]

A systematic review and meta-analysis of 47 studies that investigated the effects of soy protein or isoflavones on circulating hormone concentrations in pre- and postmenopausal women concluded that isoflavone-rich soy products decrease FSH and LH in premenopausal women, and may increase estradiol in postmenopausal women. In premenopausal women, the meta-analysis demonstrated that isoflavone consumption did not affect estradiol, estrone, or SHBG concentrations, but did reduce FSH and LH by approximately 20%. Menstrual cycle was increased by 1.05 days. In postmenopausal women, there were no statistically significant effects on estradiol, estrone, SHBG, FSH, or LH. However, there was a small nonsignificant increase in estradiol.[58]

Overall, the current data indicate a weak effect of isoflavones on the hypothalamic-pituitary-gonadal axis in women. These data should be interpreted with caution because of the wide variety of soy products with markedly varying isoflavone content used in different studies. The clinical relevance of these modest hormonal changes requires confirmation through additional research. Historically, the consumption of soy products in Asian cultures from a very young age has not had any apparent negative effects related to hormone imbalances.

Mechanisms of Action of Soy Isoflavones

There are many proposed mechanisms for the therapeutic effects of isoflavones. These include:

- Binding of estrogen receptors[59]
- Inhibition of protein tyrosine kinase[60]
- Antioxidant properties[61]
- Interaction with peroxisome proliferator–activated receptors (PPAR alpha and gamma)[62]
- Weak competitive inhibition of thyroid peroxidase[63]

Several other mechanisms have also been proposed, including modulation of steroid synthesis and metabolism,[64] induction of DNA strand breakage resulting in apoptosis or cell death,[65] inhibition of angiogenesis,[66] modulation of SHBG,[67] inhibition of thrombin formation and platelet activation,[68] increase of LDL receptor activity,[69] and increase of membrane fluidity.[70]

CLINICAL APPLICATIONS

Cancer

Consumption of soy foods may contribute to lower incidences of certain types of cancers, such as breast and prostate cancers. The first clues that soy diets might provide protection from cancer

came from epidemiologic studies in which people from Asian cultures eating a diet high in soy foods demonstrated lower rates of several types of cancers. Messina et al[71] reviewed 21 epidemiologic studies that evaluated the effect of soy diets on 26 different cancer sites. An evaluation of the effect of nonfermented soy products in these studies found that 10 showed decreased risks for rectal, stomach, breast, prostate, colon, and lung cancers, and 15 showed no significant effect. Only one, in which fried bean curd was evaluated, showed an increased risk for esophageal cancer. On the other hand, the effects of fermented soy products—miso soup and soybean paste—were much less consistent. In 21 studies evaluating fermented soy products involving 25 cancer sites, a higher cancer risk was found in 4, mixed results were obtained in 4, no significant effects were found in 14, and a decreased risk was found in 3. The higher risks of cancer from consumption of fermented soy products appear to involve primarily the gastrointestinal tract—esophageal, stomach, colorectal, and pancreatic cancers.

A community-based prospective study of more than 30,000 Japanese adults (35 years and older) was conducted over 7 years. Data on soy and isoflavone intake from food frequency questionnaires determined that men in the highest tertile of soy intake had a significant inverse risk of death from stomach cancer. The same was seen in women, although the inverse association was of marginal significance. These results suggest that soy intake may reduce the risk of death from stomach cancer.[72] A 2010 systematic review of epidemiologic studies on the relationship between soy consumption and colorectal cancer risk identified a 21% reduction in colorectal cancer risk in women but not in men,[73] whereas a 2009 meta-analysis of epidemiologic studies investigating the associations between soy intake and the risk of endocrine-related gynecologic cancers (endometrial and ovarian) showed protective effects.[74]

Studies have shown that in addition to higher consumption of soy foods, Asian communities have demonstrated higher levels of biomarkers of isoflavone intake. Adlercreutz et al[75] found high urinary excretion of the soy isoflavones equol, daidzein, and O-desmethylangolensin in both men and women living in rural Japan. Mean plasma concentrations of the isoflavones genistein and daidzein in Japanese men were 492.7 and 282.5 nmol/L, respectively; men consuming a Western diet had 33.2 nmol/L for genistein and 17.9 nmol/L for daidzein.[76] An unanswered question related to the study of isoflavones in the treatment of cancer is whether the concentration achieved by dietary consumption of soy products is enough to influence tumor growth. Studies on human volunteers consuming soy beverages, which provided 42 mg genistein and 27 mg daidzein daily, resulted in peripheral blood concentrations of 0.5 to 1.0 mM,[4] concentrations much lower than necessary to inhibit growth of cultured cancer cells.[77] However, the same researchers found nontransformed mammary epithelial cell cultures to be much more sensitive to genistein, with inhibition of growth stimulation occurring in the range of 1 to 2 mM. This finding suggests a role for isoflavones in chemoprevention rather than as chemotherapeutic agents.

Breast Cancer

The breast cancer rate among Chinese and other Asian women is one-third to one-half that of Caucasian women, and evidence suggests that this variation is due to environmental rather than genetic differences.[78] Case-controlled, epidemiologic, in vitro, and animal studies point to the effectiveness of isoflavones in the prevention of breast cancer. The largest of the case-controlled studies, a prospective study of over 35,000 Singapore Chinese women, demonstrated that breast cancer risk was reduced significantly among women with high soy intake relative to women with lower soy intake. The study found a significant 18% reduction in breast cancer risk in association with the above median isoflavone intake. The association was more apparent in postmenopausal women, but this may be because of the relatively few premenopausal women included in the study. The authors concluded that these prospective findings suggest that approximately 10 mg of isoflavones per day, obtained in a standard serving of soy food, may have lasting beneficial effects against breast cancer development.[79] Another epidemiologic study showed that higher soy intake during adolescence is associated with a lower risk of breast cancer in adulthood. During adolescence, breast tissue is most sensitive to environmental stimuli, and exposure to soy isoflavones during this life stage may have an effect on the subsequent risk of developing breast cancer. The Shanghai Breast Cancer Study analyzed 1459 breast cancer cases and 1556 age-matched controls. Adolescent soy-food intake was inversely associated with the risk of developing breast cancer in a dose-dependent fashion for both pre- and postmenopausal women.[80]

Several other case-controlled studies have investigated the association between soy intake and breast cancer risk. Of these, several were conducted in Western populations with very low soy intake (average 1 to 2 mg/day) and not considered relevant.[81] Some studies conducted in populations with moderate to high soy intake have also demonstrated an inverse association between soy intake and breast cancer risk,[82] whereas others have demonstrated no relationship.[83,84] Emerging evidence suggests that the timing of soy exposure is an important codeterminant of risk, with stronger effects resulting from exposures at earlier ages.[80] Overall, there is a strong case for the cancer-inhibitory effects of soy on breast cancer that is underpinned by biological plausibility; it is supported by animal and in vitro evidence, as well as compelling results from several epidemiologic studies demonstrating an inverse relationship between soy intake and the incidence of breast cancer.

Prostate Cancer

The incidence of prostate cancer is lower in Japan than in Western nations. However, when Japanese men immigrate to regions where a Western diet is consumed, the prostate cancer rates are six times higher than those among native Japanese.[85] Environmental factors such as diet have been implicated in the development of prostate cancer. Isoflavones in the plasma of Japanese men were between 7 to 110 times the levels in Finnish men, with genistein present in the highest concentrations.[86] Similarly, low plasma isoflavone levels have been observed in men from other Western regions.[76]

Epidemiologic evidence points to the benefits of soy constituents in the prevention of prostate cancer.[85,87,88] For example, a case-controlled study of Japanese men examined associations between nutritional and other lifestyle factors and the prevalence of prostate cancer. In this study of 200 men and 200 age-matched controls from three geographic areas of Japan, BMI, physical activity, occupation, family history of prostate cancer, and medical history were not associated with prostate cancer risk. Intake of isoflavones and the aglycones genistein and daidzein were significantly associated with decreased risk.[85] In other experimental studies, soy protein or isoflavones have shown anticancer effects on biomarkers of cancer development and progression in cell lines[89,90] and in patients with prostate cancer.[91–93] However, in one study, supplementation with soy protein providing 116 mg of isoflavones daily did not lower serum total or free prostate-specific antigen in healthy men.[94] Overall, evidence suggests that consuming soy foods and the associated isoflavones may affect levels of prostate-specific antigen in cancer patients and high-risk men but not in healthy men. Additional studies are necessary to further

elucidate the relationship between isoflavone intake and the prevention of prostate cancer development or progression.

Cardiovascular Disease

There has been great interest surrounding soy protein and isoflavones and their potential role in reducing risk factors associated with cardiovascular disease. The majority of this interest focuses on the health claim approved by the FDA in 1999 for soy foods and coronary heart disease.[18] This claim was based on data showing the cholesterol-lowering effects of soy protein, not isoflavones. Conflicting data have emerged since the FDA-approved health claim for soy protein, and the FDA has announced its intent to reevaluate the evidence in support of the health claim. The American Heart Association (AHA) has acknowledged that soy foods are beneficial to cardiovascular health and overall health because of their high content of polyunsaturated fats, fiber, vitamins, and minerals and low saturated fat content, but concluded that the direct cholesterol-lowering effects of soy protein were of relatively little significance.[2] The beneficial cardiovascular health effects of consuming soy foods are likely magnified when these foods are used to replace other dietary proteins that are higher in saturated fat and common in Western diets.

Epidemiologic studies have shown that a higher intake of soy foods is inversely associated with coronary events, such as nonfatal myocardial infarction[95,96] and mortality from heart disease.[97] Animal studies have also demonstrated the cardioprotective effects of soy. In monkeys, soy protein diets compared with casein diets resulted in significant improvements in lipid profiles and insulin sensitivity and a decrease in arterial lipid peroxidation.[98] To date, however, human studies have not confirmed these findings. The cardiovascular benefits of soy may not be limited to reducing elevations of LDL cholesterol. Soy has been investigated for its impact on other cardiovascular disease risk factors with mixed results. Other possible cardiovascular benefits of soy may include its ability to modestly raise high-density lipoprotein (HDL) and lower triglycerides,[2,99] improve endothelial function,[100,101] and elicit mild antihypertensive effects, which are discussed below.

Lipid-Lowering Effects

In 1995, Anderson et al published a large meta-analysis of 38 controlled studies comparing soy- and animal-protein diets that found a statistically significant 12.9% decrease in serum lipids in the soy group. These changes were most significant in subjects with hypercholesterolemia.[102] The intakes of energy, total fat, saturated fat, and cholesterol were similar in the two groups. Subsequent to this meta-analysis, several additional well-controlled studies on the LDL-lowering effect of soy protein have emerged. Meta-analyses that included the newer data show a consistent LDL lowering effect of soy protein; however, the magnitude of the reduction is more modest, averaging 3%.[2,99] The AHA science advisory council has concluded that the cholesterol-lowering effect of soy protein is very small relative to the large amount of soy protein intake required to achieve this effect, which averages 50 grams daily. This is about half of the total daily protein intake for an adult. Several studies have tested the effects of soy protein and isoflavones separately, and a meta-analysis of existing data does not support a significant role of isoflavones in the cholesterol-lowering effects of soy protein.[103]

Hypotensive Effects

Dietary soy may have modest effects on blood pressure (BP). Several studies have evaluated the effect of a variety of isoflavone preparations on BP. One double-blind randomized trial of 40 men and women with mild to moderate hypertension examined the effect of soy milk consumption (isoflavone content unknown) on hypertension. Three months of soy milk consumption resulted in modest decreases in diastolic, systolic, and mean BP values compared with the same values in those subjects who consumed cow's milk (placebo). Urinary genistein measurements showed a significant association with the decrease in BP, which suggests a hypotensive effect of isoflavones.[104] In another study, 213 healthy subjects (108 men and 105 postmenopausal women) aged 50 to 75 years received either soy protein isolate (40 g soy protein, 118 mg isoflavones) or casein placebo for 3 months. A statistically significant decrease in BP in the soy protein group was observed.[105] However, several other studies have demonstrated less clinically significant results. In five other studies, reductions in BP were insignificant, with a weighted average reduction of only 1 mm Hg systolic pressure.[2] In 2005, the Agency for Health Research and Quality made a careful evaluation of 22 studies and concluded that neither soy protein nor isoflavones had a hypotensive effect,[106] and this conclusion has been echoed by the AHA.[2] However, a more specific meta-analysis reported the effect of the different soy preparations on BP with varied results. Soy protein isolate significantly reduced diastolic BP (by 1.99 mm Hg), although the effect on systolic BP was not significant. Soy foods or isoflavone supplements did not show a significant reduction in systolic or diastolic BP, but soy foods' reduction of both systolic and diastolic BP was nearly significant. The data for isoflavone extracts suggest a reduction in systolic BP that was close to significant but showed no effect on diastolic BP.[107] Additional research is needed to better understand the relationship between soy and BP, particularly work that focuses on comparing the effects of different soy preparations.

Other Cardiovascular Risk Factors

Limited evidence suggests that soy protein modestly raises serum HDL[2,99] and lowers serum triglyceride levels,[99] but a comprehensive review concluded that the effect was minimal to nil.[2] Several clinical studies have evaluated the effects of different soy preparations on endothelial function and have yielded mixed results. Overall, the evidence suggests a possible improvement in endothelial function with the consumption of soy products,[106] with some evidence suggesting that improvements may be more prominent in patients with initially impaired endothelial function[108] and higher levels of serum isoflavones.[109]

Menopause

Isoflavones are classified as phytoestrogens, which has led to much speculation about their ability to act as a natural alternative to hormonal therapy in postmenopausal women. Observational data indicate that Japanese women, who consume 50 to 100 times greater amounts of isoflavones than women consuming Western diets, have a nearly ten-fold lower incidence of vasomotor symptoms, such as hot flashes.[110] Over 50 studies have been conducted on various soy and isoflavone preparations (including those derived from non-soy sources) for their ability to reduce symptoms of menopause, primarily hot flashes. Many of these studies demonstrate the ability of isoflavones to diminish the severity and frequency of hot flashes in postmenopausal women, whereas others do not. Systematic reviews of existing data have concluded that isoflavones are efficacious,[111–113] whereas other reviews have concluded that they are no better than placebo.[114,115] Reviews that have failed to show an effect of isoflavones on hot flashes have not accounted for the potential for the type of soy preparation and relative isoflavone content to influence results. Critical reviews of studies that

used interventions with well characterized isoflavone content have concluded that the consumption of genistein, rather than total isoflavones, is responsible for reducing menopausal hot flashes and that 15 mg of genistein is minimally required to achieve benefit.[113]

Conflicting results from a large number of clinical trials that investigated the potential influence of isoflavones on menopausal hot flashes make it difficult to draw firm conclusions. The heterogeneity among trial results may be related to baseline frequency of hot flashes,[111,116] individually varying metabolism of isoflavones, and the genistein content of the intervention.[117] Overall, it appears that daily consumption of as little as 30 mg isoflavones (containing at least 15 mg genistein), in soy protein or as a dietary supplement may reduce hot flashes by as much as 50%. A 50% reduction in hot flashes accounts for a 30% placebo effect and a 20% benefit of isoflavones over placebo, which results in clinically relevant improvements in quality of life. Efficacy increases with increasing dose, up to 100 mg isoflavone daily; the benefit is greatest in women with the highest number of baseline hot flashes and when isoflavones are consumed in divided doses throughout the day.[112] In considering reports suggesting that hormone replacement therapy may be associated with negative side effects, health professionals are justified in recommending 50 to 100 mg isoflavones (with a minimum of 15 mg genistein) to women for relief of menopausal hot flashes. The efficacy of the treatment can be individually determined, and the benefits should be evident within 4 weeks.[118]

Osteoporosis

A large body of research has investigated the impact of isoflavones on various markers of bone health, including bone mineral density (BMD) and markers of bone formation and resorption. A meta-analysis of randomized controlled trials concluded that there is evidence demonstrating that isoflavone intervention attenuates bone loss of the spine and decreases markers of bone resorption while increasing markers of bone formation in menopausal women.[119] Similar results have been shown in postmenopausal women.[120,121] Importantly, evidence indicates that soy protein and isoflavone-poor soy protein do not improve markers of bone health, suggesting that isoflavones are the constituents responsible for the beneficial effects and that soy protein may negate the improvements on the relevant markers.[5]

A 2010 meta-analysis conducted to explore the effect of ingesting soy isoflavone extracts on BMD in menopausal women included 11, 7, 5, and 5 randomized controlled trials for estimating the effects on spine, femoral neck, hip total, and trochanter BMD respectively. The analysis included data from 1240 menopausal women and showed that an average intake of 82 mg (47 to 150 mg) isoflavones for 6 to 12 months significantly increased spine BMD by 22.25 mg/cm^2 (2.38%) compared with controls. Varying effects among all the studies appeared to be dependent on intervention duration, region of participation (Asian versus Western) and baseline BMD. No significant effects were found for areas of the hip. Overall, the data suggest a positive role for isoflavones in the prevention of bone loss, but more human trials are needed to address factors affecting the magnitude of this effect, and to determine why results have been generally more favorable in the spine and not in the hip.[122]

Cognitive Function

Epidemiologic studies have associated decreased brain size and memory with tofu consumption.[123,124] On the other hand, epidemiologic studies also point to lower rates of dementia in Asian populations.[125]

Human studies investigating the effect of isoflavones on cognitive function have reported beneficial effects.[126] Long-term administration of soy or isolated isoflavones for menopausal support has also been found to improve learning, logical thinking, and planning ability in postmenopausal women.[127,128] Other studies have demonstrated that isoflavone consumption enhances spatial working memory in men[129] and immediate and long-term episodic memory and mental flexibility in men and women.[130] Although the association between tofu consumption and reduced brain size in men raises interesting questions, clinical studies suggest that soy foods and their constituents may enhance cognitive function and have not been shown to be detrimental to central nervous system function.

Safety Considerations

The estrogen-like properties of isoflavones proposed to be responsible for several health benefits have also raised questions about potential adverse health effects at specific stages of life. The primary concern is the potential risk of isoflavone exposure to estrogen-sensitive breast cancer patients and women at high risk of developing the disease. In vitro and animal studies have shown growth-promoting effects of genistein on mammary tumors.[131] However, there are many limitations to drawing conclusions from these experimental models.[132] The available human research, including both clinical and epidemiologic evidence, is supportive of safety. In fact, a large epidemiologic study in China showed that, among women with breast cancer, soy-food consumption was significantly associated with decreased risk of recurrence and death. This population-based cohort study of 5033 breast cancer patients followed for over 3.9 years showed that women in the fourth quartile of soy intake experienced a reduced risk of tumor recurrence and lower total mortality.[133] Previous epidemiologic studies have demonstrated similar results,[134,135] and clinicians with expertise in nutrition have concluded that in light of the in vitro experiments together with the epidemiologic observations and clinical experience, isoflavones can be considered to be safe compounds and their consumption as whole soy foods to be safe for breast cancer patients.[132,136] Additional data on the impact of soy-food and isoflavone consumption on breast cancer prognosis are necessary before these nutrients should be recommended in the treatment of breast cancer.

Like the breast, the endometrium is a hormone-dependent tissue that has estrogen receptors. Estrogen-only therapy is known to increase endometrial cancer risk.[137] The cumulative data providing evidence related to isoflavone intake on risk markers for endometrial cancer have not demonstrated clinically significant changes in endometrial histology that would support the hypothesis of risk associated with isoflavone intake.[74,115]

Isoflavones act as weak competitive inhibitors of thyroid peroxidase, which converts triiodothyronine (T3) to thyroxine (T4).[138] This mechanism has led to concerns that isoflavone consumption may exacerbate thyroid dysfunction in subjects with subclinical hypothyroid disease. All polyphenols from fruits and vegetables are inhibitors of thyroid peroxidase, many with more potent inhibition than soy isoflavones.[139] It is possible that in individuals with very low iodine intake, polyphenol-induced reductions in thyroid peroxidase could result in a low production of thyroid hormones; however, attempts to demonstrate thyroid deficiency in consumers of soy or isoflavones have failed. A comprehensive review concluded on the basis of 14 clinical trials that in euthyroid individuals consuming sufficient iodine, there is no evidence that isoflavones exposure affects thyroid function.[140] Iodine-deficient individuals should be advised to consume the recommended

amount of iodine and not to avoid fruit and vegetable polyphenols such as isoflavones.

DRUG-NUTRIENT INTERACTIONS

Dietary supplementation of soy protein concurrent with oral levothyroxine therapy appears to decrease absorption of levothyroxine.[141] This effect can be mitigated by separated dosing.

In a model of estrogen receptor–positive postmenopausal breast cancer, lower doses of genistein have been shown to inhibit the therapeutic effects of tamoxifen therapy.[142] An animal study demonstrated that tamoxifen suppression of breast tumor growth in ovariectomized athymic mice was negated by the administration of 1000 ppm dietary genistein.[143] Therefore, it has been proposed that postmenopausal women undergoing tamoxifen therapy for estrogen-responsive breast cancer should use caution in consuming dietary genistein. In contrast, other in vitro studies showed that isolated genistein, as well as an isoflavone-rich soy concentrate, markedly inhibits tumor growth and enhances rather than inhibits the efficacy of tamoxifen.[144,145] In addition, the largest epidemiologic study of breast cancer survivors specifically designed to evaluate the influence of soy-food intake on breast cancer outcomes found no evidence that isoflavones inhibited the efficacy of tamoxifen.[133] Despite conflicting evidence, the totality of the data suggest that isoflavones may have a synergistic or additive effect to that of tamoxifen in patients with breast cancer. However, until more clinical data become available, patients should be advised that a moderate intake of soy foods is safe and potentially beneficial, whereas the therapeutic use of isolated isoflavones is not advised for women being treated for breast cancer with tamoxifen.

CONCLUSION

Research indicates that soy and its individual constituents have several potential health benefits. The primary isoflavones—genistein and daidzein—as well as their metabolites exert a wide array of effects that may offer protection against cancer, cardiovascular disease, and osteoporosis. Soy and its constituents also appear to have therapeutic applications in menopause. Whether soy has a negative or positive effect on cognitive function remains to be elucidated. Results of controlled human trials on the potential health benefits of soy and its constituents—such as the reduction of risk factors associated with heart disease, prevention of postmenopausal bone loss, reduction of risk of certain types of cancer, and relief of menopausal hot flashes—remain promising but inconclusive. Interindividual differences in response to isoflavone consumption and differences in the chemical composition of soy products have contributed to inconsistencies in these results. Future research that takes these variables into account will generate a more specific understanding of the health effects of soy-food and isoflavone consumption.

Soy constituents, particularly the isoflavones, have raised certain safety questions owing to their phytoestrogen effects. Because in some cases they act as estrogen agonists and in others as antagonists, the use of these isoflavones in patients with hormone-sensitive cancers remains open to debate. Further study is needed to determine whether isoflavone use in these situations is harmful or beneficial. Data and analyses have attenuated theoretical concerns that isoflavones may inhibit thyroid function or act as endocrine disruptors in children consuming soy-based infant formula.

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CHAPTER 125

Tabebuia avellanedae (syn. *T. impetiginosa*, Lapacho, Pau D'Arco, Ipe Roxo)

Terry Willard, CIH, PhD, and Michael T, Murray, ND

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INTRODUCTION

The taxonomic division of plants with medicinal uses in the Bignoniaceae family is confusing. The literature often interchanges the genera of *Tecoma* and *Tabebuia*. Some are now using the name *Tabebuia impetiginosa* as a synonym. At least four species have been called lapacho:

- *Tecoma ochracea*
- *Tecoma ipe*
- *Tabebuia cassinoides*
- *Tabebuia avellanedae* syn. *Tabebuia impetiginosa*

This chapter considers the *Tabebuia* genus.

GENERAL DESCRIPTION

The tree from which lapacho is obtained is a member of the Bignoniaceae family known as *Tabebuia avellanedae, Tabebuia impetiginosa,* or *Tabebuia ipe*. There are about 100 species of these evergreen trees or shrubs, native to tropical America. They can grow up to 125 ft tall and have very showy rose- to violet-colored flowers that bloom in profusion just before the new leaves appear.

Because the taxonomy of these plants is so difficult, it is quite possible that there is confusion even among trained gatherers.

CHEMICAL COMPOSITION

Many of the studies and chemical analyses on *Tabebuia* species have been performed on the heart wood, but the bark and inner bark are the products available in the marketplace and the parts used in folklore. The major components of *T. avellanedae* are 16 quinones (mostly with C_{15} skeleton) containing both naphthoquinones (seven, C_{10} to C_5) and anthraquinones (nine, C_{14} to C_1). Both of these groups of quinones rarely occur in the same plant. The lapachol content is usually 2% to 7%. The quinones are listed in Box 125-1. Other compounds found are lapachenole, quercetin, and *o*- and *p*-hydroxybenzoic acids.[1] The action of lapacho comes from an array of quinones and other constituents, not just one or two.

HISTORY AND FOLK USE

The indigenous peoples of Brazil also refer to this tree as pau d'arco or ipe roxo. The inner bark has been used for medicinal purposes for centuries as a folk remedy for a wide variety of afflictions, including the following[2-5]:

- Boils
- Chlorosis
- Colitis
- Diarrhea
- Dysentery
- Enuresis
- Fever
- Pharyngitis
- Snakebite
- Syphilis

BOX 125-1 **Quinones in *Tabebuia avellanedae***

Naphthoquinones
- Lapachol
- Menaquinone-I
- Deoxylapachol
- Beta-lapachone
- Alpha-lapachone
- Dehydro-α-lapachone

Anthraquinones
- 2-Methylanthraquinone
- 2-Hydroxymethylanthraquinone
- 2-Acetoxymethylanthraquinone
- Anthraquinone-2-aldehyde
- 1-Hydroxyanthraquinone
- 1-Methoxyanthraquinone
- 2-Hydroxy-3-methylquinone
- Tabebuin (a newly discovered compound)

- Wounds
- Ulcers
- Respiratory problems
- Arthritis
- Cystitis
- Constipation
- Prostatitis
- Poor circulation
- Constipation
- Cancers of the esophagus, head, intestine, lung, prostate, and tongue

Lapacho is reported to be alexiteric, analgesic, anodyne, antidotal, antimicrobial, diuretic, and fungicidal.[2]

PHARMACOLOGY

During the nineteenth century, Lapacho was subjected to scientific scrutiny, with the first active constituent, lapachol, isolated by Paterno in 1882 (Figure 125-1).

Interestingly, many of the scientific studies have found lapacho and lapachol to be more effective in treating malaria and cancerous tumors through oral ingestion rather than intravenous or intramuscular injection.[6]

An herbalist's interpretation would be that the body's recuperative powers are more effectively stimulated by the natural route of nutrient plant material absorption through the digestive tract. Although most of the studies have been of individual chemicals, some show significantly better results with the whole extract and diminishing effectiveness as the extracts are refined or individual chemicals are tested.[6,7]

Antimicrobial Activity

Antibacterial Activity

Lapachol isolated from the *T. avellanedae* tree has exhibited antimicrobial activity against gram-positive and acid-fast bacteria and *Brucella* species as well as fungistatic behavior.[8,9] It is important to note that the research team found that progressive purification reduced the antimicrobial activity of the extract. This finding led to the conclusion that more than one active substance was present in the original extract.

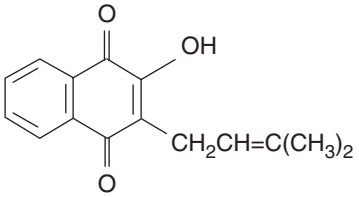


FIGURE 125-1 Lapachol.

It was eventually found that, along with lapachol, the extract of the *Tabebuia* tree contained α-lapachone, β-lapachone, and a newly discovered quinone called xyloidone.

Several of the naphthoquinones[1] exhibit strong microbicidal and fungicidal activities (Table 125-1).

Lapachol has been shown to have both antimicrobial and antiviral activity.[8,10,11] Beta-lapachone shows diversified antiparasitic activity as well as antiviral action.[12,13] Alpha-lapachone is also active against certain parasites, and xyloidone is active against numerous bacteria and fungi.[14,15] Another lapacho component, the flavonoid quercetin, is cytotoxic for certain parasites.[16]

Xyloidone is effective against a wide array of organisms, including *Staphylococcus aureus* and the *Brucella* species. This component also inhibits the causative agents of tuberculosis, dysentery, and anthrax.

Mechanism of Action. Lapachol, like many naphthoquinones, acts as a respiratory poison by interfering with electron transport in microbes.[17,18] At concentrations of 100 mg/L, lapachol was found to inhibit O_2 uptake by *Plasmodium knowles* by 74% and succinate oxidase systems by 26% and thus to exhibit antimalarial activity.[19,20] Mitochondrial respiration is inhibited by 50% at a lapachol concentration of less than 110 μmol/L.[21] Increasing doses of lapachol produced progressive respiratory inhibition in tumor cells isolated from animals. Oxygen consumption and oxygen metabolite production are inhibited in neutrophils on administration of lapachol.[22]

Lapachol has now been shown to act as an uncoupler of oxidative phosphorylation. Lapachol prevents synthesis of adenosine triphosphate by stimulating respiration in the absence of a phosphate acceptor. This effect is most pronounced at a high pH, at which lipid solubility is the lowest.[23]

Lapachol inhibits certain enzymes; in particular, it is a competitive inhibitor of glycolase I in erythrocytes. Lapachol also demonstrates noncompetitive inhibition of α-keto-aldehyde dehydrogenase, leading to the accumulation of toxic α-ketoaldehydes.[24] Lapachol demonstrated 64% inhibition of 3-α-hydroxysteroid–mediated transhydrogenase at a concentration of 10^{-5}M (well within the dosage range).[25]

Antiviral Activity

Lapachol has proved to be active against certain viral strains, including herpesvirus hominis types I and II.[25] Hydroxynaphthoquinone has been shown to effectively inhibit four influenza viruses. Lapachol also significantly inhibits poliovirus and vesicular stomatitis virus.[10]

Beta-lapachone's antiviral activity has been demonstrated by its ability to inhibit certain enzymes, such as DNA and RNA polymerases.[26] Beta-lapachone was tested against avian myeloblastosis virus and Rauscho murine leukemia virus and found to inhibit retrovirus reverse transcriptase.[27] In the presence of dithioreitol, β-lapachone inhibits eukaryotic DNA polymerase-alpha activity. Although the mechanism of action for enzyme inhibition is complex, it may be related to superoxide production.[26] This issue has

TABLE 125-1 **Antimicrobial Activity of *Tabebuia avellanedae****

MICROORGANISM	LAPACHOL	CHOROHIDRO-LAPACHOL	ALPHA-LAPACHONE	BETA-LAPACHONE	XYLOIDONE
B. subtilis	60.0-80.0	8.0-10.0	40.0-50.0	1.0-2.0	4.0-6.0
B. mycoides	40.0-60.0	10.0-15.0	40.0-50.0	5.0-8.0	20.0-30.0
B. anthracis	40.0-60.0	20.0-30.0	40.0-50.0	4.0-6.0	20.0-30.0
S. aureus	60.0-80.0	30.0-40.0	30.0-40.0	2.0-4.0	15.0-20.0
Sar. lutea	40.0-60.0	15.0-20.0	30.0-40.0	4.0-6.0	20.0-30.0
S. hemolyticus	>100.0	60.0-80.0	60.0-80.0	10.0-15.0	>50.0
M. tuberculosis	80.0-100.0	40.0-60.0	30.0-50.0	10.0-15.0	10.0-15.0
M. smegmatis	80.0-100.0	60.0-80.0	30.0-50.0	15.0-20.0	15.0-20.0
N. asteroids	>100	40.0-60.0	60.0-80.0	10.0-15.0	20.0-30.0
N. catarrhalis	40.0-60.0	30.0-50.0	80.0-100.0	10.0-15.0	<20.0
E. coli	>100.0	>100.0	>100.0	>100.0	>100.0
K. pneumoniae	>100.0	>100.0	>100.0	>100.0	>100.0
S. typhosa	>100.0	>100.0	>100.0	>100.0	>100.0
Br. suis	15.0-20.0	2.0-4.0	20.0-30.0	0.6-1.0	0.8-1.0
Br. abortus	15.0-20.0	2.0-4.0	30.0-40.0	1.0-2.0	1.5-2.0
Br. melitensis	10.0-15.0	2.0-4.0	30.0-40.0	1.0-2.0	1.5-2.0
C. albicans	>100.0	40.0-60.0	80.0-100.0	80.0-100.0	30.0-50.0
C. krusei	>100.0	40.0-60.0	80.0-100.0	80.0-100.0	50.0-60.0
C. neoformans	>100.0	40.0-60.0	50.0-80.0	30.0-50.0	40.0-60.0

*Minimum inhibitory concentrationn (mcg/mL).

great significance for possible treatment of both human immunodeficiency virus and Epstein-Barr virus (the implicated viruses in acquired immunodeficiency syndrome and Epstein-Barr syndrome, respectively).

Beta-lapachone also inhibits Friend virus and was the only substance among a number tested that prolonged survival time of chickens infected intraperitoneally with Rous sarcoma virus.[28]

Antiparasitic Activity

The trematode *Schistosoma mansoni* is the causative agent of the common tropical disease schistosomiasis. The cercariae of this blood fluke live in water and enter the host by penetrating the skin. This debilitating disease, a serious problem in many tropical areas, causes weakening of the host and increases susceptibility to a variety of other pathogens, some of which may be fatal.

Lapachol has been tested as a topical barrier to the cercariae and has been found to be highly effective at preventing its penetration.[26,29] Oral lapachol was also tested and found to significantly reduce penetration. After being consumed, the lapachol was secreted onto the skin, apparently by the sebaceous glands, where it again acted as a topical barrier. The cercariae seek to penetrate the host through or near the sebaceous glands, suggesting that dietary administration of lapachol would be an efficient means of protecting against infection. Alpha-lapachone and β-lapachone, also components of lapacho, both exhibited activity against *S. mansoni*.[8] Beta-lapachone is notably effective against *Trypanosoma cruzi,* a zoomastigote responsible for trypanosomiasis, or Chagas' disease, which occurs in both acute and chronic forms and has no known cure.

Beta-lapachone causes complete inhibition of *T. cruzi* at concentrations of 0.8 to 5.0 μg/mL and progressively inhibits motility with increasing concentrations. When *T. cruzi* epimastigotes were incubated with the quinone, they were subjected to nuclear, mitochondrial, endoplasmic reticular, and cytoplasmic membrane damage and underwent alterations in the chromatin distribution. Respiration rates were lowered, the mitochondria became swollen, and glucose and pyruvate oxidation was inhibited. Lipid peroxidation was stimulated, leading to decreased cell viability.

In addition, in vitro testing resulted in the rapid decay of DNA, RNA, and protein as well as DNA breakage in *T. cruzi*. This was accompanied by inhibition of DNA, RNA, and protein synthesis and the instigation of "unscheduled" DNA synthesis.[30,31]

It is thought that this toxic action against parasites is at least partly due to superoxide production.[32] Both O_2^- and H_2O_2 are intermediates of oxygen reduction, and both are toxic to living organisms. When β-lapachone is introduced to *T. cruzi*, it rapidly enters the epimastigote and is reduced to its semiquinone form in the mitochondria and microsomes of the pathogen.[33] Superoxide is produced by the reduction of molecular oxygen, which is facilitated by autooxidation of the semiquinone free radical. Superoxide is then converted to hydrogen peroxide via superoxide dismutase. Stimulation of lipid peroxidation follows and the cell degenerates.

Antifungal Activity

In addition to its activity against a variety of bacteria, components of lapacho are known to possess potent antifungal capabilities.[11,34] The quinone xyloidone inhibits several species of fungus (including *Candida albicans*, *Candida krusei*, and *Cryptococcus neoformans*).[11] The antifungal activity of aqueous, dichloromethane, and methanol extracts from *T. avellanedae* were also compared, and it was found that the aqueous and methanol extracts showed the highest antifungal activity.[35] *T. avellanedae* bark was found to be active against *Aspergillus fumigatus*, *C. neoformans*, *Microsporum gypseum*, *Penicillium purpurogenum, Saccharomyces cerevisiae,* and *Trichophyton mentagrophytes*.[35]

Antineoplastic Effects

Because of the folklore information surrounding the tumor-reducing qualities of the herb lapacho, it underwent extensive study by the National Cancer Institute (NCI). After initial positive results, lapachol was judged to be the most active antineoplastic agent. Lapachol entered phase I clinical trials at the NCI in 1968 on the basis of its activity against Walker 256 tumors (with a confidence rate exceeding 90%). During these trials it was difficult to obtain therapeutic blood levels of lapachol without some mild toxic side effects, such as nausea, vomiting, and anti–vitamin K activity. This occurrence is quite difficult to understand, because later studies found the toxicity to be very low.[2] The investigative new drug (IND) status for the drug was closed in 1970 due to these toxicity issues.[36]

It has been shown, however, that some of the anthraquinones in lapacho have vitamin K activity; therefore, use of the whole herb would compensate for lapachol's effect on vitamin K.[37]

The approach just described indicates a flaw in the underlying philosophy of the pharmaceutical sciences and the NCI program. Because the initial studies came from a whole plant, the detailed studies should have been undertaken on the whole plant. Some of the other quinones have also been shown to have antineoplastic activities. Was it too complex to consider the chemical reactions of the more than 20 components found in lapacho? Or was the standard economic/political incentive for patenting an analog an impediment to the investigation of a plant species?

Lapachol is rapidly absorbed through the gastrointestinal tract after oral administration to rats bearing Walker 256 tumors. It is taken up by all tissues except the brain and blood cells. A significant amount appears in the tumor after 6 hours, with most of the drug disappearing from the other body tissues. The half-life of intravenous lapachol is 33 minutes in mice (75 minutes in dogs). Lapachol is extensively metabolized and excreted mostly in the feces.[38] Beta-lapachone has been shown to inhibit the growth of a large variety of tumor cells, including epidermoid laryngeal cancer; prostate, colon, ovary, and breast cancers; and also different types of leukemia cells.[39]

The theories on how lapachol works as an antineoplastic agent vary considerably. One of the most prominent involves reduction-oxidation (redox) cycle capabilities. Lapachol was found to be an in vivo inhibitor of respiration at chemotherapeutic doses.[5] Later, lapachol was shown to augment the flow of electrons from reduced nicotinamide adenine dinucleotide phosphate to form oxygen-related free radicals. These seem to be site-specific free radicals that bind to the cancerous DNA or RNA, producing either superoxides or free hydroxyl radicals.[40,41]

There seems to be a redox potential that is important for the inhibition of electron transfer in coenzyme Q_{10}.[42] Bennett et al[43] argued that this respiration poisoning is not the mechanism of antitumor activity. In their study, lapachol was shown to significantly reduce the pool of uridine triphosphate, the largest pool of the pyrimidine nucleotides (exposure time was very short, 2 to 4 hours).

Lapachol is theorized to be like dichloroallyl lawsone in that it blocks pyrimidine biosynthesis through inhibition of dihydroorotate dehydrogenase.[17] It is also believed that the antineoplastic activities of lapachol might stem from its interaction with nucleic acids,[41] and it has been proposed that interaction of the naphthoquinone moiety between base pairs of the DNA helix occurs with subsequent inhibition of DNA replication and/or RNA synthesis. Free amino groups in the sugar moiety are necessary for DNA binding.[44]

Beta-lapachone has an effect on the modulation of cell growth and apoptosis in human colon carcinoma tumor (HCT-116) cell lines. Exposure of HCT-116 cells to β-lapachone resulted in growth inhibition and induction of apoptosis in a dose-dependent manner. The researchers suggest, therefore, that β-lapachone–induced apoptosis may be partly regulated through the inactivation of the second messenger NF-κβ system.[45]

Beta-lapachone was also shown to decrease the viability of sarcoma cells by stimulating lipid peroxidation. This was accomplished through the following activities[32]:

- Reduction of lapachone at the mitochondrial and microsomal membranes with generation of the semiquinone form
- Autooxidation to produce O_2
- Production of H_2O_2 via superoxide dismutase

More than one mechanism has been shown to underlie the antineoplastic effect.[7] There is ongoing positive research on cancers of the liver,[46,47] bladder,[48] prostate,[49,50] lung,[51] colon,[45] and breast (estrogen receptor site inhibition).[52]

Antiinflammatory Activity

Extracts of the bark from *T. avellanedae* demonstrate clear antiinflammatory activity with low toxicity.[53] Pau d'arco douching and the use of tampons soaked in an alcoholic extract of lapacho have been shown to be very successful against a wide range of inflammations, such as vaginitis, cervicitis, and cervicovaginitis.[1,27,34]

An aqueous extract of the inner bark of *T. avellanedae* has demonstrated antinociceptive and antiedematogenic activities in mouse models, with a possible antinociceptive effect correlated with the adenosine system.[54] Adenosine itself is posited to interact with receptors coupled with G protein for this effect.[53,55] Two animal studies using carrageenan-induced subplantar edema have also exhibited the antiinflammatory abilities of lapachol.[54,56] In one study, the second phase of inflammation, which is correlated with the appearance of prostaglandins and kinins, was where lapachol seemed to exert the greatest antiinflammatory effect.[56] Lapacho compounds have also demonstrated potent activity against the growth of human keratinocytes and appear to be promising as effective antipsoriatic agents; β-lapachone displayed activity comparable with that of the antipsoriatic drug anthralin. It has been shown that the decoction similar to ethnobotanical use suppresses PGE_2.[57] Beta-lapachone has been found effective in wound healing by inducing cell proliferation, including keratinocytes, fibroblasts, and endothelial cells.[58]

Other studied actions:

Possible antidepressant[59]; also active against ulcers (as well as *H. pylori*),[60,61] immune modulation,[62] platelet aggregation,[63] and antioxidant volatile fractions.[64]

Quercetin

Quercetin is a highly active flavonoid that inhibits a wide range of enzymes and suppresses the synthesis of DNA, RNA, and proteins.[65] Quercetin's cytotoxicity may be due to the fact that it inhibits mitochondrial electron transport.[66] Hodnick et al[66] have noted that quercetin produced a substrate-independent potassium cyanide–insensitive respiratory burst in mitochondria. Other flavonoids that have demonstrated this activity produced O_2^- and H_2O_2, suggesting that quercetin may also generate these cytotoxic chemicals.

The following are among the enzymes inhibited by quercetin[30,32,67]:

- Nicotinamide adenine dinucleotide (NADH) oxidase
- Phosphodiesterase

- Cyclic adenosine monophosphate (cAMP)–independent protein kinases
- Ca^{2+} phospholipid–dependent protein kinase
- Tyrosine protein kinases

Shapiro et al[16] suggested that the cytotoxicity of quercetin may be due to its chelating abilities. This agent is trypanocidal to *Trypanosoma brucei*, a livestock parasite belonging to the same genus as *T. cruzi*. Soon after the parasite enters the host, the host's unsaturated iron-building proteins remove iron from the hemoflagellate. Because the parasite is unable to synthesize heme, it encounters a shortage of iron. By chelating the host's iron, quercetin blocks utilization of iron by the parasite yet does not adversely affect the host. This flavonoid is also cytotoxic against *Crithidia fasciculata*. The fact that quercetin is small and lithophilic seems to be important to its activity.

Like lapachol, quercetin inhibited O_2 consumption and H_2O_2 production in neutrophils.[68] Many flavonoids exhibit antiviral activity. When mice that had been intracerebrally infected with attenuated viruses, including rabies, were given quercetin in their diet, a prophylactic effect was observed.[69] Quercetin inactivates the following viruses (*inactivation* is defined as reducing viral infectivity tenfold):

- Herpes simplex type 1
- Respiratory syncytial virus
- Pseudorabies/Aujesky's virus
- Poliovirus type 1
- Parainfluenza type 3
- Sindbis virus
- Potato virus x

CLINICAL APPLICATIONS

The spectrum of clinical applications of *T. avellanedae* is quite broad. Current use has focused on lapacho's antineoplastic and antimicrobial activity. Its use is extremely popular in the treatment (both topical and internal) of intestinal candidiasis and vaginal candidiasis. Research has also focused on antipsoriatic and antiedema properties. There are also many anecdotal reports of remission of different forms of cancer with use of this botanical.[68]

Unfortunately, because of lack of quality control and confusion about the portion of the plant to use, it is highly likely that many practitioners are not using effective materials. This likelihood could explain varying clinical results.

DOSAGE

The usual form of administration of lapacho is as a decoction, with the standard dose being 1 cup of decocted bark two to eight times per day. The decoction is made by boiling 1 teaspoon of LaPacho for each cup of water for 5 to 15 minutes.

A more precise dosage based on a lapachol content of 2% to 4% would be 15 to 20 g of bark boiled in 500 mL or 1 pint of water for 5 to 15 minutes three to four times daily.

Dosages of other forms (aqueous extract, fluid extract, solid extract) should be based on lapachol content, providing a daily lapachol intake of 1.5 to 2 g/day.

A tampon that has been soaked in the decoction or fluid extract is used in the treatment of vaginitis and cervicitis. The tampon is inserted vaginally and changed every 24 hours until resolution.

TOXICOLOGY

Although anti–vitamin K activity has been reported for lapachol, the presence of several vitamin K–like substances in the whole plant suggests that this is not a problem.

Long-term administration of lapachol at a dose of 0.0625 to 0.25 g/kg per day to monkeys was found to produce moderate to severe anemia. The anemia was most pronounced during the first 2 weeks of treatment. Death occurred in monkeys after six doses of lapachol at 0.5 g/kg per day and after five doses of 1 g/kg per day.[6]

There have been no reports in the literature of human toxicity when the whole bark is used as a decoction. Long-term use of large doses of the decoction by indigenous peoples has shown no adverse reactions. Because low doses have been reported to cause nausea and vomiting,[70] only a qualified naturopathic physician, herbalist, or other practitioner experienced in its use should attempt to use this botanical medicine.

DRUG INTERACTIONS

No interactions with pharmaceutical drugs have been reported, but because of its known anti–vitamin K–like activity, there may be an interaction with anticoagulant medications, such as warfarin, that could theoretically result in increased bleeding tendencies. This effect would probably be minimized if treatment involved the whole herb rather than specific components. In any case, caution is warranted.

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CHAPTER 126

Tanacetum parthenium (Feverfew)

Kathy Abascal, BS, JD, RH(AHG), and Eric L. Yarnell, ND, RH(AHG)

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Tanacetum parthenium (family: Asteraceae)
Synonym: *Chrysanthemum parthenium*
Common names: feverfew, featherfew

GENERAL DESCRIPTION

Feverfew *(Tanacetum parthenium)* is a composite plant cultivated in flower gardens throughout Europe and the United States. The name feverfew is a corruption of the word *febrifuge,* signifying its fever-dispelling properties.

CHEMICAL COMPOSITION

The major active chemicals in the plant have been hypothesized to be sesquiterpene lactones, principally parthenolide. However, many investigators have found evidence of other active constituents, including both lipophilic compounds (like sesquiterpene lactones) and hydrophilic compounds, although their exact identity has not been determined.[1-3] The flowering herb also contains 0.02% to 0.07% volatile oils (L-camphor, L-borneol, terpenes, and miscellaneous esters).[4,5] Various compounds in the volatile oil have shown pharmacologic activity.[6]

HISTORY AND FOLK USE

Feverfew has been used for centuries as a febrifuge and for the treatment of migraines and arthritis. Other historic uses of feverfew have been in the treatment of anemia, earache, dysmenorrhea, dyspepsia, trauma, and intestinal parasites.[4] It has also been used as an abortifacient and in gardens to control noxious pests (its pyrethrin component is an effective insecticide and herbicide).

PHARMACOLOGY

Feverfew has demonstrated some remarkable pharmacologic effects in experimental studies. Extracts of feverfew have been shown to inhibit the synthesis of compounds that promote inflammation, including inflammatory prostaglandins, leukotrienes, and thromboxanes. No adverse effects reported for feverfew mimic those of aspirin or nonsteroidal antiinflammatory drugs (NSAIDs), suggesting that the effects of feverfew are in some way distinct from those of the drugs. Inhibition of phospholipase A_2 is more like the effects of corticosteroids.[7]

Feverfew also has favorable effects on the behavior of blood platelets in vitro,[7,8] including inhibition of platelet aggregation and the secretion of inflammatory and allergic mediators like histamine and serotonin. Parthenolide components also exert a tonic effect on vascular smooth muscle.[9]

The combined effect on smooth muscle and platelets is probably responsible for feverfew's effect in preventing and treating migraine headaches.

CLINICAL APPLICATIONS

Feverfew has been used for centuries to relieve fever, migraines, and arthritis. The only condition with confirmed scientific documentation at present is in the prevention and treatment of migraine headache.

MIGRAINE HEADACHE

Physician John Hill, in his book *The Family Herbal* (1772), noted, "In the worst headache this herb exceeds whatever else is known." A 1983 survey found that 70% of 270 migraine sufferers who had eaten feverfew daily for prolonged periods claimed that the herb decreased the frequency and/or intensity of their attacks.[10] Many of these patients had shown no response to orthodox medicines.

Numerous double-blind trials have been conducted on the efficacy of feverfew in migraine patients,[10-15] the results of which have been assessed in three meta-analyses.[16-18] The first two of these concluded that the majority of studies show that feverfew extracts are superior to placebo for decreasing the frequency and severity of migraine headaches, although most of the studies were of relatively low methodologic quality, and efficacy was not proved beyond a reasonable doubt.[14,17] The third meta-analysis concluded that feverfew extracts have not been proved in controlled trials to prevent migraine better than placebo.[18]

The highest-quality study among feverfew clinical trials used a granulated ethanol extract of feverfew and found it ineffective compared with placebo, whereas all the other trials used unextracted powdered feverfew. As a result, careful attention must be paid in future studies to the types of products used, and the results of trials using different products should probably not be combined in meta-analyses.

One double-blind, randomized clinical trial compared the effects of a combination of a feverfew extract (100 mg) with riboflavin 400 mg and magnesium 300 mg taken daily with riboflavin 25 mg.[19] The control, riboflavin 25 mg, appeared to be just as active as the combination formula, and the trial showed that combining feverfew and magnesium with riboflavin adds no additional benefits for preventing migraine headaches.

In an open trial, feverfew combined with *Salix alba* (white willow) extracts, 300 mg of each twice a day, has been shown effective at preventing and reducing the severity of migraine without aura.[20] A combination of *Zingiber officinale* (ginger) and feverfew was effective in an open trial for relieving acute migraine pain.[21] It is not clear if either extract is superior to feverfew alone, and double-blind randomized trials are necessary.

RHEUMATOID ARTHRITIS

Inflammatory compounds released by white blood cells and platelets contribute greatly to the inflammation and cellular damage found in rheumatoid arthritis. Inhibition of the release of inflammatory particles by feverfew is much greater than that achieved by NSAIDs like aspirin.[8] This finding, coupled with many of feverfew's other effects, indicates that feverfew can reduce inflammation in rheumatoid arthritis.

Although a double-blind, placebo-controlled study demonstrated no apparent benefit from oral feverfew in rheumatoid arthritis, the dosage used was small (76 mg dried powdered feverfew leaf, corresponding to two medium-sized leaves), the level of parthenolide was not determined in the product, and patients continued to take NSAIDs, a practice that has been suggested to reduce the efficacy of feverfew.[22] Therefore, the benefit of feverfew in rheumatoid arthritis has not yet been determined.

DOSAGE

The effectiveness of feverfew was thought to depend on adequate levels of parthenolide, although multiple studies confirm that there are multiple active compounds in feverfew and that parthenolide-free extracts are still active.[23,24] It is difficult to determine the relevance of measuring parthenolide in extracts; assessments of activity of extracts would perhaps be superior although more expensive.

The preparations used in some successful clinical trials had a parthenolide content of 0.4% to 0.66%. The dosage of feverfew used in the London Migraine Clinic study was one capsule containing 25 mg of the freeze-dried pulverized leaves given twice a day.[6] In the Nottingham study it was one capsule containing 82 mg of dried powdered leaves given once a day.[7] Therefore, the daily dosage of parthenolide that may be effective in preventing a migraine headache is roughly 0.25 to 0.5 mg.

Although these low dosages may be effective in preventing an attack, a higher dose (1 to 2 g) is necessary during an acute attack: dried pulverized leaves 25 to 50 mg given twice a day.

TOXICITY

There were no reports of toxic reactions in patients taking feverfew in the 6-month migraine study. Feverfew has been used by large numbers of people for many years without reports of toxicity. Chewing the leaves, however, may result in aphthous ulcerations, and some sensitive persons experience an exudative dermatitis from external contact.[25] In clinical trials, neither mouth ulcers nor dermatitis was more common in the feverfew groups than the placebo groups; in one trial, aphthous ulcers were actually more common in the placebo group.[12]

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CHAPTER 127

Taraxacum officinale (Dandelion)

Michael T. Murray, ND

Taraxacum officinale (family: Compositae)
Common names:
- English: dandelion, wet-a-bed, lion's tooth
- French: *dent-de-lion, pissenlit*
- German: *Lowenzahn, Pfaffenrohrlein*
- Spanish: *diente de leon*
- Italian: *tarassaco*
- Chinese: *p'u kung ying, Ching p'o po, chiang-nou-ts'ao, huang-hua-tii-ting*

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GENERAL DESCRIPTION

Dandelion *(Taraxacum officinale)* is a member of the Compositae family and is closely related to chicory. Several origins have been attributed to the name *Taraxacum,* the most likely being from the Greek *taraxo* ("disorder," "disturbance"), and *akos* ("remedy"), and *akeomai* ("I heal") and from *tharakhcharkon,* possibly a derivative of a Persian-Arabic word for "edible" and the name by which the plant is referred to in a thirteenth-century Arabian botanical work.[1]

Taraxacum is known around the world by a variety of names. In English-speaking countries, dandelion (from the French *dent-de-lion,* referring to the plant's lion's tooth leaves) is its most common name. It is also known as wet-a-bed (after its diuretic action), lion's tooth, fairy clock, priest's crown, swine's snout, blowball, milk gowan, wild endive, white endive, cankerwort, puffball, and Irish daisy.

Dandelion is a variable perennial growing to a height of 12 in. Its spatula-like leaves are deeply toothed, shiny, and hairless and are arranged in a ground-level rosette. The yellow flowers bloom for most of the year and are sensitive to light and weather—opening at daybreak and closing at nightfall, and opening in dry weather and closing in wet weather (a closed dandelion flower signals rain). When the flower matures, it closes up, the petals wither, and it forms into a puffball containing seeds that are dispersed by the breeze.

The rosette formation of grooved leaves channels rainwater into the center and down to a taproot, which is thick and dark brown, almost black on the outside. The root is cylindrical, tapering, and somewhat branched. It has a slight odor and sweetish taste. The inside of dried dandelion root is yellowish, very porous, and without pith. It is believed that the plant originated in Central Asia and spread throughout most of the world, preferring the cooler climates. Although *Taraxacum* is very adaptable, it prefers moist, nitrogen-rich soils at altitudes less than 6000 ft. Most species occur in the temperate zones of the northern hemisphere, with the greatest concentration in northwest Europe.

The portion of the plant that is most commonly used is the root; however, the leaves and whole plant can also be used. In addition to its medicinal use, dandelion is a nutritious food and beverage. Tender leaves are used raw in salads and sandwiches or lightly cooked as a vegetable. Tea is made from the leaves, coffee substitute from the roots, and wine and schnapps from the flowers.

CHEMICAL COMPOSITION

Dandelion root's calorie count is exceptionally low—a cup is only 25 calories—and its nutrient content is exceptionally high. In fact, dandelion root has greater nutritional value than many other vegetables. It is particularly high in vitamins and minerals, protein, choline, inulin, and pectin. Its carotenoid content is extremely

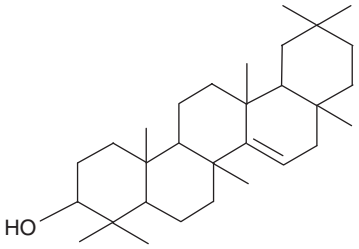


FIGURE 127-1 Taraxerol.

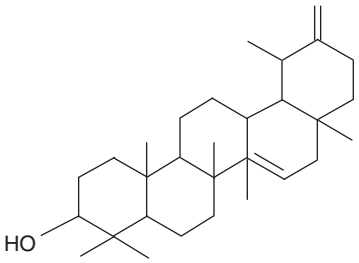


FIGURE 127-2 Taraxasterol.

high, as reflected by its having a higher vitamin A content (as beta-catotene) than carrots (dandelion has 14,000 IU of vitamin A per 100 grams, compared with 11,000 IU for carrots). Dandelion greens are an outstanding source of vitamin A and an excellent source of vitamin C, riboflavin, vitamin B_6, and thiamine as well as calcium, copper, manganese, and iron.[2]

The primary therapeutic actions of dandelion are believed to be due to the bitter principle of taraxacin, various terpenoids, inulin, and its high concentration of nutrients, especially choline.[3] Other constituents of dandelion that may contribute to its pharmacologic effects are resins, pectin, taraxanthin (a carotenoid pigment in the flowers), fatty acids, and flavonoids.

The roots of *T. officinale* contain the triterpenes b-amyrin, taraxasterol, and taraxerol and the sterols sitosterin, stigmasterin, and phytosterin (Figures 127-1 and 127-2).[4]

Later research has elicited several compounds that are likely to be clinically significant. Three flavonoid glycosides—luteolin 7-glucoside and two luteolin 7-diglucosides—have been isolated from dandelion flowers and leaves, together with free luteolin and chrysoeriol in the flower tissue. Three hydroxycinnamic acids—chicoric acid, monocaffeyltartaric acid, and chlorogenic acid—have been found throughout the plant, and the coumarins cichoriin and aesculin have been identified in leaf extracts. Chicoric acid and the related monocaffeyltartaric acid were found to be the major phenolic constituents in dandelion flowers, roots, leaves, and involucral bracts and also in the medicinal preparations tested.[5]

HISTORY AND FOLK USE

Although many individuals may consider the common dandelion an unwanted weed, herbalists all over the world have revered this valuable herb. Generally regarded as a liver remedy, dandelion has a long history of folk use throughout the world. In Europe, dandelion has been used in the treatment of the following conditions:

- Fevers
- Boils
- Eye problems
- Diarrhea
- Fluid retention
- Liver congestion
- Heartburn
- Various skin problems

In China, dandelion has been used to treat the following disorders:

- Breast problems (cancer, inflammation, lack of milk flow, etc.)
- Liver diseases
- Appendicitis
- Digestive ailments

Dandelion's use in India, Russia, and most other parts of the world has revolved primarily around its action on the liver.

PHARMACOLOGY

The primary pharmacologic actions of dandelion relate to digestion, liver function, and diuresis.

Digestive Effects

Bitter herbs like dandelion are used to aid digestion on the basis of the belief that bitter principles stimulate the initial phase of digestion, including the secretion of salivary and gastric juices. Dandelion goes beyond this initial phase by stimulating the release of bile by the liver and gallbladder.

The digestive tonic properties attributed to dandelion are now believed to be due to a bitter principle researchers have named *taraxacin* and have identified as belonging to a class of active substances called guaianolides, which have intestinal antiseptic, germicidal, and expectorant effects.[6]

Dandelion root contains a very high concentration (up to 40%) of inulin, which serves as food source for the "friendly" colonic bacteria species *Bifidobacterium* and *Lactobacillus* and thus promotes their growth. Aqueous root extracts of Taraxacum officinale were tested for their activity in stimulating the growth of 14 different strains of bifidobacteria. The growth of six strains (*B. adolescentis* 1 and 2, *B. bifidum* 1, *B. catenulatum,* and *B. longum* 2) was significantly enhanced; two strains were slightly enhanced, whereas the remaining six strains exhibited no enhancement.[7]

Diabetes

Inulin is also helpful in improving blood sugar control and diabetes. In one study, dandelion given to diabetic rats in the form of a water extract significantly improved the rats' production of antioxidant liver enzymes; it also decreased their blood sugar, total cholesterol, and triglyceride level, and raised their concentrations of beneficial high-density-lipoprotein cholesterol.[8] In vitro studies have shown that *Taraxacum* extracts exert insulin secretagogue activity, whereas administration to alloxan-induced nonobese diabetic mice significantly decreased their glucose and fructosamine levels.

Liver Tonic

Studies in humans and laboratory animals have shown that dandelion root enhances the flow of bile, improving such conditions as liver congestion, bile duct inflammation, hepatitis, gallstones, and jaundice.[9-11] Dandelion's action in increasing bile flow is twofold: it has a direct effect on the liver, causing rises in bile production and flow to the gallbladder (choleretic effect), and a direct effect on the gallbladder, causing its contraction and the release of stored bile (cholagogue effect). The high choline content of the root may be a major factor in dandelion's ability to act as a "tonic" to the

liver. Historically, dandelion's positive effect on such a wide variety of conditions is probably closely related to its ability to improve liver function.

In one animal study, dandelion significantly improved the liver's ability to clear toxins by 244%. Dandelion's effectiveness in improving the liver's ability to clear potentially toxic agents was also demonstrated in a study in which rats were given the antimicrobial drug ciprofloxacin (Cipro). In those rats that also received dandelion, levels of the drug were rapidly and significantly lowered by 73% compared with the rats that did not receive the dandelion.[12] Several studies have shown that the aqueous extract of *T. officinale* root has protective action against alcohol or chemically induced toxicity in the liver by elevating antioxidative potentials and decreasing lipid peroxidation.[13,14] In carbon tetrachloride–induced liver fibrosis, *Taraxacum* extract also inactivated the hepatic stellate cells responsible for fibrosis and enhanced hepatic regenerative capabilities.[15,16]

Diuretic and Weight-Loss Effects

The leaves of dandelion have confirmed diuretic activity. In one study in mice, dandelion exerted a diuretic effect comparable with that of furosemide (Lasix).[17] Because dandelion replaces potassium lost through diuresis, it does not have the potential side effects of furosemide, such as hepatic coma and circulatory collapse. The dose given was 8 mL/kg body weight of the aqueous fluid extract of the leaves. This dose produced a 30% loss of body weight in mice and rats in a 30-day period. Much of the weight loss was attributed to the significant diuretic effect.

Anticancer and Immune-Enhancing Effects

Various dandelion extracts and components have demonstrated antitumor properties in animal experiments.[18-20] Evidence also indicates that dandelion enhances cell-mediated, humoral, and nonspecific immunity; induces the secretion of tumor necrosis factor-alpha; and influences the production of nitric oxide.[21,22] In one study, three aqueous extracts were prepared from the mature leaves, flowers, and roots and tested for their effects on tumor progression–related processes such as proliferation and invasion.[23] Dandelion leaf extract decreased the growth of breast cancer cells, whereas the aqueous extracts of dandelion flower and root had no effect on such growth. Dandelion root extract was found to block invasion of breast cancer cells, and the leaf extract blocked the invasion of prostate cancer cells.

CLINICAL APPLICATIONS

Dandelion's specific action is on the liver, but as an alterative or tonic it benefits the body as a whole. It is often used as:

- A diuretic
- A laxative
- A cholagogue
- A general stimulant for the urinary system
- A choleretic
- A depurative (purifier)
- A hypoglycemic agent
- An antitumor agent

Two human studies have demonstrated the liver-healing properties of dandelion. In a 1938 study in Italy, 12 patients with severe liver imbalances—many exhibiting classic symptoms such as loss of appetite, low energy, and jaundice—were treated with dandelion extract (one 5-mL injection daily for 20 days).[1] Of the 12 patients, 11 showed a considerable drop in blood cholesterol. In the other study, dandelion extract was shown to successfully treat hepatitis, swelling of the liver, jaundice, and dyspepsia with deficient bile secretion.[9]

In a pilot study to assess its diuretic activity in humans, dandelion leaf extract at a dosage of 8 mL three times a day produced a significant increase in the frequency of urination in the 5-hour period after the first dose, a significant increase in the excretion ratio in the 5-hour period after the second dose, and no effect after the third dose.[24] These results indicate that dandelion produces an acute diuretic effect.

DOSAGE

As a general tonic and mild liver remedy, dandelion root can be used at the following dosages three times per day:

- Dried root: 2 to 8 g by infusion or decoction
- Fluid extract (1:1): 4 to 8 mL (1 to 2 tsp)
- Tincture: Alcohol-based tinctures of dandelion are not recommended because of the extremely high dosage required
- Juice of fresh root: 4 to 8 mL (1 to 2 tsp)
- Powdered solid extract (4:1): 250 to 500 mg

Preparations of the leaves can be used as a mild diuretic and weight-loss agent at the following dosages three times a day:

- Dried leaf: 4 to 10 g by infusion
- Fluid extract (1:1): 4 to 8 mL (1 to 2 tsp)

TOXICITY

No toxic or adverse effects have been reported for either the external or internal use of dandelion. It is considered safe to use even in large amounts, with virtually no documented side effects.[1] There has been one case report of an atopic individual experiencing an anaphylactic reaction after the oral ingestion of an herbal combination containing *T. officinale*. In this case, the herbal compound was found to have trace amounts of pollen from *T. officinale* and several other medicinal plants, which resulted in this systemic reaction.[25] This single case report indicates a possible need for caution in individuals with pollen allergy to other plants of the Compositae family.

The carcinogenicity of *T. officinale* has been investigated in an animal model. No carcinogenic activity was observed after 120 days of administration.[26]

DRUG INTERACTIONS

In an animal study, administration of an extract of the whole dandelion plant concomitantly with ciprofloxacin decreased absorption of the drug.[27] The investigators found that this effect was due to the high mineral content of the dandelion herb. Until further information is available, ciprofloxacin should not be taken within 2 hours of any dandelion supplement, including tea.

In general, it is often recommended that botanical medicines having a diuretic effect be avoided by anyone taking diuretic medications because the former may enhance the effect of the latter and lead to possible cardiovascular side effects.

Dandelion ingestion may increase the hypoglycemic effect of insulin. A single case report exists describing a 58-year-old-woman with type 2 diabetes mellitus on insulin therapy presenting to an emergency department with a hypoglycemic episode after 2 weeks of daily ingestion of fresh dandelion leaves in salad.[28]

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CHAPTER 128

Taxus brevifolia (Pacific Yew)

Michael T. Murray, ND, Cathryn M. Flanagan, ND

Taxus brevifolia (family: Taxaceae)
Common names: Pacific yew

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General Description, *1059*
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GENERAL DESCRIPTION

The Pacific yew is now well known as the original source of the chemotherapy agent paclitaxel. Because of the low yield, cost of extraction, and environmental concerns, alternative sources were developed. Nonetheless, the success of paclitaxel provides strong support that mining nature for new medicines is an extremely viable approach to drug development.

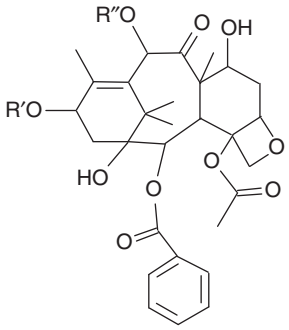
Yews are evergreen trees or shrubs that were difficult to class taxonomically because they look like conifers but, because of the absence of cones and resin ducts, they were placed in a separate order. Although the yew appears to be tenacious, it is slow to reproduce. The species is dioecious, with female trees producing relatively scarce fruits. Seedlings are rare. Most often, new yew trees come from offshoots of a "mother tree," which is why they are usually found in clusters. They grow best on deep, moist, rich rocky or gravelly soils. The largest known living Pacific yew is in Lewis County, in Washington State, near Mount Rainier. It stands 21.3 m tall, has a girth of 4.5 m, and is estimated to be 1000 years old.

Paclitaxel (Taxol) and complex diterpenoid taxanes are compounds found in *Taxus brevifolia*. Docetaxel (Taxotere) is a semisynthetic agent similar in action to paclitaxel derived from 10-deacetyl baccatin III, a taxane isolated from the needles of *Taxus baccata*, the English yew. Prior to their formal drug development, these compounds were cited as among the most promising plant compounds tested for anticancer properties in 1990.[1] The Pacific yew was first collected in 1962 by a U.S. Department of Agriculture team in Washington State as part of the large natural products screening program of the U.S. National Cancer Institute. Confirmed activity by a bark extract against the KB cell line in tissue culture was reported in 1964. Isolation studies began in 1965, and by 1971, Wall et al[2] at the Research Triangle Institute (Durham, N.C.) had identified paclitaxel as the active constituent.[2] Paclitaxel became big news in 1989, when investigators at the Johns Hopkins Oncology Center in Baltimore reported a 30% response rate in cases of refractory ovarian cancer, a remarkable rate for this type of cancer.[3] The development of docetaxel began in 1981 in France. Taxanes used in conjunction with chemotherapy and irradiation have demonstrated improved results as compared with either of these therapies alone as well as better tolerance of these therapies.[3a]

From 1967 to 1993, almost all paclitaxel produced was derived from the bark of the Pacific yew, the harvesting of which kills the tree. Currently, all paclitaxel production uses plant cell fermentation technology. This starts from a specific *Taxus* cell line propagated in aqueous medium in large fermentation tanks. Paclitaxel is then extracted directly, purified by chromatography, and isolated by crystallization.

CHEMICAL COMPOSITION

The Pacific yew is poisonous because it contains at least 11 alkaloids, known collectively as *taxines*. The structure of only two of the alkaloid constituents is known: taxine A, which accounts for 30%, and taxine B, which accounts for 2%. Paclitaxel (Figure 128-1) is a pseudoalkaloid but not a constituent of taxine because its nitrogen is acylated with benzoic acid and has no basic principle. The concentration of paclitaxel in yew bark is low, only 0.01%.



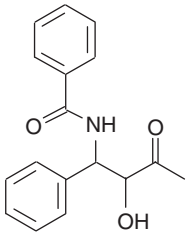
	R′	R″
10-Deacetylbaccatin III	H	H
Taxol		

FIGURE 128-1 Paclitaxel.

HISTORY AND FOLK USE

Historically, the yew has been highly valued for its dense, resilient, decay-resistant, tight-grained wood and its medicinal properties. The Greeks named the yew *toxus* in reference to its use for making a strong bow *(toxon),* and its poisonous nature *(toxikon).*[2] It was used as an animal and fish poison by primitive cultures as well as for murder and suicide. In the first century AD, Claudius suggested its use as an antidote for viper bites. Europeans used it as an abortifacient as well as to treat heart ailments and hydrophobia.[2] Native Americans used the yew for many ailments, as follows:

- Rheumatism
- Lung ailments
- Colds and fever
- Pain and numbness
- Paralysis
- Scurvy
- Stomachache
- Bowel ailments
- Dysmenorrhea
- Gonorrhea

Women ate yew berries to prevent conception. Youths rubbed smooth sticks of yew on their developing bodies to gain its strength. Both the bark and the leaves have been brewed for tea, and powders have been made from the bark alone. The fleshy red aril (berry) that surrounds the seed is not poisonous, although the seed itself is.[4]

There is a lot of folklore about the yew's supernatural powers. Because it is a slow-growing, long-lived tree, it was associated with immortality and used in spells to raise the dead.[5] Because it was regarded as among the most potent of trees for protection against evil, it was considered unlucky to cut down or damage a yew tree. Many were planted in churchyards/graveyards and alongside homes for protection. Specimens survive today in spite of main trunks being hollowed out from decay following hundreds of years of existence.

PHARMACOLOGY

Paclitaxel's anticancer action is unique in that it inhibits cell division by promoting the formation of microtubules, the rodlike structures that function as a cell skeleton, making cells more stable and resistant to depolymerization. In contrast, other anticancer phytoagents (e.g., colchicine and vinca alkaloids) induce the polymerization of microtubules. In addition, under the influence of paclitaxel, the microtubules polymerize independently of the microtubule-organizing center, which is in a perinuclear area, and instead localize predominantly in the cell's periphery.[6] This interferes with the mitotic spindle and selectively blocks cells in the G_2 and M phases of the cell cycle, the most radiosensitive phases. Additionally, paclitaxel induces the formation of abnormal spindle asters that do not require centrioles for enucleation and are reversible after treatment.[7-10] Furthermore, in vivo, paclitaxel has demonstrated an ability to activate the local release of an apoptosis-inducing cytokine.[11] Studies on cancer cell lines induced with *gml*, a novel gene, have demonstrated a marked increase in sensitivity to paclitaxel via apoptosis. An assay for *gml* expression could serve as a clinically useful predictor of chemotherapeutic sensitivity.[12]

CLINICAL APPLICATIONS

Paclitaxel has demonstrated a broad spectrum of antitumor activity. Phase I trials, begun in 1983, demonstrated paclitaxel`s antineoplastic activity against several tumor types, such as the following[13-20]:

- Melanoma
- Adenocarcinoma of unknown origin
- Refractory ovarian carcinoma
- Small cell and non–small cell lung carcinoma
- Gastric, colon, prostate, breast, and head and neck carcinomas
- Lymphoblastic and myeloblastic leukemias

In early studies, impressive results were seen using paclitaxel in combination with other antineoplastic agents, such as cisplatin.[21] Having treated patients who were previously resistant to cisplatin with the combination of cisplatin and paclitaxel, the Gynecology Oncology Group reported a 33% response rate.[22] Trials were quickly conducted on a number of solid tumor types, including small cell and non–small cell lung, renal, gastric, breast, advanced ovarian, colon, and cervical carcinomas; head and neck cancers; small cell lung and prostate carcinomas; and low-grade non-Hodgkin's lymphoma.[23] Paclitaxel also has activity in other malignancies that are refractory to conventional chemotherapy, including previously treated lymphoma, small cell lung cancers, and esophageal, gastric, endometrial, bladder, and germ cell tumors. Paclitaxel is also active against AIDS-associated Kaposi's sarcoma. Although paclitaxel is a well-accepted treatment option for these cancers and others, significant toxicities, such as myelosuppression and peripheral neuropathy, limit the effectiveness of paclitaxel-based treatment regimens.[24,25] These toxicities will be discussed further.

TOXICITY

Human poisoning from the deliberate consumption of yew leaves or seeds is now rare. Published cases involving psychiatric patients and prisoners describe the first symptoms of intoxication as appearing 1 hour after ingestion. The manifestations include

mydriasis, nausea, vomiting, abdominal cramping, and arrhythmia. Death occurs from cardiac arrest 3 to 24 hours after ingestion.[26] The lethal dose in humans is approximately four or five handfuls of leaves, corresponding to 150 needles. No specific antidote is known.

Paclitaxel binds 95% to 98% with plasma proteins yet is readily eliminated through hepatic metabolism, biliary excretion, and/or extensive tissue binding. Total urinary excretion has been insignificant, indicating that renal clearance contributes minimally to systemic clearance.[20,27-29] Hepatic metabolism via cytochrome P450 (CYP) is involved for both paclitaxel and docetaxel. However, the former is hydroxylated by CYP2C8, whereas the latter is hydroxylated by CYP3A4.[30]

Toxicity manifests as follows:

- Bone marrow suppression
- Hypersensitivity
- Cardiovascular abnormalities
- Neurotoxicity
- Arthralgias and myalgias
- Alopecia
- Gastrointestinal upset

Junctional tachycardia via conduction block rather than direct primary toxicity on myocytes has been suggested.[31] Hypersensitivity, skin reactions, and accumulated fluid retention syndrome are minimized with a 3- to 5-day regimen of corticosteroids prior to paclitaxel infusion.[32]

Patients with leukemia who are treated with high doses of paclitaxel exhibited mucositis, which has also appeared in response to lower, cumulative dosing. An accumulation of epidermal cells with abnormal paclitaxel-induced spindle asters has been evident in ulcerated mucosa, indicating that the cell cycle was arrested in mitosis.[33]

Paclitaxel has been known to inhibit neurite growth and induce prominent morphologic effects, such as microtubule bundles in neurons, satellite cells, and Schwann cells in organotypic dorsal root ganglion cultures.[34-39] Clinically, the most common symptoms have been glove-and-stocking paresthesias and perioral numbness. Distal sensory loss to large-fiber (proprioception, vibration) and small-fiber (pinprick, temperature) modalities and loss or decrease of distal deep tendon reflexes have been noted, although motor nerves seem to be spared. In general, the clinical incidence and severity of peripheral neurotoxicity have been dose-related. Patients with a history of substantial alcohol use have appeared to be more predisposed to the development of the neurosensory toxic effects of cisplatin and paclitaxel.[13-16,40-42]

The development of a suitable clinical formulation has been hampered by paclitaxel`s poor aqueous solubility. Cremophor is being used as the vehicle for administration and has been implicated in side effects, such as type 1 hypersensitivity reactions.[43]

Neutropenia, the principal dose-limiting toxic effect of paclitaxel, resolves rapidly (in 15 to 21 days) after treatment is stopped.[40]

BOX 128-1 Medications That Interact with Paclitaxel

- Amphotericin B by injection (e.g., Fungizone)
- Antithyroid agents
- Azathioprine (e.g., Imuran)
- Chloramphenicol (e.g., Chloromycetin)
- Colchicine
- Flucytosine (e.g., Ancobon)
- Ganciclovir (e.g., Cytovene)
- Interferon (e.g., Intron A, Roferon A)
- Plicamycin (e.g., Mithracin)
- Zidovudine (e.g., AZT, Retrovir)

Data from U.S. Pharmacopeia. Drug interactions, vol. II. Rockville, MD: United States Pharmacopeial Convention, 1997:1237-1238.

BOX 128-2 Medical Problems That May Affect the Use of Paclitaxel

- Chickenpox
- Herpes zoster
- Cardiac arrhythmias
- Infection

The major clinical risk factor for neutropenia seems to be the extent of prior myelotoxic chemotherapy and/or irradiation.

Bradyarrhythmias, which have been noted as transient and asymptomatic, have been reported during paclitaxel infusion in at least 29% of patients with ovarian cancer.[40] This development appears to be related more to paclitaxel, because other agents formulated with Cremophor have not been associated with similar arrhythmias. Atypical chest pains during paclitaxel infusion have been observed, but they are believed to be a manifestation of a hypersensitivity reaction.[26,41]

Other paclitaxel- or Cremophor-related side effects are sudden and complete alopecia, often occurring in a single day; local venous toxic effects such as erythema, tenderness, and cellulitis in areas of dermal extravasation; as well as fatigue, headaches, taste perversions, significant elevations in serum triglycerides, and minor rises in hepatic and renal function values.[20]

Additional precautions may be necessary with the concurrent use of the medications listed in Box 128-1.

Medical problems that may affect the use of paclitaxel are listed in Box 128-2. Studies in rats and rabbits have shown that paclitaxel causes miscarriages and fetal deaths. Breastfeeding is contraindicated during paclitaxel therapy. Paclitaxel bound to albumin rather than using a solvent results in fewer and less severe side effects, with much reduced allergic reactions.[44]

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CHAPTER 129

Urtica dioica (Stinging Nettle)

Eric L. Yarnell, ND, RH(AHG), and Kathy Abascal, BS, JD, RH(AHG)

Urtica dioica ssp. *dioica* (family: Urticaceae)
Synonym: *Urtica dioica*
Common names: stinging nettle, nettle, great nettle

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GENERAL DESCRIPTION

Urtica dioica is a prolific Eurasian perennial that has become naturalized around the globe. Two major subspecies are recognized as important in medicine in the West: *dioica*, the standard stinging nettle, and *gracilis*, the California nettle. *Urtica urens*, the dwarf or dog nettle, is also used interchangeably. The leaves, fruit (often inappropriately called seeds), and root are all used, each somewhat differently.

CHEMICAL COMPOSITION

Nettle leaves are known to contain flavonoid glycosides (including quercetin and kaempferol), phenylpropanoids (including caffeic malic acid), sterols, carotenoids, vitamins, and minerals.[1] The stinging hairs contain formic acid, histamine, serotonin, and choline, among other irritants. Very little is known about the chemistry of the fruits except that they contain protein, carbohydrate, and 30% fatty acids.[1]

The chemistry of the roots of stinging nettle has been the most thoroughly examined.[2] Acidic polysaccharides, lectins, sterols including β-sitosterol, triterpenoids, the coumarin-like compound scopoletin, phenylpropanoids, ceramides, and lignans are all potentially related to the physiologic effects of the roots (Figures 129-1 and 129-2).[3] Lignans of potential importance include neoolivil and secoisolariciresinol, which are metabolized by human gut flora to enterodiol and enterolactone, well-characterized phytoestrogenic compounds.[4]

HISTORY AND FOLK USE

Urtica species have long been employed as medicine in Europe and Asia. The steamed or dried leaves were eaten as a vegetable or seasoning and often still are.[4] Nettle fiber was formerly processed into thread used to make clothing, rope, and sailcloth, although it was ultimately replaced by flax. The source of the fiber known as "ramie" comes from the plant *Boehmeria nivea*, which is also in the Urticaceae family. The word *nettle* appears to be derived from the old Anglo-Saxon *noedl*, "needle," and even before that to the common Indo-European verb *ne*, "to spin/sew." There is little record of use of the roots in traditional cultures except as a source of yellow dye.[4]

Medicinally, stinging nettle leaves were once considered a spring tonic, taken each year in particular by patients with chronic skin or rheumatic conditions.[5] The leaves' diuretic (also ascribed to the fruits), tonifying, lactagogue, antiasthmatic, antihemorrhagic, and "blood-building" properties are consistently referenced by European herbalists.[6] Up to modern times, there are descriptions of applications of fresh leaves to aching joints, intentionally causing stings to relieve symptoms. Stinging nettle leaves are also frequently said to promote hair growth.

PHARMACOLOGY

The two principal effects of stinging nettle leaves are inhibition of inflammation and promotion of diuresis. Most research has involved a proprietary 50% ethanol 10:1 extract of the leaves known as IDS 23 (Strathmann AG & Co, Hamburg,

Germany). In vitro, IDS 23 extract and caffeic malic acid inhibit 5-lipoxygenase and cyclooxygenase (isotype not determined); the whole extracts are more potent than caffeic malic acid alone.[7] IDS 23 also inhibits the secretion of tumor necrosis factor-α and interleukin-1-β induced by lipopolysaccharide in human blood; phenylpropanoids and flavonoids isolated from the leaves were not effective in this system.[8] Perhaps even more important, IDS 23 has been shown to inhibit activation of nuclear factor kappaB (NFkappaB) by preventing degradation of its inhibitory subunit, IkappaB, in vitro.[9]

In vitro, IDS 23 stimulated production of IL-4 by monocytes and inhibited production of IL-2 and interferon-γ (IFN-γ).[10] IL-4 production promotes formation of type 2 helper T cells, which are associated with much less inflammation than type 1 helper T cells. Preliminary in vitro research also shows that nettle leaves are strong antioxidants.[11] The multiple inflammation-modulating, immunomodulating, and antioxidant effects of stinging nettle leaves help explain how they could be helpful for so many inflammatory diseases.

A continuous intravenous infusion of an aqueous stinging nettle leaf extract increased natriuresis and urine volume in rats, leading to a reduction in blood pressure.[12] In a small uncontrolled trial of patients with congestive heart failure, stinging nettle leaf juice showed a diuretic effect.[13] Although much more work is needed, existing data support the traditional belief that stinging nettle leaves are a mild diuretic. An extract combining stinging nettle root and *Prunus africanum* (pygeum) bark weakly inhibited 5-α-reductase and moderately inhibited aromatase in prostate tissue.[14] A separate study found that stinging nettle root extract inhibited aromatase in vitro, although much less potently than *Serenoa repens* (saw palmetto) extract.[15] The two combined showed some additive effects. No effect was noted for another stinging nettle root extract on prostatic α_1-adrenergic receptors.[16]

A double-blind placebo-controlled trial confirms that stinging nettle root extracts inhibit or reduce sex hormone–binding globulin (SHBG) levels in men with benign prostatic hyperplasia (BPH).[17] In vitro, ethanolic extracts were shown to decrease the binding of dihydrotestosterone by SHBG.[18,19] Lignans and trihydroxyoctadecenoic acids but not triterpenoids were active in this study. These results clearly suggest that multiple active compounds in stinging nettle give this medicinal plant a broad spectrum of effects.

Stinging nettle root extracts have also been repeatedly shown to interfere with binding of epidermal growth factor, a major stimulus of BPH, to its receptor on prostate cells.[4,20] Lectins appeared to be the most active compounds isolated in these studies.

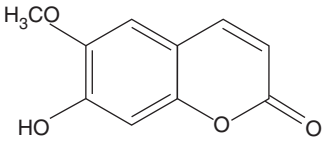


FIGURE 129-1 Scoploetin.

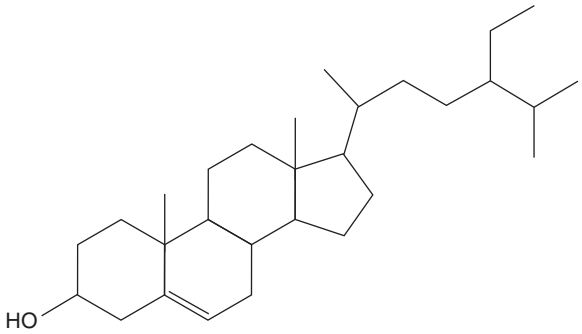


FIGURE 129-2 Sitosterol.

CLINICAL APPLICATIONS

The major uses of stinging nettle, organized according to the part being used and the route of administration, are shown in Table 129-1.[21] Published clinical trial data are available on three of these indications, as discussed here.

Benign Prostatic Hyperplasia

Extracts of stinging nettle root have been the subject of a number of clinical trials showing it beneficial for symptoms of BPH (Table 129-2). Many of these are small, older, short trials, although longer, modern trials have also been conducted and all show at least some benefit over placebo. The three most rigorous trials are reviewed in more depth below.

In one double-blind trial, 50 men with stage I or II (mild to moderate) BPH symptoms were randomly assigned to receive either placebo or 300 mg of an extract of stinging nettle root standardized to an unspecified amount of an unspecified steroid glycoside twice a day.[22] SHBG levels were significantly lower and

TABLE 129-1 **Major Uses of *Urtica dioica* by Plant Part**

PLANT PART	ROUTE OF ADMINISTRATION	MAJOR ACTION	MAIN INDICATIONS	LEVEL OF CLINICAL SUPPORT[a]	APPROVED BY COMMISSION E[b]
Leaf	Internal	Antiinflammatory, diuretic	Urinary tract Infection	Absent	Yes
			Allergic rhinitis	Poor	No
			Arthritis	Poor	Yes
			Kidney stone prevention	Absent	Yes
Leaf	Topical	Anti-inflammatory, counterirritant	Arthritis	Poor	No
Seed	Internal	Nephroprotective	Chronic renal failure	Absent	No
Root	Internal	Interference with sex hormone–binding globulin and growth factors, aromatase inhibition	Benign prostatic hyperplasia	Good	Yes

[a]*Level of clinical support* refers to the number of published clinical trials with positive results. Poor, one or two trials and mostly of low quality; Good, more than two trials of good or high quality.
[b]Data from Blumenthal M, Busse WR, Goldberg A, et al, eds. The complete German Commission E monographs: therapeutic guide to herbal medicines. Boston: Integrative Medicine Communications, 1998:216-217.

urine volume and maximum flow (but not average flow) significantly higher in the stinging nettle group than in the placebo group. Residual urine volume rose slightly and nonsignificantly in both groups. No adverse effects were reported.

The most rigorous trial to date was a 1-year trial involving 246 men in which 459 mg of a stinging nettle root extract was significantly more effective than placebo at improving BPH symptoms, although the difference was small.[25] Urine flow and residual volume were minimally affected, with no statistical difference between the nettle extract and placebo. Adverse effect rates did not differ between the treatment groups.

In the largest double-blind trial to date, 558 men with BPH were randomized to take either 120 mg of a 20:1 diethyl ether extract in 18 drops of liquid three times a day or placebo for 1 year.[26] Symptoms, maximum flow rate, and postvoid residual urine amounts improved significantly in the nettle group compared with placebo. There was also a small decrease in prostate volume (approximately 3 mL) versus none in the placebo group, a significant difference. There were no adverse effects in either group.

So far no clinical trial has compared nettle root alone with available drugs for treatment of BPH, although combination studies have done so. Stinging nettle combined with saw palmetto was as effective as finasteride (Proscar) and had significantly fewer adverse effects in a double-blind trial.[27] This trial ran for 1 year and involved 543 men with symptomatic BPH. An uncontrolled postmarketing study that monitored 2080 patients with mildly symptomatic BPH who took the same saw palmetto and stinging nettle extract documented only 15 mild adverse events.[28] The extract combination was very helpful in relieving symptoms.

In summary, these trials support the notion that stinging nettle root has some benefit in men with symptomatic BPH. More controlled clinical trials of higher quality would help confirm this conclusion. Of particular importance are trials comparing stinging nettle extracts with other phytomedicines for BPH (saw palmetto, pygeum, and β-sitosterol) and combination extracts with drug control groups for comparison. If stinging nettle could be definitively shown to be just as effective as these other medicines, this highly sustainable, cheap herb could reduce the need for reliance on the other three less sustainable or more expensive extracts.

Arthritis

Stinging nettle leaves have been used internally and topically to treat arthritis. An initial uncontrolled clinical trial found that 1340 mg a day of a nettle leaf extract (6.4:1 to 8.1:1) reduced the need for nonsteroidal anti-inflammatory drugs (NSAIDs) by 50% in patients with osteoarthritis of the knee.[29]

A subsequent open trial involving patients with acute exacerbations of various forms of arthritis compared the use of a standard 200-mg dose of the NSAID diclofenac (Cambia, Cataflam, Voltaren, Voltarol, Zipsor) with a subtherapeutic 50-mg dose of diclofenac combined with 50-g of freeze-dried nettle once a day for 2 weeks.[30] The two groups had similar levels of improvement (no significant differences between the groups) compared with baseline on various pain rating scales. There were no serious adverse events. Double-blind trials to confirm these results are warranted.

Two case studies published in 1994 heralded the first mention in the modern medical literature of topical stinging nettles as potentially effective pain relievers for patients with arthritis.[31] The practitioner who noted these cases went on to publish a case series, again showing that many patients treating themselves with topical nettle stings were experiencing noticeable pain relief, allowing for reductions in NSAID dosage.[32]

The nature of the therapy made designing a double-blind trial seem a near impossibility. However, such a trial has been conducted in patients with osteoarthritis of the thumb or index finger.[33] The placebo chosen was *Lamium album* (white deadnettle) leaf, a stingless mimic of *Urtica dioica.* Each patient used the leaf of the plant he or she was being treated with once a day, applying it to three different spots for 30 seconds each. After 1 week of treatment, there was a 5-week washout period; then all patients "crossed over" for another week's treatment with the other plant. When patients were treated with stinging nettle, their pain and disability scores were significantly better than during deadnettle treatment. Although the use of a nonstinging placebo may have compromised this trial, it does provide support for the folk use of topical application of nettles to reduce arthritis symptoms.

A similar single-blind, randomized trial using nonstinging *Urtica galeopsifolia* as a control did not find that stinging nettle leaves were more effective for patients with knee osteoarthritis, although treatment was considered tolerable.[34]

Allergic Rhinitis

A single double-blind trial has been reported on the efficacy of stinging nettle leaves for allergic rhinitis.[35] A total of 69 patients with acute onset of allergic rhinitis symptoms took 600 mg of freeze-dried stinging nettle or placebo at the onset of symptoms,

TABLE 129-2 **Randomized Controlled Trials of Nettle Root for Benign Prostatic Hyperplasia**

TRIAL	SUBJECTS (N, ON NETTLE; P, ON PLACEBO)	EXTRACT AND DOSE	DURATION	OUTCOME
Vontobel et al[22]	n = 25, p = 25	300 mg bid (5:1 methanol extract)	9 wk	Nettle improves maximum flow better than placebo
Dathe and Schmid [23]	n = 35, p = 37	300 mg bid (5:1 methanol extract)	6-8 wk	Nettle not superior to placebo
Fischer and Wilbert [17]	n = 20, p = 20	300 mg bid (5:1 methanol extract)	7 mo	Nettle superior to placebo for symptoms, mean flow improvement
Engelmann, 1996[24]	n = 47, p = 47	459 mg qd of a 7-14:1 methanol extract	6 mo	Nettle superior to placebo for IPSS* > and maximum flow
Schneider and Rübben, 2004[25]	n = 124, p = 122	459 mg qd of a 7-14:1 methanol extract	12 mo	Nettle superior to placebo for IPSS reduction
Safarinejad, 2005[26]	n = 287, p = 271	120 mg tid of 20:1 diethyl ether extract	6 mo	Nettle superior to placebo for IPSS and maximum flow

*International Prostate Symptom Score, a standardized seven-item questionnaire used to monitor symptoms of BPH.

then recorded their responses 1 hour later. The total number of doses and general responses were recorded over the remaining week. Overall assessment of the efficacy of stinging nettle was better than that of placebo, although differences in daily symptom logs did not show a strong difference. No statistical analysis was provided. Two patients in the nettle group dropped out owing to intensification of symptoms, but no other significant adverse effects were noted.

Chronic Renal Failure

The seed of nettle may have the ability to nonspecifically protect nephrons from multiple insults and thus delay progression of chronic renal failure. Two case studies have been published, one patient having lupus nephritis and a kidney transplant and another who underwent nephrectomy for cancer and whose serum creatinine levels declined during treatment with a nettle seed tincture.[36] The dosage used was 5 mL three times a day.

DOSAGE

Stinging nettle leaf and root are available in a number of dosage forms, as summarized in Table 129-3. Fresh leaves are applied one to two times a day to every few days depending on symptoms, so treatment obviously requires ongoing access to growing plants.

TABLE 129-3 **Dosage Forms of Stinging Nettle**

DOSAGE FORM	LEAF	ROOT
Tea	Infuse 4 g in 150 mL water three times a day[37]	Decoct 4-6 g in 150 mL water once a day[37]
Freeze-dried capsules	300 mg twice a day, up to 50 g once a day[30,35]	Not available
Concentrated extracts	Not available	5:1-10:1 extract 500 mg three times a day[29]
Tincture	30% ethanol, 1:2-1:5 weight to volume, 3-14 mL three times a day[38]	50% ethanol, 1:2-1:5, 4-9 mL three times a day[38]

TOXICITY

Oral use of stinging nettle leaf, fruit, or root is not associated with any significant adverse effects. Topical application of fresh leaf raises mildly painful, inflamed wheals because of the stinging hairs. As previously noted, this effect is sometimes exploited therapeutically. The welts usually clear completely within 2 hours, with lessening of symptoms after 30 minutes. As with all herbal medicines, it is possible for patients to be allergic to stinging nettle, although this reaction is exceedingly rare.

DRUG INTERACTIONS

There are no documented negative interactions between stinging nettle and any other medication. Some open trials (described previously) suggest that stinging nettle leaves potentiate NSAIDs, allowing for dose reductions of these agents.

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CHAPTER 130

Uva ursi (Bearberry)

Michael T. Murray, ND

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Arctostaphylos uva ursi (family: Ericaceae)
Common names: bearberry, upland cranberry

GENERAL DESCRIPTION

Arctostaphylos uva ursi is a small evergreen shrub found in the northern United States and in Europe. A single long, fibrous main root sends out several prostrate or buried stems 4 to 6 inches long. The bark is dark brown, the leaves are obovate to spatulate and 0.5 to 1 inches long, the flowers are pink or white and grow in sparse terminal clusters, and the fruit is a bright red or pink.

CHEMICAL COMPOSITION

The most active ingredient of *uva ursi* is arbutin, which typically composes 7% to 9% of the leaves. Other constituents are as follows:[1-4]

- Tannins (6% to 7%)
- Flavonoids (quercetin)
- Allantoin
- Gallic and ellagic acids
- Volatile oils
- A resin (urvone)

HISTORY AND FOLK USE

This plant has a long history of use for its diuretic and astringent properties. Conditions for which *uva ursi* was used include chronic cystitis, nephritis, kidney stones, and bronchitis.[1]

PHARMACOLOGY

Antimicrobial Effects

Although pharmacologic research has focused primarily on arbutin, the pharmacology of the whole plant is different from that of arbutin alone. The crude plant extracts are much more effective medicinally than the isolated constituent arbutin.[5] This fact appears to be related to the activity of gallic acid, which prevents the splitting of arbutin by such enzymes as β-glucosidase contained in gut bacteria.[2] Arbutin undergoes hydrolysis in the stomach or intestinal tract to produce hydroquinone, its aglycone, which has urinary antiseptic properties.[6] The hydrolysis of arbutin is responsible for much of the therapeutic effect of *uva ursi*.[1,6] By preventing the splitting of arbutin, the flavonoid components allow more arbutin to be hydrolyzed and absorbed than when arbutin is administered as an isolated component. Approximately 65% of an arbutin dosage is excreted in the urine as hydroquinone glucuronide or sulfate.[7,8]

Arbutin alone has been reported to be an effective urinary antibiotic, but only if taken in large doses and if the urine is alkaline (once again documenting the value of whole-plant medicines).[1] It is reported to be active against *Candida albicans* and *Staphylococcus aureus* and especially against *Escherichia coli*.[5,9] *Uva ursi* also has diuretic properties.[1]

Antiinflammatory Effects

Some early animal research is now showing that arbutin, and possibly other constituents of *uva ursi*, potentiate the activity of commonly prescribed antiinflammatory drugs. One study found that an aqueous extract increased the inhibitory activity of dexamethasone in allergic and inflammatory models without increasing any of the side effects.[10] Similar results have been demonstrated with isolated arbutin combined with indomethacin.[11]

Inhibition of Melanin Synthesis

Uva ursi extract has been shown to inhibit the enzyme tyrosinase.[12] This effect impairs melanin synthesis, which indicates that *uva ursi* extract may be effective as a whitening agent for the skin. In fact, hydroquinone is approved by the U.S. Food and Drug Administration as an agent in over-the-counter skin products for bleaching age spots and hyperpigmentation.

CLINICAL APPLICATIONS

Crude extracts are widely used in Europe as components in certain diuretic and laxative products, but the major use of *uva ursi* is as a urinary disinfectant in cases of urinary tract infection.[1]

Urinary Tract Infections

Uva ursi is reported to be especially active against *E. coli.*[6] As well as exerting direct antibiotic effects, *uva ursi* extract promotes the aggregation of *E. coli* in vitro.[9] These combined effects indicate that *uva ursi* can be used both in the immediate treatment and in the prevention of recurrent cystitis. In one double-blind study, the prophylactic effects of a standardized *uva ursi* extract and a placebo on recurrent cystitis were evaluated in 57 women.[13] At the end of 1 year, 5 of 27 women in the placebo group had a recurrence, whereas none of the 30 women receiving *uva ursi* extract had a recurrence. No side effects were reported in either group. These impressive results indicate that regular use of *uva ursi* is a safe and effective measure to prevent recurrent cystitis. In a study of normal subjects, consuming *uva ursi* tea was shown to have bacteriostatic effects greater than normal urine.[6] The effectiveness of the tea in inhibiting bacterial growth (*S. aureus* and *E. coli*) depended on adequate excretion products of arbutin (hydroquinone paired with glucuronate or sulfur) and a pH above 8. Alkalinization of the urine with bicarbonate or citrate salts in conjunction with *uva ursi* may enhance the therapeutic effects in acute urinary tract infections.

DOSAGES

The dosages for *uva ursi* are as follows:

- Dried leaves or as an infusion: 1.5 to 4.0 g (1 to 2 tsp) three times daily
- Freeze-dried leaves: 500 to 1000 mg three times daily
- Tincture (1:5): 4 to 68 mL (1 to 2 tsp) three times daily
- Fluid extract (1:1): 2 to 4 mL (1/2 to 1 tsp) three times daily
- Powdered solid extract (10% arbutin): 250 to 500 mg three times daily

TOXICOLOGY

The toxicologic concern with *uva ursi* is related to the conversion of arbutin to hydroquinone, but toxicity is extremely unlikely with consumption of commercial preparations.[7,14] Hydroquinone is metabolized in the liver by phase II enzymes into hydroquinone glucuronate or sulfate and then excreted in the urine. In various laboratory animals, the oral LD_{50} (dose at which 50% of the subjects are killed) of hydroquinone in 2% aqueous solution is between 320 and 550 mg/kg body weight. Signs and symptoms of *uva ursi* toxicity include the following:

- Tinnitus
- Nausea
- Vomiting
- Sense of suffocation
- Shortness of breath
- Cyanosis
- Convulsions
- Delirium
- Collapse

The only significant side effect reported in the medical literature with *uva ursi* consumption was that of a 56-year-old woman who ingested *uva ursi* for 3 years and presented with vision loss.[15] Diagnosis indicated bilateral bull's-eye maculopathy, presumably due to inhibition of retinal melanin synthesis. This report raises the question of the appropriateness of long-term therapy with *uva ursi*.

DRUG INTERACTIONS

An extract of *uva ursi* has been found to markedly potentiate the effects of beta-lactam antibiotics, such as oxacillin (Bactocil) and cefmetazole (Zefazone), against methicillin-resistant *S. aureus*.[16] The effective compound was identified as the polyphenol corilagin. Corilagin reduced the mean inhibitory concentrations (MICs) of various beta-lactams 100- to 2000-fold, but not the MICs of other antimicrobial agents tested. The effect of corilagin and oxacillin was synergistic. Corilagin showed a bactericidal action when added to the growth medium in combination with oxacillin.[17]

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CHAPTER 131

Vaccinium macrocarpon (American Cranberry)

Rhonda Dorren, BScPharm, Sherry Torkos, BScPharm, and Michael T. Murray, ND

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GENERAL DESCRIPTION

The shiny scarlet cranberry, like its cousin the blueberry, belongs to the genus *Vaccinium* and is found growing in the wild in northern Europe, northern Asia, and North America. The American Cranberry *(Vaccinium macrocarpon)* is the species associated with the majority of the scientific research on health benefits. Cultivated cranberries are grown in huge sandy bogs on low, trailing vines. Cranberries have also been called "bounce berries," because ripe berries bounce, and "crane berries," a reference to the cranberry shrub's pale pink blossoms, which resemble the heads of the cranes that frequent cranberry bogs.

Cranberry is gaining a lot of attention as a possible alternative to antibiotics in the prevention of urinary tract infections (UTIs). Low-dose antibiotics are often prescribed as the preferred method for prevention of infections, but this regime leads to increases in antibiotic resistance. The emergence of multiple antibiotic–resistant organisms in the general community is a potentially serious threat to public health.[1] A paradigm shift in the prevention and treatment of infectious disease, particularly chronic infections, may be required to prevent antibiotics from becoming obsolete; where appropriate, alternatives to antibiotics require consideration.[2] As a result, for prevention of infections, there has been an increase in the use of natural products as well as the consumption of cranberries (processed and fresh) in North America.

The majority of research on cranberry involves urinary tract health. However, the historical bibliography of investigations on cranberry also includes but is not limited to type 2 diabetes, prevention of blockage in urinary catheters, deodorizing of offensive urine, healing skin around urostomy stomas, and as an anticarcinogen, antifungal, and antioxidant agent.[3-9]

CHEMICAL COMPOSITION

In addition to ascorbic acid, cranberry juice contains a variety of substances that may be biologically active. Cranberries contain flavonoids and other phenolic compounds.[10] The quantity of flavonoids in cranberry juice (approximately 31.9 mg per serving) is higher than in red wine (approximately 22 mg) but lower than in dark chocolate containing high flavanol levels (approximately 165 mg) and apples (approximately 147 mg). In a sample of freshly squeezed cranberry juice, one study found 400 mg of total flavonoids and phenolic compounds per liter of sample, which was distributed as about 44% of phenolic acids and 56% of flavonoids. Benzoic acid was the major phenolic compound, and the major flavonols were quercetin and myricetin. Anthocyanins are also found in cranberry and are responsible for the red pigmentation of the fruit. They are abundant in the form of cyanidin glycosides (sugar groups attached).[11,12] Cranberries also contain organic acids, including quinic, malic, and citric acids.[13]

Cranberries contain proanthocyanidins (also referred to as condensed tannins), which are composed of epicatechins linked together by unusual A-type bonds, not found in most other tannin-containing foods These different forms of polyphenols are often mentioned in the scientific literature on cranberry.

HISTORY AND FOLK USE

Native Americans used cranberry both as food and for the treatment of bladder and kidney diseases. The Pilgrims learned about cranberry from local tribes for a

condition referred to as "bladder gravel" (small bladder stones) and to remove blood toxins. Cranberries were served to ships' crews as a source of vitamin C to prevent scurvy. Other documented medical applications in the seventeenth century include the relief of stomach ailments, liver problems, blood disorders, and cancer. The boiled berry and seal oil were used to reduce the severity of gallbladder attacks.[14]

Cranberry's beneficial effects on urinary tract health were thought to be due to acidification of the urine. Direct antibacterial and antifungal effects of cranberry juice have been shown.[15-17] Hippuric acid, converted from the quinic and benzoic acids in cranberry, is a strong bacteriostatic agent, and its potential to acidify urine has been investigated.[5,18-20] In brief, these early studies focused on the ability of cranberry juice to lower urinary pH, on the basis of its apparent ability to suppress infections and enhance antibiotic activity.[21-24] Yet clinically, the concentration of hippuric acid in cranberry does not routinely reach levels adequate for antibacterial action.

Further research failed to validate the proposed theory that cranberry reduced urinary pH. Cranberry continued to be a popular remedy for urinary health and only in the past decade has its true mechanism of action been elucidated. Current evidence is strongest for its effectiveness in promoting urinary tract health while sparing the patient the experience of unwanted side effects and the continued use of prophylactic low-dose prescription drugs.[25]

PHARMACOLOGY

The primary application of cranberry is in the prevention of UTIs. Cranberry components interfere with bacterial adherence to mucosal cells—an important step in the development of infection. For bacteria to successfully attach to the host, they must identify and attach to epithelial cell receptor sites. Proteinaceous fibers on the cell wall of uropathogenic *Escherichia coli* called fimbriae, produce adhesion molecules that attach to these monosaccharide or oligosaccharide receptors on uroepithelial cells. Two different fimbrial types are most important for initiating UTI: Type 1 fimbriae, which adhere to mannose-specific receptors, and P fimbriae, which adhere to disaccharide α-D-Gal(1,4)-β-D-Gal (Gal-Gal) receptors.

Modern research has revealed that the proanthocyanidins (PACs) in cranberries can inhibit the adhesion of uropathogenic P-fimbriated strains of *E. coli* to bladder cells.[26-28] Cranberry contains two different inhibitors: fructose, effective for inhibiting the type 1 fimbriae, and a second, unidentified inhibitor that is effective for obstructing the Gal-Gal–specific fimbriae.[29] However, fructose is fully metabolized after consumption and does not reach the urine. Therefore, it does not influence bacterial adhesion in the body. In addition, scientific evidence suggests that cranberry acts on the cell wall not only by preventing attachment of the fimbrial subunits but also by serving as a genetic control, preventing the expression of normal fimbrial subunits, or both.[30-33]

In animal models, investigations of approximately 77 clinical isolates of *E. coli* demonstrated that cranberry juice inhibited bacterial adhesion to the bladder by more than 75% for more than 60% of the strains of bacteria.[34] Further research demonstrated that cranberry significantly reduced the adherence of pathogens to urinary epithelial cells isolated from patients with UTIs, including *Proteus mirabilis, Staphylococcus aureus, Klebsiella pneumoniae, Enterobacter* species, and *Pseudomonas aeruginosa.*[35,36]

The cumulative effects of cranberry have now been demonstrated as successfully acting on cell walls to prevent proper attachment of the fimbrial subunits, thus inhibiting bacterial adherence to uroepithelial cells, and cellular elongation.[37]

Current evidence demonstrates that consumption of cranberry PACs results in an antiadhesion response in the urine to provide protective effects from bacteria that migrate from the perineum and vagina. [38] Research continues to determine if the PACs induce a urinary response or are broken down to bioactive metabolites that reach the urine. Larger PACs that are eliminated through the colon may bind to rectal uropathogenic bacterial isolates in the gut, thus decreasing the virulence of these microbes if they come in contact with the uroepithelium. Researchers in Finland who studied the UTI preventive effects of a commercially available cranberry-lingonberry juice concentrate stated that their findings support bacterial selection in the stool, because subjects in the cranberry group had no increase in UTI recurrence during the six months after they had stopped the cranberry prophylaxis.[39]

Emerging concepts regarding preventive considerations for the management of recurrent UTIs (RUTIs) suggest taking cranberry supplements as part of the protocol.[40]

Numerous investigations have been completed on cranberry. The following discussion provides an overview of some of the recent data, including a review of studies on cranberry and urinary tract health.

CLINICAL APPLICATIONS

Urinary Tract Applications

Reduction of Bacteriuria and Pyuria after Ingestion of Cranberry Juice

An early study conducted by Avorn et al[41] evaluated the effects of cranberry on bacteriuria in 153 elderly women. Participants consumed 300 mL/day of either a commercially available cranberry beverage or a placebo drink that was similar-tasting and contained vitamin C but no cranberry content. After 1 month of treatment, 15% of the urine samples of those who had been drinking cranberry juice had bacteriuria with pyuria, compared with 28% of those in the placebo group. Most patients with bacteriuria were asymptomatic. Although statistical significance was not achieved, there was a trend toward less antibiotic use for treatment of UTIs in the cranberry group (1.7 vs. 3.2 antibiotics per 100 patient-months). A criticism of this trial is that the control group had a higher rate of urinary infection before the study, suggesting there may have been sampling bias, and the main outcome, identified as asymptomatic bacteriuria, does not generally require treatment.[42] Although there was a trend toward fewer clinically relevant urinary infections, the study was not designed to demonstrate that effect. This trial, like others, had a high dropout rate, which casts doubt on the long-term tolerability of cranberry juice.[43,44]

Urinary Tract Infections and Sexual Activity

Foxman et al[45] randomly sampled 288 control subjects (college students), studying first-time UTIs in young unmarried women. Participants were recruited from a university health service and all had engaged in sexual intercourse at least once. Compared with the general population of students, intercourse significantly increased the risk of UTIs (43%), as did drinking carbonated soft drinks (237%), but it was found that drinking cranberry juice reduced the risk (52%).

A more recent study in France investigated the impact of consuming a single postcoital dose of cranberry on the development of UTIs. This double-blind study evaluated 120 female patients

with recurrent UTI (6 or more in the previous 12 months). Patients were randomized to one of three groups and received either one capsule of infused cranberry powder made by a patented procedure (Bio-Shield, Cran-Max), known commercially in France as GynDelta), one capsule of dry cranberry extract containing 36 mg of PAC or one capsule containing a placebo. Patients were instructed to take their test product within 6 hours following intercourse. Over the course of the study period of 45 days, 10.8% of patients in the GynDelta group suffered a UTI, compared with 18.9% in the cranberry PAC group and 43.2% in the placebo group. The results for the GynDelta were statistically significant ($P = 0.005$).[46]

Cranberry Juice and the Adhesion of Antibiotic-Resistant Uropathogens

Howell et al[47] carried out an *ex vivo* study verifying cranberry's ability to prevent the adhesion of certain *E. coli* strains that are resistant to trimethoprim-sulfamethoxazole.[47] The researchers obtained 39 uropathogenic P-fimbriated *E. coli* isolates, 24 of which were resistant, from women with culture-confirmed UTIs. Incubation of the bacteria in urines collected from participants who consumed 240 mL of cranberry juice cocktail prevented adhesion in 31 of 39 isolates, including 19 of 24 resistant isolates; antiadhesion activity began within 2 hours of exposure and persisted for up to 10 hours. Because the mechanism of action is not bactericidal, the use of cranberry does not increase the selection for antibiotic-resistant bacterial strains. A reduction in the frequency of infections may decrease the frequency of antibiotic use, saving first-line antibiotics for other infections.[48]

Trials Involving Catheterization, Neurogenic Bladders, and Spinal Cord–Injured Patients

Rates of bacteriuria and symptomatic UTIs in individuals who receive clean intermittent catheterization are an enduring concern. Schlager et al,[49] comparing cranberry with placebo, completed a 3-month double-blind placebo-controlled crossover trial of children (n = 15) with neurogenic bladders treated with intermittent catheterization. The researchers reported that 75% of 151 cultures indicated bacteriuria at both sample intervals. In this case, there was no difference between the children drinking cranberry concentrate and those receiving a placebo. Reid et al[50] examined 15 spinal cord–injured (SCI) patients to ascertain whether cranberry juice altered bacterial biofilm load in the bladder. They found that cranberry juice significantly diminished biofilm load compared with baseline, with a reduction in the adhesion of both gram-positive and gram-negative bacteria to cells. Water intake did not affect bacterial adhesion.

Linsenmeyer et al[51] completed a prospective double-blind placebo-controlled crossover study of 21 individuals with neurogenic bladders secondary to SCI who were randomly assigned to receive either 400-mg cranberry tablets or placebo three times a day for 4 weeks.[51] Cranberry tablets did not modify urinary pH or reduce bacterial counts, urinary white blood cell counts, or the number of UTIs in individuals with neurogenic bladder.

The most recent study evaluated the effect of cranberry tablets for the prevention of UTI in SCI patients with neurogenic bladder. Patients were randomized to receive 6 months of cranberry tablets (Cran-Max) or placebo, followed by the alternate preparation for an additional 6 months. Forty-seven subjects completed the trial. The researchers found a reduction in the likelihood of UTI and symptoms for any month in patients receiving the cranberry tablet (P <0.05 for all). During the cranberry period, 6 subjects had 7 UTIs, compared with 16 subjects and 21 UTIs in the placebo period ($P < 0.05$ for both number of subjects and incidence). The frequency of UTI was reduced to 0.3 UTIs per year versus 1 UTI per year in those receiving placebo. Subjects with a glomerular filtration rate (GFR) greater than 75 mL/min received the most benefit.[52]

Further long-term studies evaluating specific types of bladder management and UTI will help to determine the role of cranberries in individuals who have neurogenic bladder, require catheterization, or have SCI.

Comparative Trial Subsequent to Antibiotic Therapy

The use of cranberry supplements in women with UTI after antibiotic treatment may reduce the recurrence of UTI. In an open-label trial in Finland, Kontiokari et al[53] treated 150 women with UTI due to *E. coli* with a standard antimicrobial regimen; then the participants were randomly assigned to receive 50 mL of cranberry-lingonberry juice concentrate daily for 6 months, 100 mL of *Lactobacillus* drink 5 days a week for 1 year, or no intervention. At 6 months, 16% of the women in the cranberry group, 39% in the *Lactobacillus* group, and 36% in the control group had UTIs. This finding demonstrates that a regular intake of cranberry juice but not *Lactobacillus* seems to reduce the recurrence of UTI.

Comparative Trials—Antibiotic versus Cranberry for UTI Prevention

McMurdo et al[54] compared the effectiveness of cranberry extract or low-dose trimethoprim in the prevention of recurrent UTIs in a group of 137 women with two or more antibiotic-treated UTIs in the previous 12 months. Subjects were randomized to receive either 500 mg of cranberry (Cran-Max) or 100 mg of trimethoprim for 6 months.

Thirty-nine of 137 participants (28%) had an antibiotic-treated UTI (25 in the cranberry group and 14 in the trimethoprim group); difference in proportions relative risk 1.616 (95% CI: 0.93, 2.79) $P = 0.084$. The time to first recurrence of UTI was not significantly different between the groups ($P = 0.100$). The median time to recurrence of UTI was 84.5 days for the cranberry group and 91 days for the trimethoprim group (U = 166, $P = 0.479$).

The researchers concluded that trimethoprim had a very limited advantage over cranberry extract in the prevention of recurrent UTIs in older women and that it had more adverse effects.[54]

Beerepoot et al[54a] conducted a double-blind study of 221 premenopausal women with recurrent UTIs who were randomized to 12-month prophylaxis use of trimethoprim-sulfamethoxazole (TMP-SMX), 480 mg once a day, or cranberry capsules (Cran-Max), 500 mg twice a day. Primary end points were the mean number of symptomatic UTIs over 12 months, the proportion of patients with at least 1 symptomatic UTI, the median time to first UTI, and development of antibiotic resistance in indigenous *E. coli*.

After 12 months, the mean number of patients with at least one symptomatic UTI was higher in the cranberry than in the TMP-SMX group (4.0 vs 1.8; P = .02), and the proportion of patients with at least one symptomatic UTI was higher in the cranberry than in the TMP-SMX group (78.2% vs 71.1%). Median time to the first symptomatic UTI was 4 months for the cranberry and 8 months for the TMP-SMX group. Although the antibiotic was slightly more effective in preventing UTI, the subjects receiving antibiotics developed significant resistance to several antibiotics primarily used to prevent and treat UTIs.

After 1 month, in the TMP- SMX group, 86.3% of fecal and 90.5% of asymptomatic bacteriuria *E. coli* isolates were TMP-SMX resistant. There were also significant increased resistance rates for trimethoprim alone, amoxicillin, and ciprofloxacin in

these *E. coli* isolates after 1 month in the TMP-SMX group. Antibiotic resistance did not increase in the cranberry group. The cranberry product and TMP-SMX were equally well tolerated.

Effectiveness as a Prophylactic against Urinary Tract Infection

Stothers[55] executed a randomized placebo-controlled trial that evaluated, from a societal perspective, the comparative effectiveness and cost-effectiveness of concentrated cranberry tablets, cranberry juice, and placebo for prophylaxis against lower UTI in adult women. Sexually active women (n = 150) aged 21 to 72 years were randomly assigned for 1 year to one of the following three groups:

- Placebo juice + placebo tablets
- Placebo juice + cranberry tablets
- Cranberry juice + placebo tablets

The tablets were a proprietary extract of cranberry (30:1), given twice a day. The juice was a pure unsweetened cranberry juice (not cranberry cocktail) given in doses of 250 mL three times a day. Outcome measures demonstrated greater than 50% decreases in both symptomatic UTIs per year and annual antibiotic consumption. Both cranberry juice and cranberry tablets, in a statistically significant manner, decreased the number of patients experiencing at least one symptomatic UTI per year (20% and 18%, respectively) compared with placebo (32%). Total annual antibiotic consumption was lower in both treatment groups than in the placebo group. Cost-effectiveness ratios showed that cranberry tablets were twice as cost-effective as juice for the prevention of UTIs.

A Cochrane review of clinical trials on cranberry for preventing UTIs was conducted in 2008. Ten studies (n = 1049) met the inclusion criteria (five crossover, five parallel-group). Cranberry/cranberry-lingonberry juice versus placebo, juice or water was evaluated in seven studies, and cranberry tablets versus placebo in four studies (one study evaluated both juice and tablets). Cranberry products significantly reduced the incidence of UTIs at 12 months (RR 0.65, 95% CI 0.46 to 0.90) compared with placebo. Cranberry products were more effective reducing the incidence of UTIs in women with recurrent UTIs, than elderly men and women or people requiring catheterization. Side effects and dropouts or withdrawals were common in all studies, and in several of the studies were high. The authors concluded, "there is some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12-month period, particularly for women with recurrent UTIs. Its effectiveness for other groups is less certain. The large number of dropouts/withdrawals indicates that cranberry juice may not be acceptable over long periods of time. It is not clear what the optimum dosage or method of administration (e.g., juice, tablets, or capsules) is. Further properly designed studies with relevant outcomes are needed."[56]

Subsequent to Cochrane's review, further studies have evaluated the impact of cranberry supplements, including two studies that compared cranberry (Cran-Max) to antibiotics (McMurdo and Beerepoot as previously discussed) for reducing UTI recurrence. Three other studies will be discussed.

Sengupta et al[57] evaluated the effects of a standardized cranberry product (PACran) on reducing the recurrence of symptomatic UTI in culture-positive subjects. This 90-day randomized clinical trial involved 60 female subjects aged 18 to 40 years, who were randomly assigned to three groups including an untreated control group (n =16), a low dose (500 mg daily, n = 21) and a high dose (1000 mg daily, n = 23) treatment group. The safety of the cranberry product was assessed by evaluation of biochemical and hematologic parameters on days 10, 30, 60, and 90, comparing the values with those at the baseline. Occurrence of UTI at baseline and during the follow-up period was characterized by the presence of symptoms and *E. coli* in the culture of urine samples. At the end of the study, change in the presence of *E. coli* in the untreated control group was not significant, whereas there was significant reduction (P <0.05) in the subjects positive for *E. coli* in both the high- and low-dose treatment groups, compared with baseline evaluation. However, there were no significant differences in bacteriuria between the urine in the cranberry groups and the untreated control group at any time point after the study commenced. Symptomatic relief was also reported in the low- and high-dose treatment groups, while none was reported by subjects in the untreated control group.[57]

Prophylaxis Urinary Tract Infections in Men with Prostate Disease

Lower urinary tract symptoms (LUTS) are a common condition in older men, particularly among those with benign prostatic hyperplasia (BPH) and chronic prostatitis (CP). It is postulated that cranberry may offer benefits for men with prostate disease above and beyond its ability to inhibit uroepithelial bacterial adhesion and reduce UTI occurrence. Among recently reported effects of cranberry are its antiinflammatory action through reduced cyclo-oxygenase-2 expression, suppression of IkBa degradation in human colon cancer cells,[57a] and inhibition of the growth and proliferation of several types of tumor cells including prostate.[57b]

A study was conducted to evaluate the effect of a 6-month daily consumption of 1500 mg cranberry fruit powder (PACran) on urinary tract function in men with LUTS based on the International Prostate Symptom Score (IPSS), elevated prostate-specific antigen (PSA), BPH, and histopathologically confirmed non-bacterial CP. In contrast to the control group, patients in the cranberry group had statistically significant improvement in International Prostate Symptom Score, Quality of Life score, urination parameters, including voiding parameters (rate of urine flow, average flow, total volume and post-void residual urine volume), and lower total PSA level on day 180 of the study. There was no statistically significant improvement in the control group. The results of this preliminary trial are the first firm evidence that cranberries may ameliorate LUTS, independent of benign prostatic hyperplasia or C-reactive protein level.[57c]

Reducing Asymptomatic Bacteriuria in Ileal Enterocystoplasty

Bacteriuria is a usual complication of enterocystoplasty following cystectomy. Botto et al[57d] evaluated the effectiveness of treatment with a cranberry supplement in prevention of repeated bacteriuria in patients with an ileal enterocystoplasty. This open study included 15 patients with a history of repeated urinary infection and/or bacteriuria during the pretreatment phase. During the treatment phase, patients received a cranberry preparation with 36 mg PACs (Urell), one capsule a day. The primary endpoint was the absence of bacteria in urine culture. The secondary endpoints were the presence or absence of symptoms (pain, fever), continence status, and upper excretory tract enlargement. There was a significant decrease in the number of positive urine cultures during cranberry compound treatment. These results need to be validated by further double-blind randomized studies.

Reduction in Urinary Odor

Urinary odor, common in elderly people, may be reduced after the administration of cranberry.[4,58,59] Ammonia odor may be reduced by cranberry because the bacterial populations are lower and they are producing less ammonia as a by-product of metabolism.

Other Clinical Applications

Although much of the focus on the benefits of cranberry has been on UTIs, cranberry may offer other health benefits, some of which are described below.

Antioxidant

Oxidation, or the production of free radicals, is involved in the progression of many bodily processes that can lead to disease and afflictions, especially as we age. Cranberry contains antioxidants that can scavenge free radicals. Of the berries, blackberries, blueberries, cranberries, and raspberries have the highest levels of antioxidants.[60-62] Pedersen et al[63] studied the effects of blueberry and cranberry consumption on the plasma antioxidant capacity of healthy female volunteers.[63] Daily ingestion of 500 mL of cranberry juice increased plasma phenolic content and antioxidant capacity. Consumption of a similar amount of blueberry did not have this effect.

Cancer

Antiangiogenic approaches to prevent and treat cancer represent a priority area in investigative tumor biology. Vascular endothelial growth factor plays a crucial role in the vascularization of tumors. *In vitro* research on human dermal microvascular endothelial cells has shown that edible berries impair angiogenesis.[64] Several *in vitro* studies on cranberry have reported similar promising outcomes.

Researchers at the University of Western Ontario discovered that mice receiving cranberry juice and cranberry products had a significantly lower number of breast cancer than the control group, and the development of tumors was delayed in the cranberry-fed group. The proliferation of tumors to the lungs and lymph nodes was markedly reduced in the cranberry-fed group. A greater effect was demonstrated by the cranberry solids than the juice. Ongoing research is examining whether the activity of the berry solids traces largely to one component or to several potentially acting in synergy.[65]

A PAC fraction, an extract of concentrated flavonoids and triterpenoid esters of cranberry were evaluated in an *in vitro* cell culture model and exhibited potential anticarcinogenic activity, demonstrating an ability to inhibit tumor cell growth.[66-68]A synergistic or additive antiproliferative interaction of the anthocyanins, PACs, and flavonol glycosides within cranberry extract have also been demonstrated by *in vitro* research on human tumor cells.[69]

A combination of six berry extracts (wild blueberry, bilberry, cranberry, elderberry, raspberry seeds, strawberry) were studied for antioxidant efficacy, cytotoxic potential, cellular uptake, and antiangiogenic properties. The combination of anthocyanin-rich berries was reported to show antiangiogenic, antioxidant, and anticarcinogenic potentials.[70]

Vascular Disease

Research indicates that the consumption of flavonoids in foods and beverages may reduce the risk of atherosclerosis.[71] *In vitro* and *in vivo* experiments with cranberry flavonoids demonstrate that they inhibit the oxidation of low-density lipoprotein cholesterol (LDL-C), platelet aggregation and adhesion, and enzymes involved in lipid/lipoprotein metabolism (which affects the immune response to oxidized LDL-C and its uptake by endothelial macrophages). It may also induce endothelium-dependent vasorelaxation and increase reverse cholesterol transport, thereby decreasing total cholesterol and LDL-C values. Wilson et al[72] showed *in vitro* that cranberry extracts reduce oxidation of LDL-C.[72] A review by Reed[73] examined the effects of flavonoids on atherosclerosis with an emphasis on the positive potential effects of the flavonols and PACs in cranberries.[73]

Youdim et al[74] investigated the putative antioxidant and anti-inflammatory effects of blueberry and cranberry anthocyanins and hydroxycinnamic acids. The polyphenols isolated from both berries afforded protection for endothelial cells against stressor-induced upregulation of oxidative and inflammatory insults. This may have beneficial actions against the initiation and development of vascular diseases and may be a contributing factor in the reduction of age-related deficits in neurologic impairments.[74]

Ruel et al[74a] examined the effect of daily consumption of low-calorie cranberry juice cocktail on plasma oxidized LDL (oxLDL), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E- selectin concentrations in men. Thirty men (mean age 51 years) were recruited and asked to consume increasing daily doses of cranberry juice cocktail (125, 250 and 500 mL/d) over three successive periods of 4 weeks. Plasma OxLDL and adhesion molecule concentrations were measured by ELISA before and after each phase. The researchers noted a statistically significant decrease in plasma OxLDL, ICAM-1 and VCAM-1.

Helicobacter pylori

Burger et al[75] argue that because cranberry has been shown to inhibit bacterial adhesion to uroepithelial cells, it may also be useful as antiadhesion therapy in *H. pylori* infections. In a number of small *in vitro* studies, the investigators demonstrated that a high-molecular-weight (HMW) constituent of cranberry inhibits sialyllactose-specific adhesion of *H. pylori* to a human gastric cell line and mucus as well as human erythrocytes.[75] This research warrants further investigation into the use of cranberry as it relates to *H. pylori.*

Oral Bacteria

The effect of cranberry on the coaggregation (massing together) of oral bacteria has been tested. Weiss et al[76] discovered an HMW nondialyzable material, composed mainly of PACs isolated from cranberry juice. Although the molecular structure of this material and its mechanism of action are not known, *in vitro* studies showed that coaggregation of pairs of bacteria were inhibited, and pilot *in vivo* studies showed that coaggregation of a large number of different pairs was reversed.[77]

Studies using mouthwash demonstrated positive results and warrant additional research. Weiss[78] conducted a small pilot study of individuals (n = 59) using a standard mouthwash that contained this HMW constituent.[78] After 6 weeks of daily use, results showed a reduction in colony-forming units of bacteria in saliva compared with placebo. These data and those of other similar studies prompt the theory that inhibition of oral streptococci colonization and attachment to the tooth surface in vivo is due to the antiadhesion activity of the cranberry constituent.[79] Another study hypothesized the inhibition of extracellular polysaccharide synthesis, which promotes the sucrose-dependent adhesion of oral bacteria.[80]

Peristomal Problems

Tsukada et al[6] conducted a small study on the incidence of peristomal problems in 13 patients who had undergone urostomy. Patients drank 160 to 320 g/day of cranberry juice for an average of 6 months; As a result, 4 of 6 patients who initially had erythema, maceration, or pseudoepithelial hyperplasia at the stoma site showed improvement. This apparent protective effect for the skin against urine may be relevant for patients who are immobile

and incontinent and suffer skin damage as a result. Additional studies to confirm this finding are warranted.[28]

Managing Calcium Oxalate Urolithiasis

Investigations of the potential influence of cranberry juice on urinary biochemical and physicochemical risk factors associated with the formation of calcium oxalate kidney stones have been reported. Older research with renal stones reported a reduction in urinary calcium excretion after the studied patients drank cranberry juice, suggesting that it may be useful in the treatment of recurrent renal stones.[81]

Urinary variables were assessed by McHarg et al[82] in a randomized crossover trial (n = 20) in participants with no previous history of kidney stones. The ingestion of cranberry juice significantly and uniquely altered three key urinary risk factors. Oxalate and phosphate excretion decreased, whereas citrate excretion increased. In addition, there was a reduction in the relative supersaturation of calcium oxalate, which tended to be significantly lower than that induced by water alone. Each of these outcomes is desirable in patients at risk for nephrolithiasis (urolithiasis). The investigators concluded that cranberry juice has antilithogenic properties and deserves consideration as a conservative therapeutic protocol in managing calcium oxalate urolithiasis. The use of cranberry may be warranted in some patients with recurrent renal stones, but supplementary research is needed.[28]

DOSAGE

There are a variety of cranberry products to choose from that vary greatly in quality, potency, and activity. Differences exist between the level of bioactives (PACs) and formulation in commercially available tablets, capsules, and juices. Many products on the market are not standardized, being either dried whole-fruit powders, juice powders, and mixed juices with undefined amounts of cranberry juice.

Although drinking cranberry juice is one way to get the health benefits of this berry, it may not be ideal for all people. Most commercial cranberry juice cocktails contain only 27% to 33% pure cranberry juice, with sugar and water making up the rest of the volume. Such drinks are often high in calories. Encapsulated cranberry powders can be a convenient alternative to cranberry juice cocktail, especially for people who do not like the taste of cranberry, are traveling, or those concerned about the calories, sugar, or other sweeteners.

Health care providers directing their patients in selecting effective products should ensure that they find the most palatable product and should encourage long-term adherence. In the case of UTI prevention, this strategy may reduce an individual's potential for development of the disorder while also decreasing the need for antibiotics.

On the basis of the clinical studies, the amount of cranberry juice recommended for the prevention of UTIs is 1 to 10 oz a day; however, the ideal dosage has not yet been determined.[41,56,83] For use as a urinary deodorizer for incontinent patients, 3 to 6 oz (90 to 180 mL) per day of cranberry juice has been used.[59]

Tablets and capsules are often taken in doses of 500 mg once or twice a day, depending on the concentration of cranberry. Approximately 1500 g of fresh fruit produces 1 L of juice.[14,83]

ADVERSE EFFECTS

Taken orally, cranberry is generally well tolerated. No significant adverse effects have thus far been reported. However, cranberry juice at high doses of 3 to 4 L per day may cause gastrointestinal upset and diarrhea.[5]

Patients with diabetes should minimize cranberry juice sweetened with sugar or fruit juice.[83]

In theory, regular cranberry juice intake may precipitate the formation of urinary stones. However, urinary oxalate excretion does not rise after the drinking of cranberry juice, and no studies have reported stone formation as a complication.

DRUG INTERACTIONS

There are no known interactions between cranberry and other herbs or supplements.[83] Interaction with warfarin has been the subject of investigation. Cranberry contains antioxidants, including flavonoids, which are known to inhibit cytochrome P450 enzymes, and warfarin is predominantly metabolized by P450 form 2C9 enzymes.[83-86] A few case reports have suggested an interaction between cranberry and warfarin, affecting INR values. However, these reports were poorly documented and confounding factors may have been involved.

Recently, several researchers have examined the potential interaction between cranberry and warfarin. Seven separate interaction studies assessed valid and accepted pharmacodynamic (PD) and/or pharmacokinetic end-points, examining a total exposure of 75 patients and healthy volunteers. Six of these studies concluded that a cranberry juice-warfarin interaction is unlikely.[87-92] One study claimed a potential PD interaction on the basis of assessment of an inappropriate and unconventional AUC-based PD parameter and the use of a single, very high dose (25 mg) of warfarin in healthy volunteers.[93]

A review of the body of research on the potential interaction between cranberry and warfarin concluded that there is no evidence of risk of a clinically relevant interaction between warfarin and cranberry products from peer-reviewed interaction studies when cranberry juice is consumed in moderation. One cannot exclude the possibility of an interaction with the consumption of excessive quantities of cranberry products. Thus, it does not appear necessary to avoid normal levels of consumption of cranberry products (two 8-ounce glasses a day).[94]

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CHAPTER 132

Vaccinium myrtillus (Bilberry)

Michael T. Murray, ND

CHAPTER CONTENTS

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Vaccinium myrtillus (family: Ericaceae)
Common names: bilberry, huckleberry, European blueberry, whortleberry, blueberry

GENERAL DESCRIPTION

The genus *Vaccinium* in the family Ericaceae comprises nearly 200 species, most of which are found in the northern hemisphere. This chapter focuses on *Vaccinium myrtillus* and the medicinal use of extracts of its fruit.

V. myrtillus, or bilberry, is a shrubby perennial plant that grows in the sandy areas of the northern United States and in the woods and forest meadows of Europe. The angular, green, branched stem grows from a creeping rootstock to a height of 1 to 1.5 ft. The 0.5- to 1-in-long leaves are oval, slightly dentate, and bright green, whereas the flowers are reddish- or greenish-pink and bell-shaped. The bilberry's flowering season is April through June. The fruit is a blue-black berry.[1]

CHEMICAL COMPOSITION

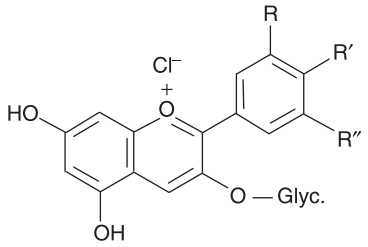
The pharmacologically active constituents of bilberries are its flavonoid components, specifically its anthocyanosides. An anthocyanoside is composed of an aglycone (e.g., anthocyanidin) bound to one of three glycosides (arabinoside, glucoside, or galactoside). More than 15 different anthocyanosides originate from the five aglycones found in *V. myrtillus* (Figure 132-1).[2] Other members of the genus *Vaccinium* as well as *Ribes nigrum* (black currant) and *Vitis vinifera* (grape) contain similar anthocyanosides.[3] Extracts of these fruits are also used for medicinal purposes in Europe.

The concentration of anthocyanosides in the fresh fruit is approximately 0.1% to 0.25%, whereas concentrated extracts of *V. myrtillus* are produced that yield an anthocyanidin content of 25%.[2] An extract with an anthocyanidin content of 25% actually contains about 37% anthocyanosides owing to the conjugation of the anthocyanidin with a glycoside. (For analytic purposes, the anthocyanosides content should always be expressed in terms of anthocyanidin.) Only very small amounts of free anthocyanidins exist in nature and in *V. myrtillus* extracts.

Bilberries are also good sources of bioavailable resveratrol[4] and quercetin,[5] although the levels of these compounds are lower than those found in other foods (e.g., the level of resveratol in bilberry is less than 10% of that reported for grapes). Nonetheless, consumption of bilberries may lead to significant elevations of these compounds in the serum because they are more bioavailable. In one study, 40 healthy men consumed 100 g/day of berries (black currants, lingonberries, and bilberries) for 8 weeks.[5] Twenty subjects consuming their habitual diets served as controls. Blood levels of quercetin were obtained at baseline and at 2, 4, and 8 weeks. During the berry consumption period, mean serum concentrations of quercetin ranged between 21.4 and 25.3 mg/L in the berry group, which translated into 32% to 51% higher than in the control group—indicating that the berries used in this study were a good source of bioavailable quercetin.

HISTORY AND FOLK USE

Bilberries have, of course, been used as food and for their high nutritive value. Medicinally, they have been used in the treatment of scurvy and urinary complaints (including infection and stones).[1] The dried berries have been used primarily for their astringent



Anthocyanin	R	R′	R″
Delphinidin 3-O-glycoside	OH	OH	OH
Cyanidin 3-O-glycoside	OH	OH	H
Petunidin 3-O-glycoside	OH	OH	OCH_3
Peonidin 3-O-glycoside	OCH_3	OH	H
Malvidin 3-O-glycoside	OCH_3	OH	OCH_3

FIGURE 132-1 Vaccinum myrtillis anthocyanosides. (Baj A, Bombardelli E, Gabetta B, Martinelli EM. Qualitative and quantitative evaluation of *Vaccinium myrtillus* anthocyanins by high-resolution gas chromatography and high-performance liquid chromatography. *J Chromatogr* 1983;279:365-372.)

qualities in the treatment of diarrhea and dysentery. Decoctions of the leaves have been used in the treatment of diabetes.[1]

PHARMACOLOGY

The pharmacology of *V. myrtillus* is discussed almost entirely in relation to its anthocyanoside content, because research has focused primarily on the anthocyanosides.

Collagen-Stabilizing Action

Anthocyanosides possess significant collagen-stabilizing action.[6-12] Collagen, the most abundant protein of the body, is responsible for maintaining the integrity of "ground substance" as well as tendons, ligaments, and cartilage. Collagen is destroyed during the inflammatory processes that occur in rheumatoid arthritis, periodontal disease, and other inflammatory conditions involving bones, joints, cartilage, and other connective tissue.

Anthocyanidins, proanthocyanidins, and other flavonoids are remarkable in their ability to prevent collagen destruction. The anthocyanidins in *V. myrtillus* extracts have been shown to affect collagen metabolism in the following ways:

- Anthocyanosides cross-link collagen fibers, resulting in strengthening of the natural cross-linking of the collagen that forms the collagen matrix of connective tissue (ground substance, cartilage, tendon, etc.).[6-10]
- Anthocyanosides, with their potent antioxidant and free radical scavenging action, prevent free radical damage.[6-9,11,60]
- Anthocyanosides inhibit enzymatic cleavage of collagen by enzymes secreted by leukocytes during inflammation.[6-8,10-12]
- Anthocyanosides and other flavonoid components of *V. myrtillus* prevent the release and synthesis of compounds that promote inflammation, such as histamine, serine proteases, prostaglandins, and leukotrienes.[6-8,13,14]
- Anthocyanosides promote mucopolysaccharide and collagen biosynthesis and stimulate reticulation of collagen fibrils.[15-17]

Normalization of Capillary Permeability

Anthocyanosides have strong "vitamin P" activity.[6] Included in their effects are the ability to raise intracellular vitamin C levels and reduce capillary permeability and fragility.[6-8] Their effect in reducing capillary fragility and permeability is roughly twice that of rutin in both intensity and duration of action.[18]

V. myrtillus extracts have been widely used in Europe in the treatment of various arterial, venous, and capillary disorders. Clinical studies have demonstrated a positive effect in the treatment of the following conditions[19-24]:

- Capillary fragility
- Blood purpuras
- Various encephalic circulation disturbances (similar to *Ginkgo biloba*)
- Venous insufficiency
- Varicose veins
- Microscopic hematuria caused by diffuse and kidney capillary fragility

V. myrtillus's efficacy in the treatment of a variety of venous disorders relates to the ability of anthocyanosides to protect altered veins (postphlebotic veins as well as varicose veins) via two mechanisms[17]: (1) increasing the endothelial barrier effect by stabilizing the membrane phospholipids and (2) increasing the biosynthesis of the acid mucopolysaccharides of the connective ground substance, thus restoring the altered mucopolysaccharide pericapillary sheath. This latter effect leads to a marked increase in newly formed capillaries and collagen fibrils.

One interesting effect of the normalization of collagen structures and capillaries is the demonstration that anthocyanosides from *V. myrtillus* reduce the permeability of the blood-brain barrier.[10,25] Greater blood-brain permeability has been linked to autoimmune diseases of the central nervous system, schizophrenia, "cerebral allergies," and a variety of other central nervous system disorders. Presumably the anthocyanosides inhibit both enzymatic and nonenzymatic degradation of the basement membrane collagen of brain capillaries, thus helping to maintain or restore the brain's protection from drugs, pollutants, naturally occurring degradation products, and other cerebral toxins.[9-12,25]

Another study further demonstrates the remarkable efficacy of bilberry in protecting and strengthening the capillaries and microcirculation. In this study, the effects of anthocyanidins on hamster cheek microcirculation after ischemia and reperfusion were investigated. The treated group had diminished adherence of leukocytes to the venules after reperfusion, resulting in prevention of the markedly increased capillary permeability seen in the placebo group.[26]

Antiaggregation Effect on Platelets

Anthocyanosides, like many other flavonoids, have been shown to have significant antiaggregation effects on platelets.[27-29] Their action in vivo appears to be direct antiaggregation effects on the platelets and an indirect effect via prostacyclin-like action.[27-29] Prostacyclin is a potent stimulator of adenyl cyclase, the enzyme that catalyzes the production of cyclic adenosine monophosphate from adenosine triphosphate. Cyclic adenosine monophosphate prevents platelets from aggregating and adhering to the endothelial surface.

Smooth Muscle–Relaxing Activity

Anthocyanoside extracts have demonstrated significant vascular smooth muscle–relaxing effects in a variety of experimental models.[30-32] The clinical application of this research may be in the treatment of dysmenorrhea, for which a preliminary study demonstrated positive effects.[33]

Effects on Cancer Cells

An in vitro study demonstrated that among ethanol extracts of 10 edible berries, bilberry extract was the most effective at inhibiting the growth of human leukemia cells and colon carcinoma cells.[34] Bilberry extract was shown to possess dual action in this regard through the induction of apoptosis (programmed cell death) and promotion of nucleosomal DNA fragmentation. Bilberry anthocyanidins have also been shown to inhibit angiogenesis. [35] Bilberry extract was the most potent of the extracts tested because it contained the largest amounts of phenolic compounds, including anthocyanins, and showed the greatest free radical scavenging activity. Pure delphinidin and malvidin, like the glycosides isolated from the bilberry extract, induced apoptosis in the leukemia cells. However, only pure delphinidin and the glycoside isolated from the bilberry extract, but not malvidin and the glycoside, inhibited the growth of human colon cancer cells. Twenty-five colorectal cancer patients scheduled to undergo resection of primary tumor or liver metastases received 1.4, 2.8, or 5.6 g (containing 0.5 to 2.0 g of anthocyanins) daily for 7 days before surgery. In tumor tissue from all patients, proliferation was decreased by 7% compared with preintervention values.[36]

CLINICAL APPLICATIONS

The primary clinical application of bilberry extracts has been in the prevention and treatment of a diverse group of disorders of the eye and vision. However, the same mechanisms of action that benefit the eye are of value for other health problems, especially those involving capillary dysfunction or inflammation.

Ophthalmologic Applications

Night Vision

Perhaps the most significant clinical applications for *V. myrtillus* extracts are in the field of ophthalmology. Interest in *V. myrtillus* anthocyanosides was first aroused when it was observed that the administration of bilberry extracts to healthy subjects resulted in improved nighttime visual acuity, quicker adjustment to darkness, and faster restoration of visual acuity after exposure to glare.[37,38] Further studies confirmed these results,[39-42] which were most impressive in individuals with pigmentary retinitis and hemeralopia. (*Hemeralopia* refers to "day blindness," or an inability to see as distinctly in bright light as in dim light.)

It appears that in addition to their effect on capillaries, *V. myrtillus* anthocyanosides have an affinity for the pigmented epithelium of the retina, which makes up the optical or functional part of the retina.[43] This feature is consistent with several of the clinical effects observed.

Anthocyanoside extracts of *V. myrtillus* appear to be of great value in both poor night vision and poor day vision. In a double-blind study in patients with eye strain and clinical symptoms of low to moderate myopia, 30 subjects were given either a purified high-dose anthocyanoside oligomer (a 100-mg tablet comprising 85% anthocyanoside oligomer) or a placebo tablet twice daily for 4 weeks. Prior to the treatment, the placebo and anthocyanoside groups were similar in terms of age and contrast sensitivity. Before and after treatment, subjects completed a questionnaire to determine their clinical symptoms, and were also assessed for nocturnal visual function using contrast sensitivity testing. Questionnaire data analysis showed that, following treatment, 22 (73.3%) anthocyanoside subjects showed improved symptoms, whereas only 1 placebo subject showed an improvement. Contrast sensitivity levels significantly improved in the anthocyanoside group and remained stable in the placebo group. The mean change in contrast sensitivity in the anthocyanoside group was 2.41, compared with –0.66 decibels (dB) for the placebo group. At all cycle per degree levels, there were greater improvements in contrast sensitivity in the anthocyanoside group than in the placebo group. This very detailed clinical assessment demonstrated that the administration of anthocyanoside oligomer improves both subjective symptoms and objective contrast sensitivity in myopia subjects with asthenopia.[44]

Glaucoma

V. myrtillus may play a significant role in the prevention and treatment of glaucoma via its effect on ocular collagen structures. In the eye, collagen provides tensile strength and integrity to the tissues—cornea, sclera, lamina cribrosa, trabecular meshwork, and vitreous.

Morphologic changes in the collagen of the eye precede clinically detectable abnormalities. These changes may result in elevated intraocular pressure (IOP) readings or, perhaps more significantly, the progression of peripheral vision loss. Changes in collagen structure would explain the following observations:

- Similar peripheral vision loss in patients with normal and elevated IOP
- Cupping of the optic disc even at low IOP levels
- No apparent anatomic reason for decreased aqueous outflow (see Chapter 168 for complete discussion and references)

Therefore primary prevention of glaucoma involves maintaining the integrity of the ground substance and collagen framework. It appears that preventing breakdown of collagen matrix is important here as it is also in other conditions involving collagen abnormalities, such as atherosclerosis, rheumatoid arthritis, and periodontal disease.

Consumption of *V. myrtillus* may offer significant protection against the development of glaucoma because of its collagen-enhancing actions. In addition, anthocyanosides may be of benefit in the treatment of chronic glaucoma, as rutin has been demonstrated to lower IOP when used as an adjunct in patients who are unresponsive to miotics alone.[45] *V. myrtillus* anthocyanosides are generally much more biologically active than rutin.[18]

Cataracts and Retinal Degeneration

V. myrtillus anthocyanosides may offer significant protection against the development of retinal (macular) degeneration and cataracts, particularly diabetic retinopathy and cataracts.[46,47] Both the rate of retinal degeneration and the occurrence of cataracts in rats can be retarded by changing their diet from a commercial laboratory chow to a "well-defined diet."[48,49] Preliminary research suggests that flavonoid components in the well-defined diet may be responsible for the protective effects against cataracts and retinal degeneration.[50] Limited research has shown that, when combined with vitamin E, bilberry significantly slows the progression of senile cataracts in humans.[51]

V. myrtillus anthocyanoside extracts are widely used in Europe for the prevention of diabetic retinopathy.[51-53] The positive effects noted in clinical trials may be due to improved capillary integrity as well as inhibition of sorbitol production (see Chapter 161). Flavonoids have been shown to be potent in vitro and in vivo inhibitors of sorbitol accumulation. In laboratory experiments, they have been found capable of inhibiting the development of diabetic cataracts.[54-56]

Other Clinical Applications

Diabetes Mellitus

A decoction of blueberry leaves has a long history of folk use in the treatment of diabetes. This use is supported by research, which has shown that oral administration reduces hyperglycemia in normal and depancreatized dogs even when glucose is concurrently injected intravenously.[53,57]

Bilberry extract ameliorates hyperglycemia and insulin sensitivity via activation of AMP-activated protein kinase.[58] The anthocyanoside myrtillin (3-glucoside of delphinidin) is apparently the most active hypoglycemic component of *V. myrtillus*. Upon injection, it is somewhat weaker than insulin, but it is also less toxic, even at 50 times the 1 g/day therapeutic dose. It is of interest to note that a single dose can have beneficial effects lasting for several weeks.[53]

However, the most important benefits from the use of anthocyanosides in the treatment of diabetes relate to their ability to improve collagen integrity and capillary permeability. Benefit also possibly derives from their ability to inhibit sorbitol accumulation, thus providing protection from the serious vascular and neurologic sequelae of diabetes.

V. myrtillus anthocyanosides have also been shown to have a protective effect on capillary fragility in diabetes and to reduce serum cholesterol and triglyceride levels in primary dyslipidemia.[59]

Although studies in rabbits have not confirmed a cholesterol-lowering effect, the anthocyanosides significantly decrease the intimal proliferation, extracellular matrix production, and calcium and lipid deposition found in the aorta of untreated atherosclerotic rabbits. Presumably this decrease is a result of greater collagen cross-linking, which thus diminishes the permeability in small and large blood vessels.[60]

Inflammatory Joint Disease

The effects of anthocyanosides on collagen structures and their potent antioxidant activity make *V. myrtillus* anthocyanoside extracts very useful in the treatment of a wide variety of inflammatory conditions, most notably rheumatoid arthritis. Bioflavonoids have been found to increase collagen synthesis and inhibit collagen catabolism in rats with adjuvant-induced arthritis (a chronic progressive polyarthritis with some similarities to rheumatoid arthritis).[15]

Blueberries, like cherries, are particularly indicated in the treatment of gout, because their flavonoid components can reduce both uric acid levels and tissue destruction (see Chapter 184).[61]

Microscopic Hematuria

The effect of *V. myrtillus* in the reduction of microscopic hematuria may reflect its tissue distribution. Pharmacokinetic studies in rats have demonstrated an affinity for the skin and kidneys.[60] Anthocyanosides' affinity for these tissues reflects the high concentration of collagen and mucopolysaccharides in the skin and kidneys and the fact that they are excreted via the kidneys.

Other Effects

As mentioned previously, the smooth muscle–relaxing effects of bilberry extract have been put to good use in the treatment of dysmenorrhea.[33] A significant improvement in pelvic-lumbosacral pain, mammary tension, nausea, and lower limb heaviness was noted when women with dysmenorrhea were given bilberry extract (115 mg anthocyanosides per day) for 3 days before and during menstruation.

Bilberry extracts have demonstrated antiulcer effects in various experimental models and have been promoted as an ulcer medication in Italy.[63]

DOSAGE

The standard dose for *V. myrtillus* is based on its anthocyanoside content, as calculated from its anthocyanidin percentage. Widely used pharmaceutical preparations in Europe are typically standardized for a 25% anthocyanidin content. Dosages are as follows:

- Anthocyanosides (calculated as anthocyanidin): 20 to 40 mg three times a day
- *Vaccinium myrtillus* extract (25% anthocyanidin content): 80 to 160 mg three times a day
- Fresh berries: 55 to 115 g three times a day

TOXICOLOGY

Extensive toxicologic investigation has demonstrated that *V. myrtillus* anthocyanoside extracts are devoid of toxic effects. Administration to rats of dosages as high as 400 mg/kg has no apparent side effects, and excess levels are quickly excreted through the urine and bile.[18,26]

DRUG INTERACTIONS

No drug interactions have been reported for *V. myrtillus*.

SUMMARY

V. myrtillus anthocyanosides exhibit significant pharmacologic activity, particularly on collagen structures. Research has demonstrated a positive effect in the treatment of the following problems:

- Capillary fragility
- Blood purpuras
- Various encephalic circulation disturbances
- Venous insufficiency
- Varicose veins
- Microscopic hematuria caused by diffuse and kidney capillary fragility
- Poor night vision
- Hemeralopia
- Diabetic retinopathy

Experimental studies indicate that anthocyanosides should also be useful in most inflammatory or degenerative conditions involving connective tissues (e.g., osteoarthritis, gout, rheumatoid arthritis, periodontal disease) as well as in glaucoma, diabetes, cataracts, retinal degeneration, and schizophrenia.

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CHAPTER 133

Valeriana officinalis (Valerian)

Michael T. Murray, ND

CHAPTER CONTENTS

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Valeriana officinalis (family: Valerianaceae)
Common names: valerian, all heal

GENERAL DESCRIPTION

Valerian is a perennial plant native to North America and Europe. The yellow-brown tuberous rootstock produces a flowering stem 2 to 4 ft high. The stem is round but grooved and hollow, with leaves arranged in pairs. The small rose-colored flowers are in bloom from June to September. The rootstock is the portion used medicinally.

CHEMICAL COMPOSITION

The important active compounds of valerian are the valepotriates (iridoid molecules) (Figure 133-1) and valerenic acid. These compounds are found exclusively in valerian. Originally it was thought that just the valepotriates were responsible for valerian's sedative effects, but an aqueous extract of valerian has also been shown to have a sedative effect. Because the valepotriates are not soluble in water, it was concluded that valerenic acid also possesses sedative action and is the chemical factor responsible for the sedative effect noted in human clinical trials with aqueous extracts of valerian root (see later).

Moreover, because the safety of valepotriates was questioned after studies demonstrated mutagenicity, most commercial extracts feature water-soluble extracts standardized for valerenic acids.[1-3]

Other components of valerian are a volatile oil (0.5% to 2%), choline (3%), flavonoids, sterols, and several alkaloids (actinidine, valerianine, valerine, and chatinine).[1]

HISTORY AND FOLK USE

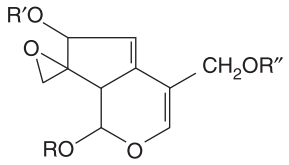
Valerian's primary traditional use has been as a sedative for the relief of insomnia, anxiety, and conditions associated with pain. Specific conditions for which it has been used are migraine, insomnia, hysteria, fatigue, intestinal cramps, and other nervous conditions.

PHARMACOLOGY

Valerian has demonstrated a number of pharmacologic effects, such as the following[4-7]:

- Normalizing of the central nervous system (it acts as a sedative in states of agitation and as a stimulant in cases of extreme fatigue)
- Lowering of blood pressure
- Enhancement of the flow of bile (choleretic effect)
- Relaxing the intestinal muscles
- Antitumor and antibiotic activity

Its prime pharmacologic effect, however, is consistent with its historic use as a sedative. Pharmacologic studies indicated that both valepotriates and valerenic acid are capable of binding to gamma-aminobutyric acid (GABA) receptors, much like the benzodiazepines.[8] However, valerian does not appear to act in a similar fashion in that side effects such as impaired mental function, morning hangover, and dependency have not been reported with valerian. In addition, valerian compounds



Compound	R	R′	R″
Valtrate	Isovaleroyl	Isovaleroyl	Acetyl
Isovaltrate	Isovaleroyl	Acetyl	Isovaleroyl
Homovaltrate	Isovaleroyl	Methyl-valeroyl	Acetyl
Acevaltrate	Isovaleroyl	O-acetyl-valeroyl	Acetyl

FIGURE 133-1 Valeopotriates in valeriana officinalis.

that do not bind to GABA receptors have also been shown to produce sedative effects. Therefore, other mechanisms may be more important, including valerenic acids modulating GABA receptors or promoting the release of GABA.[9]

Another key mechanism of action of valerian components is acting as an agonist to adenosine receptors. Adenosine is not a typical hormone or neurotransmitter but is probably the most important neuromodulator in the central and peripheral nervous systems. A neuromodulator is a compound that has a modulatory effect on neuronal activity, increasing or decreasing the rate at which a nerve cell fires.

Neuromodulators are distinct from neurotransmitters (e.g., glutamate), which are typically stored in the presynaptic terminal, are released into the synaptic cleft, and then interact with postsynaptic receptors and are either taken up or metabolized. A neuromodulator such as adenosine is more likely to be either constitutively released or released at times of high or low metabolic activity. Neuromodulators may act presynaptically or postsynaptically and may then be either taken up or metabolized.

The therapeutic exploitation of adenosine receptors is still in its infancy, although the stimulant properties of the methylxanthines (caffeine, theophylline, theobromine, etc.) are partially explained by their antagonism of adenosine receptors. In contrast, valerian has been shown to act as an adenosine agonist.[10,11]

CLINICAL APPLICATIONS

The primary clinical application for valerian is as a sedative in the treatment of insomnia. It can also be used in the treatment of stress and anxiety.

Insomnia

More than 20 double-blind clinical studies have now substantiated valerian's ability to improve sleep quality and relieve insomnia.[12-23] Most of these studies have shown positive results.[24] Several recent double-blind studies have shown no significant benefit with valerian in improving sleep parameters in insomnia. In one study, a dosage of 300 mg valerian extract failed to show any statistically significant difference versus a placebo after a single dose or after 2 weeks of nightly dosing on any measure of sleep latency, wake after sleep onset, sleep efficiency, and self-rated sleep quality.[25] In another very detailed clinical study, standardized sleep electroencephalographic (EEG) and psychometric tests were used to evaluate the clinical efficacy of valerian extract 300 mg, valerian extract 600 mg, or placebo.[26] Results showed no significant effect between valerian 300 mg, valerian 600 mg, or placebo on any EEG parameter or psychometric measure. Nonetheless, these results are not viewed as being conclusive, given the results of other trials and valerian's long history of use.[24]

The initial studies were performed on subjects who did not have insomnia. These studies showed quite clearly that extracts of valerian root improved subjective ratings of sleep quality and sleep latency (the time required to go to sleep) but left no "hangover" the next morning.[12] In one early study, the effects of valerian on sleep were studied in two groups of healthy young subjects.[13] One group slept at home and the other in a sleep laboratory. Sleep was evaluated on the basis of questionnaires, self-rating scales, and nighttime motor activity. Under home conditions, both doses of an aqueous valerian extract (450 and 900 mg) reduced perceived sleep latency and wake time after sleep onset. Nighttime motor activity was enhanced in the middle third of the night and reduced in the last third. The data suggest a dose-dependent effect. In the sleep laboratory, where only the higher dose of valerian was tested, no significant differences from placebo were obtained. However, the directions of the changes in the subjective and objective measures of sleep latency and wake time after sleep onset, as well as in nighttime motor activity, corresponded to those observed under home conditions. There was no evidence of a change in sleep stages or EEG spectra. The results indicate that the aqueous valerian extract exerts a mild sedative effect.

Although the initial studies demonstrated that valerian could improve sleep quality in normal subjects, they failed to answer the question whether valerian could improve sleep patterns in people suffering from insomnia. In a follow-up to these two preliminary studies, in more than 15 double-blind studies, valerian extract has been shown to significantly reduce sleep latency, improve sleep quality, and reduce nighttime awakenings in sufferers of insomnia.[14] These studies were usually performed under strict laboratory conditions and demonstrated quite clearly that valerian is as effective in reducing sleep latency as are small doses of barbiturates or benzodiazepines. However, although the latter compounds also increase morning sleepiness, valerian usually reduces morning sleepiness.

In one of the better-designed double-blind trials, patients 18 to 73 years of age diagnosed with nonorganic insomnia, according to the *International Classification of Diseases,* 10th edition, were treated at night with either 600 mg of valerian extract or 10 mg of oxazepam (Serax) for 6 weeks.[17] A total of 202 outpatients with a mean duration of insomnia of 3.5 months at baseline were involved in the study. Sleep quality after 6 weeks measured by Sleep Questionnaire B showed that the 600 mg dose of valerian extract was at least as efficacious as a treatment with 10 mg of oxazepam. Both treatments markedly increased sleep quality compared with baseline ($P < 0.01$). The other sleep function subscales—feeling of refreshment after sleep, psychic stability in the evening, psychic exhaustion in the evening, psychosomatic symptoms in the sleep phase, dream recall, and duration of sleep—confirmed similar effects of both treatments. The Clinical Global Impressions scale and Global Assessment of Efficacy by investigator and patient again showed similar effects of both treatments. No significant side effects or serious adverse reactions were reported in either group. Most patients assessed their respective treatment as very good (82.8% in the valerian group, 73.4% in the oxazepam group). These results show that valerian extract displays a comparable efficacy with that of 10 mg of oxazepam in the therapy of nonorganic insomnia.

In another study comparing the effects of valerian and oxazepam, 75 patients with nonorganic and nonpsychiatric insomnia between 18 and 70 years of age were randomly allocated either to receive 600 mg of valerian extract or 10 mg of oxazepam every day 30 minutes before going to bed over a period of 28 days. The results of this study were consistent with those of the other in that both

groups' measures of sleep quality improved significantly, but there was no statistically significant difference between groups.[22]

Valerian extract has also been shown to help improve sleep and relieve insomnia in people withdrawing from chronic benzodiazepine use.[18] The study consisted of patients with insomnia who complained of poor sleep despite long-term use of benzodiazepines. These patients had taken benzodiazepines nightly for an average of 7 years. Sleep EEGs of the patients were analyzed with period amplitude analysis and associated algorithms during chronic benzodiazepine use (night 1), and then after 15 days of a valerian-placebo trial (initiated after washout of benzodiazepines; night 2). The subjects given valerian extract reported significantly better subjective sleep quality than those given placebo. The EEG results also showed significant less wake time after sleep onset in valerian subjects than in placebo subjects, and that the valerian-treated patients experienced longer sleep latency and increased alpha counts in slow-wave sleep. All together these results indicate that valerian extract has a positive effect on withdrawal from benzodiazepine use.

Valerian may be helpful in patients with restless legs syndrome (RLS). In one study, [37] patients with RLS were randomly assigned to receive 800 mg of valerian extract or placebo for 8 weeks. Results indicated that valerian supplementation for 8 weeks improves symptoms of RLS and decreases daytime sleepiness.[27]

Valerian extract also appears to be useful in children. Serious sleep disturbances are particularly problematic for children with intellectual deficits and are often the source of much distress for both the children and caregivers. Conventional drugs are not suitable for long-term treatment, making valerian an attractive alternative. In one small double-blind study in five children with varying intellectual deficits and different primary sleep problems, treatment with valerian extract led to significant reductions in sleep latencies and nocturnal time awake, lengthened total sleep time, and improved sleep quality.[19] The treatment was apparently most effective in children with deficits that involved hyperactivity. Although the findings were preliminary and in need of replication, the results imply that valerian may be useful in the safe and effective long-term treatment of sleep difficulties in children with intellectual deficits.

One of the major advantages of valerian extract is that it rarely has a negative effect on reaction time, alertness, or concentration the morning after intake. In one double-blind trial, 102 male and female volunteers were studied to determine whether reaction time, alertness, and concentration might be impaired by treatment with a valerian root extract.[28] The effect was first examined the morning after a single evening dose of either valerian extract (600 mg), flunitrazepam (Rohypnol) (1 mg), or a placebo and then after 2 weeks of evening administration of valerian extract (600 mg) or a placebo. Evaluation of the primary criterion (the median of reaction time measured with the Vienna Determination Test) and secondary criteria (alertness test, tracking test, sleep quality, additional Vienna Determination Test parameters, and safety criteria) all demonstrated that neither a single administration nor 14 days of valerian extract treatment produced an impairment in reaction abilities, concentration, or coordination.

Anxiety and/or Depression

Valerian extracts, based on preliminary studies, have shown some evidence of usefulness in the treatment of generalized anxiety and depression. For example, in one study involving 36 outpatients with generalized anxiety disorder, patients underwent a 2-week washout period and then were randomly assigned to one of the following three treatments for 4 weeks: valepotriates (mean daily dose: 81.3 mg), diazepam (Valium) (mean daily dose: 6.5 mg), and placebo.[29] Although no significant difference was observed among the three groups at baseline or in the change from baseline on the Hamilton Anxiety Scale—probably because of the small sample size in each group—there was some evidence of benefit nonetheless. Specifically, only the diazepam and valepotriates groups showed a significant reduction in the psychic factor of the Hamilton Anxiety Scale.

In one study, valerian extract was shown to be effective in reducing the physiologic effects of psychological stress induced under laboratory conditions in a group of healthy volunteers.[30] Valerian extract produced a significant decrease in systolic blood pressure responsivity, no significant reductions in diastolic blood pressure, and a decrease in the heart rate reaction to mental stress.

Valerian may prove useful in relieving anxiety in a patient with comorbid depression. In an open clinical trial, the combination of valerian with St. John's wort was found to improve symptoms more quickly than did St. John's wort monotherapy.[31] The combination therapy was well tolerated, and no significant side effects occurred.

DOSAGE

As a mild sedative, valerian may be taken 30 to 45 minutes before bedtime. This timing of dosage has been verified by pharmacokinetic studies showing that the peak blood levels of valerenic acid occur within 1 to 2 hours after ingestion. Dosage recommendations are as follows:

- Dried root (or as tea): 1.5 to 3 g
- Tincture (1:5): 4 to 8 mL (1 to 2 tsp)
- Fluid extract (1:1): 2 to 4 mL (1/2 to 1 tsp)
- Solid (dry powdered) extract (4:1): 400 to 800 mg
- Valerian extract (1.0 % to 1.5% valtrate or 0.5% valerenic acid): 300 to 600 mg

For the rare patient with increased morning sleepiness, reducing the dosage will eliminate the problem. For best results, dietary factors such as caffeine and alcohol, which disrupt sleep (see Chapter 182), should be eliminated.

TOXICITY

Valerian is generally regarded as safe and is approved for food use by the U.S. Food and Drug Administration.[32] A major concern for any sedative or antianxiety medication is its potential to affect a person's ability to drive or operate potentially dangerous machinery. A randomized placebo-controlled double-blind study evaluated the impact of a valerian–lemon balm preparation on psychomotor and mental performance tests.[33] No effect was found on reaction time, concentration, or attentiveness.

One case of valerian overdose has been reported in the literature.[34] The patient presented with mild symptoms, all of which disappeared within 24 hours after the patient had taken an overdose—approximately 20 times the recommended therapeutic dose of valerian. Another case history reports valerian-induced hepatotoxicity.[35]

DRUG INTERACTIONS

Although in vitro studies have demonstrated that valerian inhibits drug-metabolizing enzymes, at typical doses it is unlikely to produce clinically significant effects on the disposition of medications dependent on the CYP2D6 or CYP3A4 pathways of metabolism.[36] There is some concern that valerian may prolong thiopental- and pentobarbital-induced sleep—a concern based on animal data indicating the need to avoid concurrent use of valerian and barbiturates.

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CHAPTER 134

Viscum album (European Mistletoe)

Michael T. Murray, ND

CHAPTER CONTENTS

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Viscum album L. (family: Loranthaceae)
Common names: European mistletoe, all-heal, birdlime, devil's fuge

GENERAL DESCRIPTION

Viscum album, or European mistletoe, is an evergreen semiparasitic plant found on the branches of deciduous trees in Europe and northern Asia. The roots of the plant penetrate through the bark into the wood of the host tree. The green branches are 1 to 2 ft long and form pendent bushes with leaves that are opposite, leathery, yellow-green, and narrowly obovate. Inconspicuous pale yellow or green flowers appear from March to May, the female developing into sticky white berries that ripen from September to November.[1,2]

Viscum is most commonly seen on old apple, ash, and hawthorn trees. Traditionally, mistletoe from oak has been the most widely used, although it does not grow as well on oak as on the previously mentioned trees.[1,2]

CHEMICAL COMPOSITION

V. album contains a variety of pharmacologically active substances, including alkaloids, polysaccharides, phenylpropanes, lignins, lectins, and viscotoxins.[3-10] Some specific compounds found in *Viscum* are as follows[2,5,6,10]:

- A wide range of carbohydrates, including simple sugars as well as polysaccharides
- Phenolic compounds such as flavonoids, caffeic acid, syringin, and eleutherosides
- Sterols, including beta-sitosterol, stigmasterol, and triterpenes
- Various amino acids as well as vasoactive amines, including tyramine, phenylethylamine, and histamine
- Fatty acids such as linoleic, palmitic, and oleic acids

The alkaloids isolated from *Viscum* appear to be related to those found in the host plant.[3,4] For example, mistletoes growing on Solanaceae shrubs contain nicotine alkaloids like hyoscine, anabasine, and isopelletierine. Cardiac glycosides have been found in mistletoe growing on *Nerium oleander*; strychnine has been found in mistletoe growing on *Strychnos* species; and caffeine has been found in mistletoe growing on coffee plants.

Because pharmacologically active compounds appear to be concentrated within the mistletoe, different host trees providing diverse chemical constituents could be used for different therapeutic actions. Also of importance is the fact that the proteins/lectins are present only in aqueous extracts, indicating that their therapeutic activity would differ from that of the alcoholic/aqueous extracts. The alcoholic/aqueous extracts also demonstrate considerably less toxicity.

HISTORY AND FOLK USE

Mistletoe was held in great reverence by the Druids who, dressed in white robes, would search for the sacred plant. When some was discovered, a great ceremony would ensue, culminating in the mistletoe's separation from the oak tree with a golden knife. The Druids believed that mistletoe protected them from all evil and that the oaks on which it was seen growing were to be respected because of the wonderful cures that the priests were able to produce with it.[1]

Mistletoe's use has been recorded in the Middle East, Africa, India, and Japan and it was mentioned as an anticancer drug by Pliny, Dioscorides, and Galen.[3] In

1720, an English physician, Sir John Colbatch, extolled the virtues of *Viscum* in a pamphlet titled *The Treatment of Epilepsy by Mistletoe*. For many years, mistletoe was used in the treatment of a variety of nervous system disorders, including convulsions, delirium, hysteria, neuralgia, and nervous debility.[1,3] It has been used in naturopathic medicine in the treatment of hypertension and vascular disorders of the uterus, bladder, and intestines.

Probably because of *Viscum's* potential toxicity, its use appears to have fallen into some disrepute shortly after Colbatch's work. For many years it was used only in external preparations for the treatment of dermatitis. Then, in 1906, a study demonstrating *Viscum*'s hypotensive effect in animals and humans was published. This paper appears to have restored its medical prestige, initially in France and eventually throughout Europe.[3]

PHARMACOLOGY

V. album exhibits diverse pharmacologic actions. The herb and various extracts have demonstrated that it serves as

- A hypotensive
- A vasodilator
- A cardiac depressant
- A sedative
- An antispasmodic
- An immunostimulator
- An antineoplastic agent

Purified mistletoe lectins are, in general, not as active in experimental studies as are crude preparations.[11,12] Presumably the crude preparations contain a number of compounds acting synergistically. It has also been proposed that alkaloid components are responsible for the maintenance of lectin structure and activity.[5] During isolation and purification procedures, alkaloid linkages are cleaved from the lectins, resulting in a loss of specificity for target molecules. Unfermented *Viscum* preparations typically demonstrate greater direct cytotoxicity to tumor cells owing to higher concentrations of the viscotoxin mistletoe lectin I (ML I).[13-15]

Cardiovascular Effects

Viscum has exhibited a variety of effects on the cardiovascular system.[3,16] In particular, *Viscum* has repeatedly demonstrated hypotensive action in animal studies. The mechanism of action for its hypotensive effect is still not entirely clear, and no recent investigations have been published. *Viscum* has been shown to inhibit the excitability of the vasomotor center in the medulla oblongata and to possess cholinomimetic activity.[16]

Viscum's hypotensive activity may depend on the form in which the mistletoe is administered and the host tree from which it was collected. Studies indicate that aqueous extracts are more effective; the highest hypotensive activity was demonstrated by a macerate of leaves of mistletoe parasitizing on willow and gathered in January.[16]

Viscum's nonprotein components—flavonoids, phenol carboxylic acids, phenylpropanes, and lignins—have been shown to possess hypotensive action. Alcoholic solutions (tinctures and fluid extracts) contain these compounds but not viscotoxins or lectins. As previously stated, however, aqueous extracts appear to be more effective.

Several *Viscum* preparations for hypertension are currently available in Europe. In fact, in Great Britain alone, more than 150 different mistletoe preparations are available.[3] These preparations typically have small amounts of *Viscum* in combination with other botanicals with hypotensive action, such as garlic, *Crataegus oxyacantha*, and *Tilia platyphyllos*.

Antineoplastic and Immunostimulatory Effects

Viscum preparations have been used clinically in Europe for the treatment of cancer since 1926, when Iscador, a fermented product made from the crude pressed juice, was introduced as an immunotherapeutic agent for cancer. This work was carried out under the direction of Rudolph Steiner. Since that time, numerous studies have shown that Iscador and other *Viscum* preparations and components are effective antineoplastic and immunostimulatory agents.[11-15,17-31]

Iscador and other fermented *Viscum* preparations differ from nonfermented extracts in their greater effectiveness and their lower toxicity.[17] Specifically, the major viscotoxin, ML I, is not found in Iscador.[18] It is thought that fermentation transforms ML I to its A and B chains, which have important immunologic properties.[13] The A chain has mitogenic effects, and the B chain stimulates macrophages and the release of lymphokines. In addition, there is a rapid decrease of lectins during fermentation.

The pharmacologic activity of Iscador has been shown to be due to its *Viscum* components rather than to other constituents, such as lactobacilli, which possess adjuvant activity. The lectins have clearly been demonstrated to be the *Viscum* components largely responsible for Iscador's adjuvant activity. Although unfermented plant juice has demonstrated a tenfold greater cytotoxicity to tumor cells than Iscador in vitro, fermented Iscador contains a great number of substances that may act synergistically. In vivo studies in mice have demonstrated Iscador to have greater adjuvant activity than purified mistletoe lectin and to be without secondary toxic effects.[19,20]

Viscum's adjuvant activity is demonstrable in both delayed-type hypersensitivity and antibody responses of mice to sheep red blood cells.[19,20] Like other adjuvants (e.g., bacille Calmette-Guérin, levamisole, muramyl dipeptide, bacterial and yeast components, etc.), Iscador is most effective when it is administered near the tumor, although systemic administration has also yielded positive results. Upon local administration, an inflammatory process ensues that promotes white blood cell (WBC) infiltration and encapsulation of the tumor.

The nonspecific host defense factors stimulated by *Viscum* include the following:

- Enhanced macrophage phagocytic and cytotoxic activity[17,20]
- Increased neutrophil production[17]
- Increased thymic weight and enhanced cortical thymocyte activity and proliferation[21,23]
- Enhanced natural killer (NK) cell activity[17,22,24,32]
- Increased antibody-dependent cell-mediated cytotoxicity[17,22]
- Inhibition of angiogenesis[33]

Iscador's effects on these immunologic parameters have been confirmed in patients with cancer.[17,22]

Iscador's effect in stimulating the thymus gland has been demonstrated in several studies.[21,23] Its ability to induce hyperplasia of the thymic cortex and accelerate the regeneration of hematopoietic cells after x-irradiation is much greater than that of any other agent reported to date.[21] In addition, thymic lymphocytes became 29 times more responsive to concanavalin A as a result of Iscador administration.

In summary, *V. album* exhibits numerous cytotoxic, adjuvant, and immunostimulatory effects that indicate a therapeutic effect in human cancer. These effects have been confirmed in vivo against murine tumors, Lewis lung carcinoma,

colon adenocarcinoma 38, and C3H mammary adenocarcinoma 16/C.[4]

CLINICAL APPLICATIONS

Cancer

The clinical application with the most significant scientific documentation is the use of *Viscum* preparations as adjuncts in cancer therapy. In published studies, the route of administration of *Viscum* preparations used has been subcutaneous or intravenous. Therefore it is not known to what degree (if any) the effects noted for Iscador as well as other preparations and *Viscum* compounds can be achieved with oral administration, although one study has shown that an enteric-coated, specially prepared *Viscum* preparation led to the absorption of intact lectins.[34]

Early clinical investigations of Iscador were not well documented. Owing to the shortage of acceptable controlled clinical trials, the use of Iscador and other *Viscum* preparations for the treatment of cancer in Europe has remained controversial, although positive effects in the postoperative treatment of lung, breast, colon, and cervical carcinomas have been shown in several controlled studies.[25] The problem is that the methodologic criteria in these studies are poor. Until their benefits are better documented, mistletoe preparations appear most useful as adjuncts to standard therapy.

The results of a prospective study indicate that Iscador is helpful in increasing the survival rate for various cancers.[35] The prospective long-term epidemiologic study sought to determine whether Iscador treatment prolongs survival time of patients with carcinoma of the colon, rectum, or stomach; breast carcinoma with or without axillary or remote metastases; or small cell or non–small cell bronchogenic carcinoma. A total of 10,226 patients with cancer were evaluated. Of these patients, 1668 had been treated with Iscador and 8475 had taken neither Iscador nor any other mistletoe product (control patients). In the nonrandomized matched-pair study, the survival time of patients treated with Iscador was longer for all types of cancer studied. In the pool of 396 matched pairs, mean survival time in the Iscador groups (4.23 years) was roughly 40% longer than in the control groups (3.05 years).

Perhaps even more beneficial than Iscador is the new generation of mistletoe preparations standardized on ML I (e.g., Eurixor, Lektinol). This greater standardization offers significant advantages. ML I is a potent inducer of cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor. Its cytotoxic effects are also related to its ability to induce apoptosis (programmed cell death).[26]

In one study, the effect of Eurixor was examined in 40 patients with advanced carcinoma of the breast. Along with standard chemotherapy (vinblastine, epidoxorubicin and cisplatin [VEC] regimen), 21 patients were assigned to receive mistletoe (treatment group) and 19 were given a placebo (control group).[27] After the fourth cycle of chemotherapy, the treatment group had statistically significantly higher leukocyte levels ($P < 0.001$) than the control group; the treatment group had an average WBC count of 3000/mm^3 and the control group an average WBC count of 1000/mm^3. Furthermore, the parameters of quality of life and anxiety revealed significantly better values in the treatment group than in the control group. These results show that adjuvant treatment with mistletoe extracts, in this case Eurixor, is a valuable addition to standard chemotherapy for patients with advanced breast cancer. These results are important because advanced breast cancer carries a very poor prognosis. Similar results in better-designed studies have been shown with various *Viscum* preparations in advanced pancreatic, colon, and liver cancers.[28,36-41]

Detailed reviews of all published studies with *Viscum* preparations indicate significant improvements in various quality-of-life parameters such as coping, fatigue, sleep, exhaustion, energy, nausea, vomiting, appetite, depression, anxiety, ability to work, and emotional and functional well-being in general and, less consistently, in regard to pain, diarrhea, general performance, and side effects of conventional treatments.[42,43]

A study in ovarian cancer consisted of two randomized matched-pair substudies: The first substudy comprised 42 ovarian cancer patients without distant metastases (Ovar) and 40 ovarian cancer patients with distant metastases (OvarRand). Patients were paired in random allocation to either Iscador or control. The second substudy comprised 150 ovarian cancer patients without distant metastases (Ovar) and 124 ovarian cancer patients with distant metastases (OvarRand). Patients who had already received therapy with Iscador were matched by the same criteria to control patients. Increased survival rates with Iscador were significant in OvarRand but not in Ovar in both studies.[44]

Presurgical treatment with *Viscum* preparations may help to prevent the decreased NK cell activity associated with surgery. In a study of colorectal cancer patients undergoing open tumor resection, patients were randomly assigned to either mistletoe infusion or no additional therapy. The NK cell activity of patients treated with mistletoe extract did not change significantly during the course of the study, whereas the control patients' NK cell activity decreased significantly after surgery (–44.4% at 24 hours).[45]

Immune Support

The immune-enhancing effects of *Viscum* preparations may extend to conditions beyond cancer. For example, Iscador was shown to reduce the rate of recurrent respiratory infections (RRIs) in children 5 to 14 years old living in areas exposed to the radioactive fallout from the Chernobyl nuclear reactor accident.[46] The dosage was two subcutaneous injections a week for 5 weeks. One year after a single-treatment course, the frequency of RRI relapses decreased by 75%. Furthermore, *V. album* therapy resulted in normalization of initial immune indices that were either below or above the normal ranges. This immunomodulatory effect was assessed by investigation of lymphocyte subsets, NK cell activity, phagocytic and oxidative activity of polymorphonuclear leukocytes, and antiviral activity of serum before and 1 week after treatment.

Clearly additional investigations into the pharmacology of *V. album* are needed. Specifically it must be determined whether the effects noted both in vitro and in vivo in animals as well as in patients receiving injectable *Viscum* preparations can be attained with oral administration. In addition, greater clarification is needed to determine optimal *Viscum* preparations. What host tree should be selected for which condition? What is the optimal harvesting time? In what form should the *Viscum* be administered—crude herb, aqueous or alcoholic extract, fermented or nonfermented?

Viscum is undoubtedly one of the most complex botanicals; current data suggest that the future medicinal use of *V. album* looks promising.

DOSAGE

The standard dose of *V. album,* based on the *British Herbal Pharmacopoeia,*[47] is as follows:

- Dried leaves: 2 to 6 g (or by infusion) three times a day
- Tincture 1:5 (45% alcohol): 1 to 3 mL three times a day
- Fluid extract 1:1 (25% alcohol): 0.5 mL three times a day
- Dried aqueous extract 4:1: 100 to 250 mg three times a day

TOXICITY

V. album possesses significant toxicity. Historically the berries have been regarded as being considerably more toxic than the leaves and stems despite the fact that they all contain similar toxic compounds. The berries are considered to be more toxic, probably because of the fatal poisonings of children who ingest the berries.

Lethal doses of *Viscum* lectins administered by various routes to mice produce the following two types of toxicity: (1) a typical type characterized by death after 3 to 4 days with marasmus-like symptoms and (2) an atypical type characterized by immediate death from respiratory paralysis.[23] In mice, the dose that is fatal to 50% of the subjects (LD_{50}) is 32 mg (dry weight) per kilogram of body weight of the plant juice administered intraperitoneally.[29]

The LD_{50} values of *V. album*, either orally administered or in extract form, have not yet been determined. As stated earlier, alcohol-based extracts contain virtually no *Viscum* proteins. This fact would imply significantly less toxicity with these preparations; however, it would also imply loss of activity, because much of the pharmacology of *Viscum* relates to its protein content, especially its immune-enhancing activity.

The toxicity of Korean mistletoe, *Viscum album coloratum*, appears to be lower than that of European mistletoe.[30,31] This other species has also demonstrated anticancer effects, but they appear to be due to highly cytotoxic alkaloids rather than to lectins.[5,30] Studies comparing Korean *Viscum* extracts with European extracts as well as their alkaloid components have demonstrated that the Korean mistletoe has greater activity in inhibiting cancer cells. In addition, fresh Korean mistletoe extracts exhibited greater activity than fermented extracts.[5,30] Korean mistletoe may ultimately prove to be superior to European mistletoe.

DRUG INTERACTIONS

There is some theoretical concern that mistletoe's hypotensive effects might be additive with conventional antihypertensive drugs and that its immunostimulant effects could counter immunosuppressant drugs. However, there appear to be no clinical reports of such effects.

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CHAPTER 135

Vitamin A

Michael T. Murray, ND

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INTRODUCTION

Vitamin A was the first fat-soluble vitamin to be recognized. Although identified as a necessary growth factor in 1913, it was not characterized chemically until 1930. The initial discovery of vitamin A was made almost simultaneously by two groups of research workers, McCollum and Davis at the University of Wisconsin and Osborne and Mendel at Yale University. They found that young animals fed a diet deficient in natural fats became very unhealthy, as evidenced by the inability to grow and poor immune function. These researchers also noted that the animals' eyes would become severely inflamed and infected with the restricted diet and that this condition could be quickly relieved by the addition to the diet of either butterfat or cod liver oil. Vitamin A was once known as the "anti-infective vitamin," and vitamin A status remains a major determinant of immune status.

Nomenclature

When isolated in its pure form, vitamin A is a pure, lipid-soluble yellow crystal with a condensed formula $C_{20}H_{29}OH$. Vitamin A is termed retinol, signifying that it is an alcohol that is intricately involved in the function of the retina of the eye. All-*trans* retinol is found in nature primarily as long-chain retinyl esters. The aldehyde form of all-*trans* retinol is commonly designated retinaldehyde or retinal, whereas the acidic form is termed retinoic acid. It has been suggested that retinol serves only as a precursor to these two active forms of vitamin A—retinal being primarily involved with vision and reproduction and retinoic acid being important in other somatic functions, such as growth and differentiation (Figure 135-1).[1]

Synthetic derivatives of retinoic acid have been developed to treat many dermatologic conditions and, more recently, certain forms of cancer. These compounds, however, are not without side effects.

Recommended Dietary Allowance

Vitamin A was originally measured in international units (IUs), with 1 IU being defined as 0.3 mg of crystalline all-*trans* retinol or 0.6 mg β-carotene. In 1967, an Expert Committee of the United Nations Food and Agriculture Organization and World Health Organization recommended that vitamin A activity be referred to in terms of retinol equivalents rather than in IU, with 1 mg of retinol being equivalent to 1 retinol equivalent (RE). The amount of beta-carotene required for 1 RE is 6 mg, whereas the amount required for other provitamin A carotenoids is 12 mg. In 1980, The Food and Nutrition Board of the National Research Council/National Academy of Sciences adopted this recommendation, and the 1980 recommended dietary allowance (RDA) for vitamin A is stated in milligrams and retinol equivalents; in 2001, the RDAs were revised to today's values (Table 135-1).

Dietary Sources

The most concentrated sources of preformed vitamin A are liver, kidney, butter, whole milk, and fortified skim milk, whereas the leading sources of provitamin A are dark-green leafy vegetables (collards and spinach) and yellow-orange vegetables (carrots, sweet potatoes, yams, and squash) (Table 135-2). Ingestion of excessive

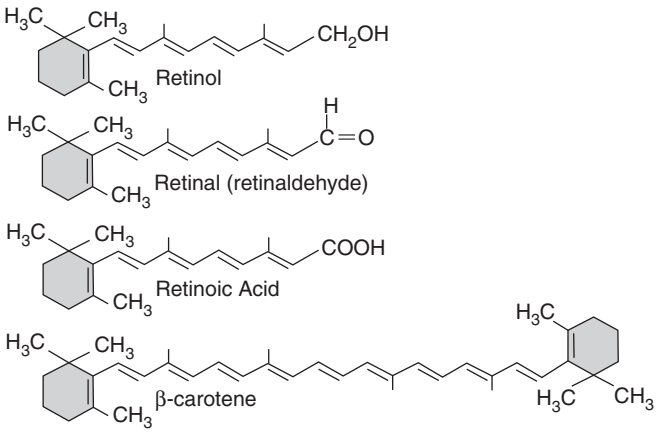


FIGURE 135-1 Forms of vitamin A.

TABLE 135-1 **Recommended Dietary Allowances**

LIFE STAGE GROUP	RETINOL MCG/DAY (RETINOL EQUIVALENTS)	INTERNATIONAL UNITS (IU)
Infants (adequate intakes)		
0 to 6 months	400	1320
7 to 12 months	500	1500
Children		
1 to 3 years	300	1000
4 to 8 years	400	1320
Males		
9 to 13 years	600	2000
14 to 18 years	900	3000
19 to >70 years	900	3000
Females		
9 to 13 years	600	2000
14 to 18 years	700	2310
19 to >70 years	700	2310
Pregnancy		
<19 years	750	3750
19 to >50 years	770	3950
Lactation		
<19 years	1200	4000
19 to >50 years	1300	4300

amounts of liver—2.7 to 11 kg/week—has been reported to cause hypervitaminosis A.[2]

DEFICIENCY

Vitamin A deficiency may be due to inadequate dietary intake (primary deficiency) or to some secondary factor that interferes with the absorption, storage, or transportation of vitamin A. Some factors known to induce a vitamin A deficiency are as follows:

- Malabsorption due to bile acid or pancreatic insufficiency
- Protein-energy malnutrition
- Liver disease
- Zinc deficiency
- Abetalipoproteinemia
- Poor conversion of beta-carotene to vitamin A

TABLE 135-2 **Food Sources of Vitamin A**

FOOD	PORTION SIZE	IU/PORTION
Meats		
Beef liver, fried	100 g	50,375
Calf liver, cooked	100 g	26,872
Chicken liver, cooked	2 livers	25,760
Vegetables		
Sweet potatoes, baked	1 medium	14,600
Carrots, raw	1 large	11,000
Spinach, raw	100 g	8100
Carrots, cooked	½ cup	8000
Pumpkin, cooked	½ cup	8000
Spinach, cooked	½ cup	7300
Collard greens	½ cup	5400
Broccoli, cooked	½ cup	1900
Fruits		
Watermelon	1/16 melon	5310
Cantaloupe	¼ melon	3400
Apricots, dried	4 halves	2275
Apricots, raw	2-3 medium	2700
Nectarines, raw	1 medium	1650

Data from Selhorst JB, Waybright EA, Jennings S, et al. Liver lover's headache: pseudotumor cerebri and vitamin A intoxication. JAMA 1984;252:3365.

Immune System Effects

Immune system abnormalities associated with a vitamin A deficiency include impaired ability to mount an effective antibody response, decreased levels of helper T cells, and alterations in the mucosal linings of the respiratory and gastrointestinal tracts. Vitamin A–deficient individuals are more susceptible to infectious diseases and have higher mortality rates. It appears that although a vitamin A deficiency may predispose an individual to an infection, vitamin A stores are also severely depleted during the course of an infection. Thus, a vicious cycle ensues. Infectious conditions associated with vitamin A deficiency include measles, chickenpox, respiratory syncytial virus, acquired immunodeficiency syndrome, and pneumonia.

Other Effects

Prolonged vitamin A deficiency results in the characteristic signs of follicular hyperkeratosis (buildup of cellular debris in the hair follicles, giving the skin a goose-bump appearance, which occurs most often on the back of the upper arm), night blindness, and a higher rate of infection. As the condition worsens, the mucous membranes of the respiratory tract, gastrointestinal tract, and genitourinary tract also become affected, and the classic eye disease known as xerophthalmia due to vitamin A deficiency ensues. Even a mild vitamin A deficiency is associated with a significant rise in mortality. This association is extremely significant, because vitamin A deficiency is particularly widespread in developing countries, especially in Asia, where as many as 10 million children are found to have xerophthalmia each year.[3]

Xerophthalmia

The term *xerophthalmia* is generally used to cover all the ocular manifestations of vitamin A deficiency. Blindness is one of the

TABLE 135-3 **Staging of the Xerophthalmias**

STAGE	DIAGNOSIS	SIGNS AND SYMPTOMS
X0	Night blindness	Poor dark adaptation
X1A	Xerosis of conjunctiva	Dryness with "lackluster" appearance, thickening, wrinkling, and diffuse pigmentation of conjunctiva
X1B	Bitot spots	Usually triangular collections of desquamated, keratinized epithelial cells and mucus
X2	Xerosis of cornea	Dryness of cornea, leading to keratinization and a hazy, milky appearance
X3	Keratomalacia	Ulceration, distortion, and softening of the cornea with eventual perforation and prolapse and infection of the iris

most serious consequences of vitamin A deficiency. Although it rarely occurs in the United States, it is the major preventable cause of blindness in Asia. The xerophthalmia of vitamin A deficiency is staged as shown in Table 135-3.

In an effort to prevent vitamin A deficiency in underdeveloped countries, large prophylactic doses (200,000 IU) are given by the World Health Organization to children every 6 months.

Determination of Deficiency

The rapid dark-adaptation test is perhaps the most sensitive of the currently available tests designed to determine vitamin A deficiency. Measurement of serum retinol levels is usually not useful because they may not drop until marked deficiency occurs. Deficiency in the United States and other developed countries is usually secondary to malabsorption, liver disease, or proteinuria.

METABOLISM

Absorption

A variety of factors are known to influence the absorptive efficiency of vitamin A and carotenoids. Although retinol does not require bile acids to facilitate absorption, carotenoids do. Other factors that affect vitamin A and carotenoid absorption are as follows:

- The presence of fat, protein, and antioxidants in food
- The presence of bile and a normal complement of pancreatic enzymes in the intestinal lumen
- The integrity of the mucosal cells

The absorptive efficiency of dietary vitamin A is usually quite high (80% to 90%), with only a slight reduction in efficiency at high doses. In contrast, beta-carotene's absorptive efficiency is much lower (40% to 60%), and it diminishes rapidly with increasing dosage. Carotene supplements are better absorbed than the carotenes from foods.[4]

Transformation in the Intestinal Mucosa

The majority of absorbed retinol is esterified with palmitic acid or another free fatty acid within the intestinal mucosal cells. It is then incorporated, along with triglycerides, phospholipids, and cholesterol esters, into chylomicra. Each chylomicron is transported through the lymphatic channels into the general circulation and eventually removed from the circulation by the liver.

TABLE 135-4 **Distribution of Vitamin A in Some Human Tissues (mcg/kg)**

TISSUE	VITAMIN A
Adrenal gland	10.4 ± 7.1
Liver	149 ± 132
Testis	1.14 ± 1.23
Fat	1.46 ± 1.55
Pancreas	0.52 ± 0.28
Spleen	0.89 ± 0.88
Lung	0.91 ± 1.89
Thyroid	0.43 ± 0.33

Transport, Storage, and Excretion

Upon reaching the liver, vitamin A is stored primarily in special perisinusoidal lipocytes (Ito cells); the hepatocytes contain only a minor fraction of the total vitamin A stored in the liver. Although small amounts of vitamin A are found in most tissues (Table 135-4), more than 90% of the total body vitamin A content is stored in the liver. It is stored as a lipoglycoprotein complex consisting of 96% retinyl esters and 4% unesterified retinol. The retinyl esters are hydrolyzed by a tightly bound retinyl ester hydrolase, which transfers the released all-*trans* retinol to intracellular retinol-binding protein (RBP). The bound retinol is then processed through the Golgi apparatus and secreted into the plasma, where it forms a reversible 1:1 molar complex with prealbumin.[1,5]

Adequate dietary protein, iron, and zinc are necessary for proper retinol mobilization. The half-lives of RBP and prealbumin are less than 12 hours, making them particularly likely to be deficient during protein-calorie malnutrition or other situations in which protein metabolism is abnormal. A zinc, iron, or vitamin E deficiency also severely impairs vitamin A metabolism, because these nutrients function synergistically in many physiologic processes of vitamin A metabolism (absorption, transport, and mobilization in particular).[6,7]

Retinol is transferred into the cell after RBP binds to a cell surface receptor. The retinol is then quickly bound by cellular retinol-binding protein (CRBP) in the cell cytosol.

Retinoic acid is metabolized differently from retinol. It is absorbed through the portal system and transported in the plasma bound to albumin. It does not accumulate in the liver or other tissues in any appreciable amounts. It is metabolized quite rapidly to more polar oxygenated compounds. Intracellularly, it is bound to the cellular retinoic acid–binding protein.

Vitamin A metabolites are excreted mainly through the feces (via the bile) and the urine. During periods of deficiency there appears to be an adaptation in utilization, as evidenced by a reduction in the rate of vitamin A catabolism.[1,5]

Conversion of Beta-Carotene to Vitamin A

Emerging research is revealing that genomic variations that result in impaired conversion of beta-carotene to vitamin A are surprisingly common. Single nucleotide polymorphisms have been identified that result in decreased activity of 15,15'-monoxygenase, the key enzyme responsible for the conversion of beta-carotene to retinol. The R267S and A379V variants are common, with frequencies in the population of 42% and 24%, respectively. Those with both 267S and 379V have a 57% reduction in conversion rate. Those with these variant have increased blood levels of beta-carotene and decreased blood levels of vitamin A.[8]

PHYSIOLOGIC ROLES OF VITAMIN A

Vision

The best-understood physiologic role of vitamin A is its effects on the visual system. The human retina has four kinds of vitamin A–containing photopigments. Rhodopsin, maximum absorption at 498 nm, is present in the rods. The three iodopsins, as follows, are in the cones:

- Blue cones (maximum absorption 420 nm)
- Green cones (maximum absorption 534 nm)
- Red cones (maximum absorption 563 nm)

The vitamin A form found in these pigments is the 11-*cis* isomer of vitamin A aldehyde (retinal). When a photon of light strikes the dark-adapted retina, the 11-*cis* configuration is converted to the all-*trans* form of the retinaldehyde and split from the rhodopsin molecule to yield opsin and all-*trans* retinol. This leads to a change in membrane potential and subsequent visual excitation. During light adaptation, because the visual processes largely depend on the cone cells, the released all-*trans* retinal or retinol from the rod cells is transported to pigment epithelial cells and stored as retinyl palmitate. During dark adaptation, these processes are reversed and the retinal is isomerized to the 11-*cis* form. The rod cells are particularly sensitive to vitamin A deficiency, so night blindness or poor dark adaptation is an early consequence of vitamin A deficiency. This sensitivity may have clinical significance in older adults with normal retinal health or early age-related maculopathy (ARM). In a double-blind, placebo-controlled experiment, 104 adults 50 years of age or older whose fundic photographs for the eye fell within steps 1 to 9 of the Age-Related Eye Disease Study Grading System were randomly assigned to a 30-day course of 50,000 IU oral retinol or a placebo. At 30 days, the retinol intervention group had significantly larger (i.e., steeper) rod slopes, indicating faster recovery of sensitivity, than did the placebo group. It is believed that the structural changes in the retinal pigment epithelium and Bruch's membrane in aging and early ARM cause a localized vitamin A deficiency.[5]

Growth and Development

Vitamin A is believed to affect growth and development through its necessary role in the synthesis of many glycoproteins (e.g., mucus), some of which may control cellular differentiation, and by its function as CRBP in controlling gene expression.[1]

The adhesion between cells is apparently related to glycoprotein synthesis, which is markedly depressed in vitamin A deficiency. Consequently there is a loss of normal stimuli for cellular growth and differentiation during deficiency. CRBP is transferred directly into the nucleus and may function much like some of the steroid hormones. The effects of a vitamin A deficiency most readily seen at the cellular level are in those differentiating tissues that have a rapid turnover rate—epithelial cells of the oral cavity, respiratory tract, urinary tract, and ducts of the secretory glands.[1]

Development and Maintenance of Epithelial Tissue

The role of vitamin A and carotenoids in the development and maintenance of epithelial tissue cannot be overstated. Vitamin A status determines whether mucin or keratin is synthesized in epidermal cells—the presence of adequate vitamin A results in mucin production, whereas a lack leads to hyperkeratinization of the skin, cornea, upper respiratory tract, and genitourinary tract. Mucopolysaccharide synthesis also appears to depend on adequate vitamin A status.[1,9]

Reproduction

The requirement of vitamin A for reproductive functions in higher animals has been known since 1922. Beta-carotene has also been reported to have a specific effect in fertility distinct from its role as a precursor to vitamin A.[10-12] In bovine nutritional studies, cows fed beta-carotene–deficient diets exhibited delayed ovulation and an increase in the number of follicular and luteal cysts.[10,12] The corpus luteum has the highest concentration of beta-carotene of any organ measured.[12] The carotene cleavage activity changes with the ovulation cycle, the highest activity occurring during the mid-ovulation stage. It has been speculated that a proper ratio of carotene to retinol must be maintained to ensure proper function of the corpus luteum.

The corpus luteum produces progesterone; therefore, inadequate corpus luteum function could have significant deleterious effects. Inadequate corpus luteum secretory function is one of the characteristic features of infertile and/or irregular menstrual cycles.[13] Furthermore, an increased estrogen/progesterone ratio has been implicated in a variety of clinical conditions, including ovarian cysts, premenstrual tension syndrome, fibrocystic breast disease, and breast cancer.[14] Because supplemental beta-carotene given to cows significantly reduced the incidence of ovarian cysts (42% in control group vs. 3% in the beta-carotene group), it may have a similar effect in humans.[11,12] Another bovine condition that has benefited from higher levels of dietary beta-carotene is cystic mastitis.[13] It appears that farmers have a greater appreciation of beta-carotene than many nutritionists. Of course there are significant financial reasons for this, because the annual monetary loss from bovine mastitis in the United States has been estimated to be at least $1.5 to $2 billion, and ovarian cysts represent the major cause of infertility in cattle.

Immune System

Vitamin A is absolutely essential to proper immune function. Vitamin A plays an essential role in maintaining the epithelial and mucosal surfaces and their secretions. These parts of the immune system constitute a primary nonspecific host defense mechanism. Furthermore, vitamin A has been shown to stimulate and/or enhance numerous immune processes, including induction of antitumor activity, enhancement of white blood cell function, and an increased antibody response.[15] These effects are not due simply due to a reversal of vitamin A deficiency, because many are further enhanced by (supposedly) excessive amounts of vitamin A. Retinol has also demonstrated significant antiviral activity and has prevented the immunosuppression induced by glucocorticoids, severe burns, and surgery. Some of these effects are probably related to vitamin A's ability to prevent stress-induced thymic involution and to promote thymic growth. The carotenes, which are better antioxidants, may turn out to be even more effective in protecting the thymus gland than vitamin A, because the thymus gland is particularly susceptible to free radical and oxidative damage.

CLINICAL APPLICATIONS

Adequate tissue vitamin A levels are vital for optimal health. In addition, this nutrient can be used beyond its "physiologic" role in the treatment of various conditions. Supplemental vitamin A is

used primarily to enhance the immune system in viral illnesses to treat numerous skin disorders.

Natural vitamin A is available as either retinol or retinyl-palmitate. Absorption may be improved via micellization or emulsification. Micellization is the process of making the fat-soluble vitamin A into very small droplets (micelles) so that the material is dispersed in water. Emulsification is the process of suspending vitamin A into a colloidal mixture with another chemical (such as lecithin) so that it can mix with water. Despite manufacturers' claims, it is important to remember that regular vitamin A is absorbed at a rate of 80% to 90%.

Infections

As discussed previously, vitamin A is absolutely critical to a healthy, functioning immune system. Vitamin A–deficient individuals are more susceptible to infectious diseases in general but especially parasitic and viral infections. Although vitamin A deficiency may predispose an individual to an infection, vitamin A stores are severely depleted during an infection.

Parasitic Infections

Vitamin A is critical not only to immune function but also to the integrity and function of the intestinal barrier. Hence, vitamin A deficiency may be a predisposing factor to intestinal parasitic infections. In one study evaluating the effects of retinol on intestinal barrier function, growth, total parasites, and *Giardia* species infections in children in northeastern Brazil, 79 children received vitamin A 100,000 to 200,000 IU (n = 39) or placebo (n = 40) at enrollment and then again at 4 and 8 months; they were followed for 36 months. Total intestinal parasitic, specifically new, infections were significantly lower in the vitamin A group compared with the control group; this outcome was accounted for entirely by significantly fewer new *Giardia* infections in the vitamin A group, indicating that adequate vitamin A stores may help to prevent *Giardia* infections.[16]

In another study, the effect of vitamin A supplementation on the overall incidence of diarrheal disease and respiratory tract infections in children was evaluated in 188 children, aged 6 to 15 months, from periurban marginalized communities of Mexico City. The children were assigned to receive vitamin A (below 12 months of age, 20,000 IU retinol; at or above 12 months, 45,000 IU retinol) or a placebo every 2 months and were followed for up to 15 months. Vitamin A supplementation had no significant effect on the risk of overall diarrheal disease but reduced mild watery diarrhea (incidence rate ratio [RR] 0.69) and cough with fever (RR, 0.69). Vitamin A supplementation also decreased diarrheal disease during the summer (RR, 0.74), among nonstunted children (RR, 0.69) and among children from higher socioeconomic level households.[17]

Measles

Vitamin A deficiency is a major problem in many developing countries. A number of well-designed studies have confirmed an effect first noted in 1932—vitamin A supplementation can significantly reduce infant mortality due to measles by at least 50%. Typically, the dosage of vitamin A in double-blind studies has been 200,000 to 400,000 IU administered only once or twice to replenish body stores.[18,19] However, the benefit of vitamin A supplementation in the treatment of measles is not limited to developing countries. A study of well-nourished children in Long Beach, California, suffering from measles indicated that 50% were deficient in vitamin A.[20] This finding supports the use of vitamin A supplementation even in the United States.

Infants with Respiratory Syncytial Virus Infections

Wide-scale immunization programs have reduced the risk of measles in children. However, vitamin A therapy appears appropriate for other childhood viral illnesses as well. One of the more common viruses is the respiratory syncytial virus (RSV), a common cause of severe respiratory disease in young children. Studies have shown that children with RSV have low serum levels of vitamin A. Furthermore, the lower the vitamin A level, the greater the severity of the disease, similar to the relation shown in measles. Because vitamin A supplementation diminishes the morbidity and death caused by measles, a group of researchers decided to determine vitamin A's safety and absorption pattern in RSV as a first step in assessing its therapeutic effectiveness.[21]

Twenty-one children with a mean age of 2.3 months (range 1 to 6 months) with mild RSV infection were treated with 12,500 to 25,000 IU of oral micellized vitamin A. Baseline vitamin A levels were shown to be low; however, within 6 hours of administration of 25,000 IU but not 12,500 IU of vitamin A, normal levels were reestablished. Despite their young age, none of the children experienced any obvious signs or symptoms of vitamin A toxicity. Although the study was not designed as a therapeutic trial, the subjects receiving vitamin A had shorter hospital stays than children with a similar severity of illness who were not enrolled in the study.

Although vitamin A supplementation is an attractive treatment of RSV infections because of its low cost, wide availability, and ease of administration, placebo-controlled trials have suggested that it may be of value only in the most severe cases. A placebo-controlled study of 180 children in Chile with RSV provided 50,000 to 200,000 IU of retinyl palmitate (according to age) within 2 days of admission.[22] Supplementation resulted in no significant benefit except for those children suffering from hypoxemia. These children experienced substantial benefit, consisting of a more rapid resolution of tachypnea and shortening of their hospital stay from 9.3 to 5.5 days. Similar results were seen in a study involving hospitalized pediatric patients with nonspecific upper respiratory infections.[23]

Acquired Immunodeficiency Syndrome

Patients with acquired immunodeficiency syndrome (AIDS) may also benefit from vitamin A supplementation. One study showed that a vitamin A deficiency is quite common during human immunodeficiency virus (HIV) infection, and that vitamin A deficiency is clearly associated with a decreased level of circulating helper T cells, one of the hallmarks of AIDS.[24]

Analysis of vitamin A levels, helper T cells, and other blood parameters in individuals with HIV indicated that more than 15% had low serum vitamin A levels. Helper T-cell levels were much lower in patients with HIV infection whose vitamin A levels were low than in those who had normal levels of vitamin A. Vitamin A deficiency was also shown to be associated with a higher rate of mortality due to HIV.

Increasing beta-carotene may be the preferred form of vitamin A for supplementation in patients with HIV, because retinoic acid, the active form of vitamin A, may actually increase HIV replication in humans. Low beta-carotene levels are common in AIDS, presumably as a result of fat malabsorption. Low beta-carotene levels are associated with greater impairment of immune function.[25]

Skin Disorders

The use of high-dose vitamin A therapy for acne and other skin disorders was introduced in dermatology in the late 1930s. It is still used by a few dermatologists, although this type of therapy is not as popular as before the advent of synthetic retinoids.

Vitamin A therapy has been shown to be quite effective in treating skin conditions associated with excessive formation of keratin (hyperkeratosis), a skin protein that can clog the pores of the skin to produce a "goose bump" effect. Examples of some skin conditions associated with hyperkeratosis include acne, psoriasis, ichthyosis, lichen planus, Darier's disease, palmoplantar keratoderma, and pityriasis rubra pilaris. The dosages of vitamin A used to treat these conditions have typically been quite high (300,000 to 500,000 IU/day for 5 to 6 months in the treatment of acne; 1 to 3.5 million IU/day for 1 to 2 weeks for the other conditions).[26-29] The use of these high dosages usually results in the development of significant toxicity (see later). Although there is some evidence that carotenes may be more useful and less toxic in some of these conditions, the pharmacologic activity responsible for the effects of vitamin A in hyperkeratosis is believed to occur when serum retinol levels exceed serum RBP capacity, causing destabilization of membranes and destruction of the keratin-producing cells.[25]

In monitoring for vitamin A toxicity, laboratory tests appear unreliable until obvious toxicity symptoms are apparent. The first significant toxic symptom is usually headache, followed by fatigue, emotional instability, and muscle and joint pain. Chapped lips (cheilitis) and dry skin (xerosis) generally occur in the majority of patients, particularly in dry weather. Because high doses of vitamin A during pregnancy can cause birth defects, women of childbearing age should use effective birth control during vitamin A treatment and for at least 1 month after discontinuation.

High doses of vitamin A may not be necessary if other nutritional factors, like zinc and vitamin E, are included. These nutrients work with vitamin A in promoting healthy skin. A safe and effective recommendation for vitamin A in the treatment of acne is less than 25,000 IU/day.

Dry Eyes

Dry-eye disorders are a complex group of diseases characterized by a localized water deficiency in the tear ducts, a mucin deficiency, or a combination of the two. Despite the diversity of underlying causes, the changes in the conjunctiva of the eye are similar in all cases—loss of goblet cells (mucin-producing cells), abnormal enlargement of nongoblet epithelial cells, and increases in cellular layers, keratin deposition and stratification, and keratinization.

Apart from topical vitamin A therapy, all other nonsurgical therapies for dry eye (i.e., the frequent application of artificial tears, lubricants, or slow-releasing polymers, and the therapeutic use of soft contact lenses) are not directed toward reversing the underlying process but rather toward alleviating the symptoms.

The hypothesis that a localized vitamin A deficiency in the lining of the outer eye may be responsible for dry eye, based on vitamin A's vital role in epithelial tissue, seems obvious. Clinical studies featuring commercial vitamin A eyedrops (Viva-Drops, Vision Pharmaceuticals, vivadrops.com, Mitchell, South Dakota) have yielded impressive clinical results in the treatment of dry eyes.[30,31]

DOSAGE

Dosage ranges for vitamin A reflect the intent of use. For general health purposes, a dosage of 5000 IU for men and 2500 IU for women appears reasonable. During an acute viral infection, a single oral dosage of 50,000 IU for 1 or 2 days appears to be safe even in infants (note, that women who might be pregnant must not use vitamin A supplements; beta-carotene, however, is fine). For the treatment of acne and hyperkeratotic skin disorders, high-dose therapy may be useful but should be monitored closely by a physician.

TOXICITY

Vitamin A supplementation must be avoided during pregnancy because large doses have been shown to be teratogenic. Unfortunately, safe dosages for pregnant women have not yet been determined, although combined human and animal data suggest that 30,000 IU/day should be considered safe.[32] Nonetheless, women who may become pregnant should keep their supplemental vitamin A levels below 5000 IU or, better yet, switch to carotenes.[33] (Emerging research is showing that 20% to 30% of the population is unable to convert beta-carotene to vitamin A. The only way to know is by measuring blood levels.) Excess dietary intake of vitamin A has been associated with birth defects in humans in fewer than 20 reported cases over the past 30 years.[34] Acute toxicity with vitamin A, which is most often seen in children as a result of the accidental ingestion of a single large dose of vitamin A (100,000 to 300,000 IU), manifests as follows:

- Raised intracranial pressure with vomiting
- Headache
- Joint pain
- Stupor
- Occasional papilledema

Symptoms rapidly subside upon withdrawal of the vitamin, and complete recovery always ensues.

Vitamin A toxicity may occur in adults who have taken more than 50,000 IU/day for several years. Smaller daily doses may produce toxicity symptoms if there are defects in the storage and transport of vitamin A, as occurs in cirrhosis of the liver, hepatitis, or protein-calorie malnutrition as well as in children and adolescents.[35,36] Signs of vitamin A toxicity generally include the following:

- Dry, fissured skin
- Brittle nails
- Alopecia
- Gingivitis
- Cheilosis
- Anorexia
- Irritability
- Fatigue
- Nausea

Serum levels of vitamin A between 250 and 6600 IU/dL are typical of toxicity. Prolonged, severe hypervitaminosis A leads to bone fragility and thickening of the long bones.

Toxicity is typically encountered during high-dose vitamin A therapy for various skin conditions. Although dosages smaller than 300,000 IU/day for a few months rarely cause toxicity symptoms, early recognition is still very important. Cheilitis (chapped lips) and xerosis (dry skin) generally appear in the majority of patients, particularly in dry weather. The first significant toxicity symptom is usually headache, followed by fatigue, emotional lability, and muscle/joint pain. Laboratory tests are of little value in monitoring toxicity because serum vitamin A levels correlate poorly with toxicity, and values of serum glutamic-oxaloacetic transaminase and serum glutamate pyruvate transaminase are elevated only in symptomatic patients.[25]

DRUG INTERACTIONS

Vitamin E and zinc are particularly important to the proper function of vitamin A. A deficiency of zinc, vitamin C, protein, or thyroid hormone will impair the conversion of provitamin A carotenes to vitamin A.

Excessive vitamin A intake can inhibit vitamin D–mediated calcium absorption, accelerate bone loss, and inhibit the formation

of new bone.[37,38] All of these actions may raise the risk of osteoporosis and hip fracture. In one prospective study, a vitamin A intake greater than 5000 IU/day, compared with a lower intake, was associated with a reduction in bone mineral density that approximately doubled the risk of hip fracture.[39]

Studies have demonstrated a link between exposure to toxic chemicals and vitamin A nutrition. Administration of compounds such as polybrominated biphenyls, dioxin, and other toxic chemicals to rats leads to a decrease in the hepatic content of vitamin A. Concurrent administration of vitamin A and the xenobiotics partially prevents the symptoms of toxicity. Exposure to these compounds results in an increased vitamin A requirement because of the enhanced degradation of vitamin A in the liver.[40,41]

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CHAPTER 136

Vitamin K

Cristiana Paul, MS Nutrition

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INTRODUCTION

When vitamin K_1 was discovered, it was believed to have only the one role of supporting coagulation, hence the name K, from the German word *Koagulation*. Research from the last decade or more has uncovered numerous functions for vitamin K beyond that of clotting. We have also become aware of different forms of vitamin K, because the vitamin K_2 family emerges with distinct properties from vitamin K_1. It seems that nature has evolved a very complex system of vitamin K forms that work together to support various physiologic functions for successful survival and reproduction even when food is scarce.

Most importantly, current knowledge of the newly discovered functions of vitamin K is causing a paradigm shift in defining vitamin K deficiency and optimal vitamin K intake for supporting overall health. This expanded knowledge of vitamin K's roles in human physiology opens exciting opportunities to intervene with the appropriate vitamin K doses for the management and potentially reversal of many common health conditions.

FORMS, SOURCES, ABSORPTION, AND METABOLISM

Forms: K_1, K_2, and K_3

The currently known forms of vitamin K can be grouped in three categories: vitamin K_1 (one type), vitamin K_2 (14 types), and vitamin K_3 (one type) (Figure 136-1). Vitamins K_1 and K_2 are fat-soluble, whereas vitamin K_3 is water-soluble.[1] Technically, only vitamin K_1 is recognized as a true vitamin, essential for human and animal well-being. Vitamins K_2 and K_3 can be derived as metabolites of vitamin K_1 in various tissues or the gastrointestinal tract in animals or humans. However, there may be many clinical situations that can benefit from supplementation with vitamin K_2 (from diet and/or supplements) or from the intravenous administration of vitamin K_3. Oral vitamin K_3 is used only in animal nutrition; for humans, it is currently allowed only for research purposes.[2]

The structures of vitamins K_1, K_2, and K_3 are similar in regard to their core molecule, called menadione (or 2-methyl-1,4-naphtoquinone). Vitamin K_3 is simply composed of the core molecule menadione (see Figure 136-1, *C*), whereas vitamins K_1 and K_2 contain the core molecule menadione plus specific side chains that distinguish them as follows[3]:

- In addition to the menadione core, vitamin K_1 contains a side chain of one unsaturated isopentenyl unit and three saturated isopentyl units (see Figure 136-1, *A*).
- In addition to the menadione core, each member of the vitamin K_2 family contains a side chain of specific length, anywhere from 1 to 14 repeats of unsaturated isopentenyl units (see Figure 136-1, *B*). The length of the side chain determines the name of each type of vitamin K_2 as follows: MK-1(with 1 unit), MK-2 (with 2 units), and so on, through MK-14 (with 14 units). In this review, a K_2 designation is added in front of their names, as follows: K_2 (MK-1), K_2 (MK-2 through MK-14) in order to avoid confusion with vitamins K_1 and K_3.

Vitamin K_1 is hydrophobic but not very lipophilic, whereas all vitamin K_2 forms become increasingly more lipophilic as the length of their side chains increases, which is relevant for their different rates of absorption and metabolism.

On average, it is estimated that 80% to 90% of dietary vitamin K intake is typically derived from vitamin K_1, with the rest coming from vitamin K_2.[4]

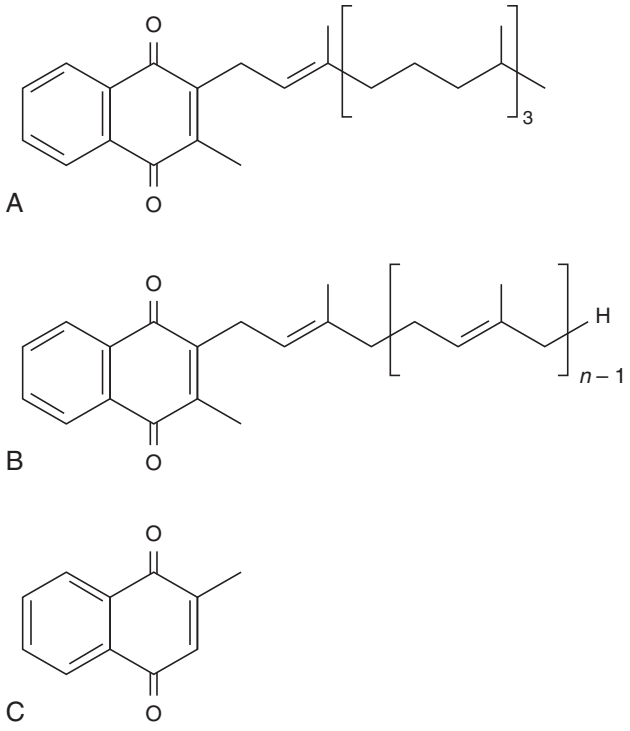


FIGURE 136-1 A, Vitamin K_1, also called phylloquinone or phytomenadione. **B,** Vitamin K_2 family, K_2 (MKn) n = 1 to 14, also called menaquinones. Menaquinones have side chains composed of a varying number of isoprenoid residues. **C,** Vitamin K_3, menadione.

Main Aspects of Vitamin K_1 (Phylloquinone or Phytomenadione)

Vitamin K_1, also called phylloquinone or phytomenadione, is synthesized only by plants or algae, where it is bound in the thykaloid membranes of chloroplasts and participates in the electron transport chain of photosynthesis. Vitamin K_1 occurs in significant amounts (50 to 800 mcg/100 g food) in certain vegetables, vegetable oils, seeds, algae, and in small amounts (<50 mcg/100 mcg food) in the rest of the vegetable and animal foods, as listed in Figure 136-2. See Table 136-1 for the typical yield of vitamin K_1 in common measures of select vegetables, which are the most significant sources of vitamin K_1 of all vegetable foods.

Vitamin K_1 is also available for oral or intramuscular injection to correct clotting deficiency in newborns or to compensate for anticoagulant overdose in adults. Studies are conflicting in regard to the concern that vitamin K_1 injection may increase the risk of various cancers, including leukemia in infants. Recent research seems to have established that the risk was related to the route of administration, specifically to injection and not via the oral route. Also, the safest and most reliable way to increase vitamin K_1 in the unborn fetus and reduce the risk of bleeding after birth seems to be by increasing the mother's vitamin K status, as some studies suggest.[5]

Absorption

Absorption of vitamin K_1 varies considerably depending on its source. When it is delivered in a vegetable, its bioavailability is low (3% to 10%) because it is trapped in the chloroplast.[6] Cooking and/or mechanical processing (blending, juicing) of the vegetables or pressing the oil out of the vegetable seeds (such as sunflower seeds) increases the vitamin's bioavailability and absorption up to as much as 50% as compared with the raw vegetable.[7]

By adding dietary fat to the vitamin K_1-containing food, absorption of the vitamin can be doubled; it may then reach 10% to 15%.[8] Following is a summary of estimated vitamin K_1 absorption values, obtained by comparing a number of studies[9–17]:

- Absorption from raw vegetables (such as spinach or broccoli): 3% to 5%; some suggest as high as 10%.
- Absorption from cooked vegetables without fat: some have found no difference compared with raw vegetables.
- Absorption from cooked vegetables with fat: approximately 2.5 times the absorption from raw vegetables.
- Absorption from vitamin K_1 dissolved in vegetable oil: approximately 50% to 80%.
- Absorption from a synthetic vitamin K_1 supplement: approximately 10% (if mixed in a capsule with 85% cellulose) and approximately 80% (if mixed in an emulsion containing lecithin and a bile acid).

Exposure to ultraviolet (UV) light inactivates vitamin K. When oils containing vitamin K_1 are hydrogenated (during industrial processing, cooking, frying, or baking), a big percentage (40% to 50%) of the vitamin K_1 content is also hydrogenated. Studies have shown that hydrogenated vitamin K_1 has very little biological activity.[18] It is important to note that a large section of the population derives a majority of its vitamin K_1 from vegetable oils as opposed to vegetables, so the effect of vitamin K inactivation by hydrogenation may have an important impact on common deficiencies of vitamin K, which may be higher than estimated from just vitamin K_1 intake surveys.

Transport, Metabolism, and Distribution in Human Tissues

Once ingested, vitamin K_1 can be metabolized through various routes in the body (see Figure 136-2).

Vitamin K_1 is transported initially in the chylomicrons through lymph and blood to the liver and other tissues. Once taken up by various tissues, vitamin K_1 may be stored and utilized unchanged, while part of it may be converted to K_2 (MK-4). For unclear reasons, the steady-state ratio of K_1/K_2 (MK-4) stored in each tissue seems to be specific to each tissue. See Figure 136-2 for a list of these ratios in various tissues and organs.[19]

One study estimates that 5% to 25% of the absorbed vitamin K_1, the same as various K_2 forms, is converted to K_3 in the intestinal cells.[20] Various cells in the body may take up vitamin K_3 and convert it to vitamin K_2 (MK-4). A portion of vitamin K_3 is converted to K_2 (MK-4) in each tissue.[21]

Part of the ingested vitamin K_1 is taken up by certain types of gastrointestinal bacteria *(Bacteroides, Escherichia coli,* and *Propionibacterium)* and converted into vitamin K_3 or into vitamin K_2 (MK-n, n = 1 to 14), the most predominant forms being the longer-chains MK-7, 8, 9, 10, and 11.

As a result of uptake in all the metabolic pathways described previously, vitamin K_1 intake can lead to an increase of various forms of vitamin K in the body, as follows: vitamin K_1 in serum and tissues, vitamin K_3 especially in the serum, vitamin K_2 (MK-4) in the tissues, and long-chain K_2 especially in the liver.

One study looked at the vitamin K stored in the rat brain in response to supplementation with either vitamin K_1 or vitamin K_2 (MK-4).[20] Contrary to what was expected, the results showed that supplementation with vitamin K_1 was able to increase the brain content of K_2 (MK-4) more than direct supplementation with vitamin K_2 (MK-4).

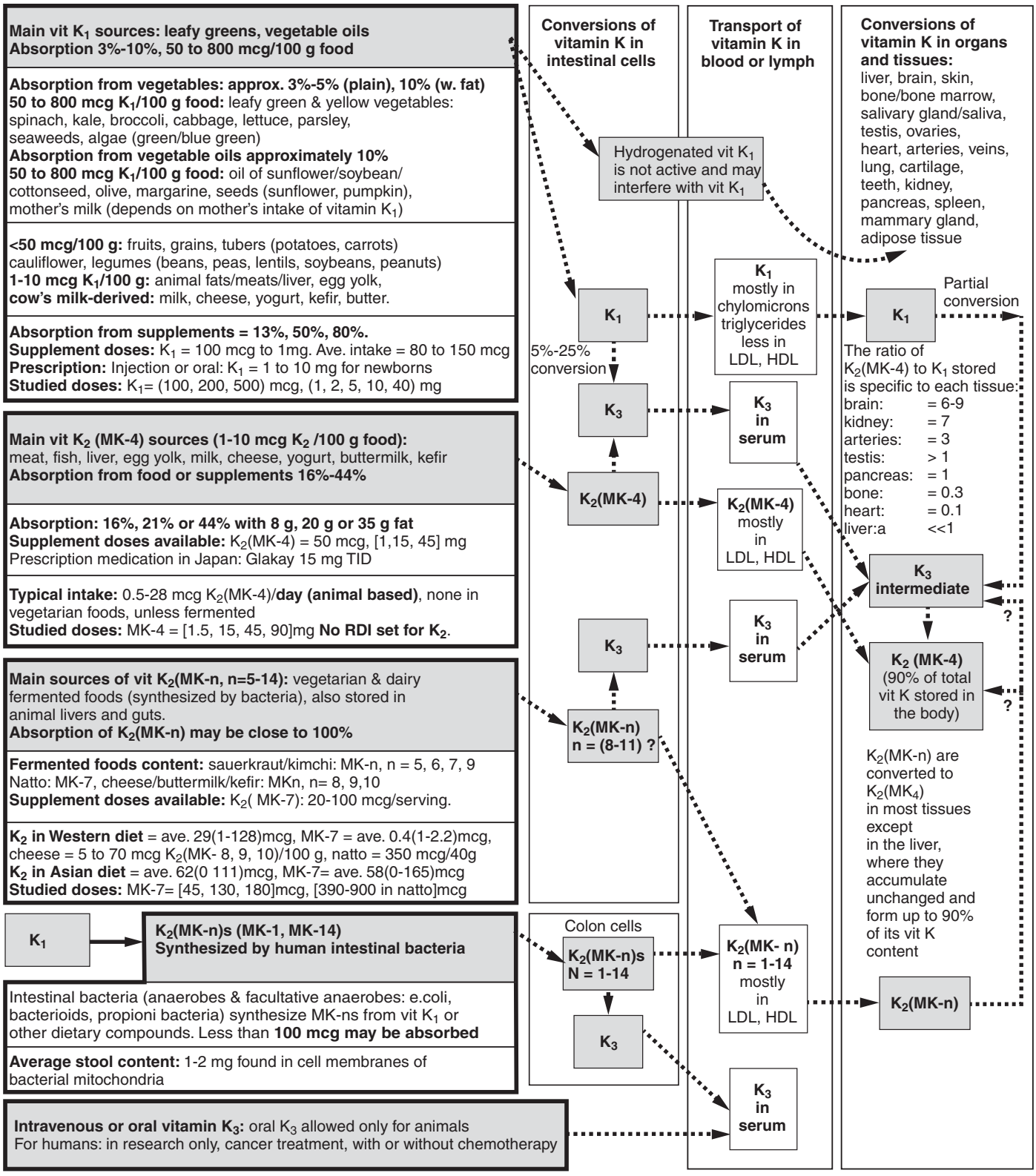


FIGURE 136-2 Vitamin K forms, sources, absorption, conversions, transport, and distribution in the blood and organs.

Main Aspects of Vitamin K_2

A Family of Menaquinones: K_2 (MK-1) through K_2 (MK-14)

Significant Menaquinones Available from Foods and Supplements: K_2 (MK-4) and K_2 (MK-7). Vitamin K_2 is not considered a vitamin in the true sense because theoretically it is not an essential nutrient; it is debatable whether it is needed in addition to vitamin K_1 for maintaining normal health. This is because animal and human tissues, as well as their intestinal bacteria, are typically able to synthesize vitamin K_2 from the vitamin K_1 ingested. It is not clear either whether vitamin K_2 can fulfill all the functions that vitamin K_1 exerts, since there is no proof that it converts into vitamin K_1.

TABLE 136-1 **Foods with High Vitamin K_1 Content**

FOOD	WEIGHT (G)	MEASURE	AMOUNT OF K_1 (MCG)
Kale, cooked and drained	130	1 cup	1062
Collards, cooked and drained	170	1 cup	1059
Spinach, cooked and drained	180	1 cup	889
Beets, cooked and drained	144	1 cup	697
Broccoli, cooked drained	156	1 cup	220
Brussels, cooked and drained	156	1 cup	219
Onions, raw	100	1 cup	207
Parsley, raw	10	10 sprigs	164
Cabbage, cooked drained	150	1 cup	163
Spinach, raw	30	1 cup	145
Asparagus, cooked and drained	180	1 cup	144
Lettuce, iceberg	129	1 head	129
Broccoli, raw	88	1 cup	89
Cabbage, raw	70	2 cups	53
Cucumber, raw	301	1 large	49

Data from USDA National Nutrient Database for Standard Reference, Release 17. Content of Selected Foods per Common Vitamin K (phylloquinone) Measure, sorted by nutrient content, http://www.nal.usda.gov/fnic/foodcomp/Data/SR17/wtrank/sr17w430.pdf. Accessed 2/13/12.

Vitamin K_2 can be viewed as a metabolite of vitamin K_1 inside human/animal tissues, but some researchers are calling it "the active form of vitamin K_1." Consequently, vitamin K_2 may be conditionally essential for certain individuals owing to their genotypes, aging, and metabolic or disease conditions where the conversion of vitamin K_1 to K_2 is inadequate.

Like the essential role of vitamin K_1 in the energy production (photosynthesis) of plants or algae, vitamin K_2 is an obligatory component of the electron transfer pathway in the mitochondria of certain bacteria, analogous to the role of the quinone coenzyme Q10 in animal mitochondria.[22]

Vitamin K_1 Conversion to Vitamin K_2 (MK-4): Tissue Distribution of Vitamin K_1 versus Vitamin K_2 (MK-n), n = 1 to 14. Vitamin K_2 (MK-4) is the most prevalent form of vitamin K in human and animal tissues, at about 90% of total vitamin K stored, with the remainder as mostly vitamin K_1 and small amounts of long chain K_2 (MK-n)s (n = 7 to 11).

The distribution of K_1 versus K_2 in animal tissues is quite variable. For unknown reasons, the steady-state ratio of K_1/K_2 (MK-4) stored in each tissue seems to be specific to that tissue.

Many studies have shown that various long-chain K_2 (MK-n)s are converted to K_2 (MK-4) in all tissues with the exception of the liver. For example, dietary supplementation with K_2 (MK-7) from natto was shown to result in a significant increase of K_2 (MK-4) in bone, whereas no MK-7 was detected in the bone.[23]

A substantial amount of long-chain K_2 [MK-n]s, n = 7 to 11 is stored in the liver unchanged, and this organ has a distinct distribution of vitamin K compared with all other tissues: that is, 90% long-chain menaquinones (K_2[MK-n]s, n=8 to 11) and 10% vitamin K_1. This may be because the liver is the first organ to have access to the vitamin K_2 synthesized by the intestinal bacteria, which is absorbed through the lower ileum. This preferential sequestering of MK-ns in the liver is hypothesized to be an evolutionary adaptation for securing a low-turnover vitamin K pool to support clotting needs and protect against the dietary variability of vitamin K_1 or K_2 (MK-4).

Dietary Sources of Various Forms of Vitamin K_2

Dietary sources of various forms of vitamin K_2 (various menaquinones) include animal meats and dairy as well as fermented foods of animal or vegetable origin, as follows:

Animal Foods:. Meats (2 to 3 mcg/100 g), egg yolk (10 mcg/one egg), and milk. These sources preferentially provide the K_2 (MK-4) form along with similar amounts of vitamin K_1. See Table 136-2 for a listing of the vitamin K_2 content of various foods. Table 136-2 lists the vitamin K_2 content of select foods from three studies in the United States, Holland, and Japan.[24]

The content of vitamins K_1 and K_2 in human milk depends on the mother's intake of these vitamins.[25] The same may be true for cow's milk and other animal milks. Similarly, the vitamin K content of animal tissues may be lower for animals fed mostly corn versus those that are exclusively grass-fed, although no studies have measured this. The vitamin K_2 content of animal-derived food may be higher when they are supplemented with vitamin K_3 (a common practice). Since vitamin K_3 supplementation has proved detrimental for humans, it may be of questionable safety for animals. Also, continuous antibiotic treatment of the animals (to enhance growth) may impair their intestinal bacterial production of vitamin K_2.

Fermented Foods (Animal or Vegetable). Various forms of vitamin K_2 are produced by certain bacteria, ranging from K_2 (MK-4) to K_2 (MK-12) (see Table 136-2):

1. Animal origin: cheese and other fermented milk products (yogurt, kefir, buttermilk, sour cream) provide vitamin K_2 forms mostly as K_2 (MK-8) and K_2 (MK-9).
2. Vegetable origin: natto, sauerkraut, kimchi. For example, the bacteria specific to natto (a fermented mix of soybeans and rice) will provide vitamin K_2 mostly in the K_2 (MK-7) form; bacteria in foods like sauerkraut (pickled cabbage) provide vitamin K_2 in a wide variety of forms, such as K_2 (MK-5) through K_2 (MK-9).

Vitamin K_2 Produced by Human Intestinal Bacteria

Certain bacteria residing in the human intestinal tract convert the ingested vitamin K_1 or other dietary components (such as alpha-ketoglutarate) to various forms of vitamin K_2 (MK-n). The types of bacteria that have this property are mostly gram-negative, such as *Bacteroides fragilis, Propionibacterium,* and particular strains of *E. coli* (normal gastrointestinal resident strain, not necessarily pathogenic). Certain strains of *Lactobacillus* were also found to produce vitamin K_2, although these are not the commonly known strains of *Lactobacillus* or probiotics used in supplements or found in yogurt. Vitamin K produced by the gut bacteria may represent a significant portion of the total vitamin K_2 acquired by some people if their vitamin K status is marginal.[26]

Vitamin K_2 Absorption and Transport

Very few studies have evaluated the absorption of various forms of vitamin K_2.[27] There is some consensus among researchers that the longer the vitamin K_2 side chain is, the more lipophilic it is, with K_2 (MK-4) being less lipophilic than the longer-chain K_2.

One study found that absorption of K_2 (MK-4) was 16%, 21%, 44%, and 44% with meals containing 8 g, 20 g, 35 g, and 45 g fat, respectively.

One study administered K_2 (MK-7) from a natto extract and claimed to have obtained "almost complete" absorption.

TABLE 136-2 **Significant Food Sources of Vitamin K_2**

	Vitamin K Forms (mcg/100 g or mcg/100 mL)						
FOOD	**K_1**	**K_2 (MK-4)**	**K_2 (MK-5)**	**K_2 (MK-6)**	**K_2 (MK-7)**	**K_2 (MK-8)**	**K_2 (MK-9)**
Meats							
Beef	0.6	1.1	–	–	–	–	–
Beef chuck	0.6	15.0	–	–	–	–	–
Beef liver	3.1	0.4	–	–	–	–	–
Chicken breast	–	8.9	–	–	–	–	–
Chicken leg	–	8.5	–	–	–	–	–
Chicken liver	4.0	14.0	–	–	–	–	–
Chicken thigh	–	27.0	–	–	–	–	–
Deer back	2.0	0.7	–	–	–	–	–
Duck breast	1.9	3.6	–	–	–	–	–
Goose leg	4.1	31.0	–	–	–	–	–
Goose liver paté	10.9	369.0	–	–	–	–	–
Ground beef (medium fat)	1.3	8.1	–	–	–	–	–
Hare leg	4.8	0.1	–	–	–	–	–
Pork liver	0.2	0.3	–	–	–	–	–
Pork steak	0.3	2.1	–	–	0.5	1.1	–
Pork thigh	–	6.0	–	–	–	–	–
Salami	2.3	9.0	–	–	–	–	–
Fish							
Plaice	–	0.2	–	0.3	0.1	1.6	–
Salmon	0.1	0.5	–	–	–	–	–
Eel	0.3	1.7	–	0.1	0.4	–	–
Vegetables							
Sauerkraut	25.0	0.4	0.8	1.5	0.2	0.8	1.1
Boiled cabbage	180.0	0.4	–	–	–	–	–
Natto	34.0	–	7.5	13.8	998.0	84.0	–
Dairy products							
Whole milk	0.5	0.8	0.1	–	–	–	–
Buttermilk	–	0.2	0.1	0.1	0.1	0.6	1.4
Whole yogurt	0.4	0.6	0.1	–	–	0.2	–
Skimmed yogurt	–	–	–	–	–	0.1	–
Whipping cream	5.1	5.4	–	–	–		–
Hard cheese	10.4	4.7	1.5	0.8	1.3	16.9	51.1
Soft cheese	2.6	3.7	0.3	0.5	1.0	11.4	39.6
Curd cheese	0.3	0.4	0.1	0.2	0.3	5.1	18.7
Egg yolk	2.1	31.4	–	0.7	–	–	–
Egg white	–	0.9	–	–	–	–	–
Fats and oils							
Butter	2.0	21.0	–	–	–	–	–
Mayonnaise (with egg)	189.0	38.0	–	–	–	–	–

Data from Kamao M, Suhara Y, Tsugawa N, et al. Vitamin K content of foods and dietary vitamin K intake in Japanese young women. J Nutr Sci Vitaminol (Tokyo). 2007;53(6):464-470; Elder SJ, Haytowitz DB, Howe J, Peterson JW, Booth SL. Vitamin K contents of meat, dairy, and fast food in the U.S. diet. J Agric Food Chem 2006(25;54(2):463-467; Schurgers LJ, Vermeer C. Determination of phylloquinone and menaquinones in food. Effect of food matrix on circulating vitamin K concentrations. Haemostasis 2000;30(6):298-307.

Vitamins K_2 (MK-4) and K_2 (MK-7) are believed to be partially cleaved (around 5% to 25%) in the intestinal wall to form vitamin K_3, which was found in the urine 2 to 3 hours after ingestion of these vitamers.

Vitamin K_2 seems to be preferentially transported by the plasma lipoproteins—low-density lipoprotein (LDL) and high-density lipoprotein (HDL)—and have very different plasma half-lives; for example, the half-life of K_2 (MK-4) is around 1 to 2 hours, whereas that of K_2 (MK-7) is around 2 days. Some hypothesize that K_2 (MK-4) is taken up by the tissues a lot faster because it is ready to be stored and utilized as such, whereas K_2 (MK-7), for example, tends to be converted slowly to K_2 (MK-4), before it is stored in

TABLE 136-3 **Average Intake of Various Forms of Vitamin K in a Dutch Population (all values in μg/day)**

			Vitamin K_2 Forms					
	K_1	TOTAL K_2	MK-9	MK-4	MK-8	MK-7	MK-5	MK-6
Mean	211.7	29.1	14.7	7.1	6.0	0.4	0.3	0.3
Standard deviation	±100.3	±12.8	±8.1	±2.1	±3.4	±0.3	±0.2	±0.2
Lower end	9.1	0.9	0	0.5	0	0	0	0
Upper end	991.1	128	81.9	28.2	32.8	2.2	2.1	1.5

Data from Gast GC, de Roos NM, Sluijs I, et al. A high menaquinone intake reduces the incidence of coronary heart disease. Nutr Metab Cardiovasc Dis 2009;19(7):504-510. Epub 2009 Jan 28.

various tissues. K_2 (MK-7) can serve as a "time-release" source of K_2 (MK-4) (Table 136-2).

Average Vitamin K_2 Intake and Comparative Absorption between Vitamin K_2 and Vitamin K_1

Table 136-3 shows the average intakes of various forms of vitamin K from an epidemiologic study of a Dutch population. The particularly high contribution from MK-9, MK-4, and MK-8 is most likely due to the high cheese consumption in Holland.

Even though the actual intake of vitamin K_1 is much higher than that of vitamin K_2 (seven times higher).The actual absorbed amount of vitamins K_1 and of total vitamins K_2 (MK-ns) may be very similar.

Vitamin K_2 Supplement Forms and Doses Available

Vitamin K_2 is currently available as a supplement in only two forms:

1. Vitamin K_2 (MK-4) (menaquinone-4 or menatrenone), which is provided in a synthetic version. It is typically available in doses in the range of 40 to 50 mcg, 1 mg, 15 mg, or 45 mg in stand-alone vitamin K formulas, vitamin D combination with vitamin K formulas, or bone-specific formulas. It is also available as a prescription medication in Japan, called Glakay, in 15-mg doses (with the indication of three times daily).[28]
2. Vitamin K_2 (menaquinone-7, MK-7) is available either in a synthetic version or as a concentrated extract from the Japanese fermented food natto. It can, of course, be ingested with the natto food itself, which provides an average of 350 mcg/50 g in each serving. K_2 (MK-7) is also found in much smaller amounts in foods such as fermented cabbage (sauerkraut and kimchi) or cheeses and fermented milks; see Table 136-3. The average vitamin K_2 intake found in young Japanese women was 61.7 mcg. From this, K_2 (MK-7) typically represents 57.4 mcg owing to the common consumption of natto.

Main Aspects of Vitamin K_3 (Menadione): Occurrence, Properties, and Special Considerations for Animal and Human Consumption

Vitamin K_3 (menadione) has not been observed to occur in natural foods in any significant amount. It is believed to be formed inside intestinal cells and possibly other tissues and organs of humans and animals and can be found in the plasma and urine 2 to 3 hours following ingestion of either vitamin K_1, K_2 (MK-4), or K_2 (MK-7). Certain intestinal bacteria can convert the ingested vitamin K_1 to K_3 or de novo synthesize vitamin K_3 from compounds such as alpha-keto-glutarate.

Vitamin K_3 is not a vitamin in the true sense; initially it was synthesized to be used as an oral provitamin K compound, most likely because of its conversion to vitamin K_2 (MK-4) in human and animal tissues.

Vitamin K_3 may have been chosen as a supplement because it is a much simpler molecule to synthesize than vitamins K_1 or K_2; thus it was less expensive to produce. However, oral consumption of vitamin K_3 was banned in humans when various side effects were noticed, such as increased red blood cell lysis, excessive oxidative stress, and nonspecific binding of thiols from large and small molecules in the blood.

However, the cytotoxic effects of vitamin K_3 were recognized as useful in support of cancer treatment, alone or in addition to chemotherapy, and K_3 has been used in the oral and intravenous forms (discussed later) in research studies involving humans. Vitamin K_3 is not currently available as a drug or supplement for human use.

It is important to keep in mind that serum vitamin K_3 can rise significantly as a result of ingesting supraphysiologic doses of vitamins K_1 or K_2 (above 1 mg), especially if given in one bolus. (This concern is discussed under "Potential Side Effects of High Doses of Vitamins K_1, K_2, and K_3").

Vitamin K_3 and Animal Nutrition

Certain animal feeding practices include synthetic vitamin K_3 as a supplement, probably because animals fed corn instead of grass receive little natural vitamin K_1. Vitamin K_3 is chosen because it costs significantly less than it would to add vitamin K_1 or incorporate foods naturally high in vitamin K_1, such as grass. No studies have reported the content of vitamin K_3 in animal foods from animals supplemented with vitamin K_3, and very few have reported the tissue content of vitamin K_2 (MK-4) in these animals. There is at least a theoretical concern that these foods may contain abnormally high levels of vitamin K_3 owing to incomplete conversion to the normally occurring K_2 (MK-4). It is not clear whether organic meats come from animals fed vitamin K_3, since they get plenty of vitamin K_1 from the grass.

PHYSIOLOGIC ROLES OF VITAMIN K: EFFECTS OF NORMAL TO SUPRAPHYSIOLOGIC DOSES

Mechanisms of Action of Vitamins K_1 and K_2

Aside from blood clotting support, new research is revealing numerous roles for vitamin K in many tissues and organs through a variety of mechanisms.

Vitamin K's actions in human physiology are very complex:

1. Posttranslational modification (through carboxylation) of a number of functional proteins, called vitamin K-dependent proteins (VDKs)

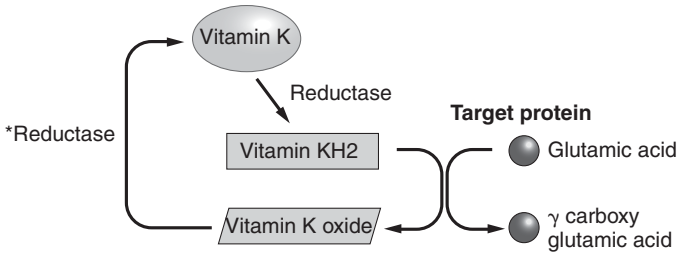


FIGURE 136-3 Vitamin K recycling and carboxylation reactions. (From Bowen RA. Vitamin K. http://www.vivo.colostate.edu/hbooks/pathphys/misc_topics/vitamink.html. Accessed 5/29/12.)

2. Modulation of inflammation through downregulation of cytokine IL-6 and prostaglandin E2 (PGE2) (by inhibiting COX-2)
3. Downregulation of cell signaling proteins (produced downstream of mevalonate and 3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA]), which affect cell differentiation and apoptosis
4. Neurologic effects through modulation of galactocerebroside sulfotransferase enzyme (GST)
5. Genetic expression modulation
6. Anticancer effects

Vitamin K activates a variety of VKDs throughout the body by carboxylating a specific number of the glutamatic acid residues they contain, which become, as a result, gamma-carboxyglutamate residues, also called Gla. One molecule of vitamin K_1 or K_2 can be recycled many times, so it is used multiple times to produce Gla residues before it is metabolized for elimination (Figure 136-3).

Once carboxylated, these residues can bind calcium or interact with cell membranes more efficiently. The more glutamate residues are carboxylated on a VKD protein, the better its functionality. Ultimately, the more vitamin K is available in the body, the higher the percentage of fully carboxylated VKDs will be.

Until now, the AI (adequate intake) for vitamin K has been defined as the amount needed to completely carboxylate prothrombin. With the discovery of new roles for various VKDs throughout the body, many researchers are now proposing redefining the AI at a level where all VKDs in the body are 100% carboxylated. A review by McCann and Ames points out that vitamin K affinity varies greatly for each type of VKD, which may influence the order in which VKDs are carboxylated. Most likely, this is done in an order of physiologic priority.[29] For example, clotting may have the highest priority in utilizing most of the vitamin K ingested when intake is around or below 100 mcg/day. In this situation, most of the other VKDs in the body will tend to be inadequately carboxylated and so have poor functionality. Unfortunately, there are no tests to verify the carboxylation of all the known VKDs except for the three that will be discussed (PIVKA II, osteocalcin, and MGP). Important cofactors affecting the rate of carboxylation of VKDs are manganese and vitamin B6, specifically P5P (pyridoxal-5-phosphate). Deficiency of these cofactors may downregulate carboxylation, whereas supplementation with P5P was shown in vitro to upregulate it twofold.

Osteocalcin is a protein produced by osteoblasts (bone-building cells) that transports calcium inside the bone for fixating it in the hydroxyappatite structure, thus supporting bone mineralization. Vitamin K has been shown to stimulate osteoblasts to increase their production of osteocalcin and collagen type I, both important components of the bone structure. Increased levels of osteocalcin are able to better support bone remodeling and thus improve bone architecture, which translates into better bone elasticity and reduced risk of fracture.[30–32]

Osteodentin (tooth dentin) is responsible for tooth mineralization, similar to osteocalcin's role in the bone.[33] Note that the salivary gland concentrates a significant amount of vitamin K, which may have a role in supporting oral health. Vitamin K is known to affect certain bacteria by participating as a cofactor in their energy production (similar to coenzyme Q10 in animal mitochondria). If it is in fact proved that salivary glands secrete vitamin K, this would affect oral bacteria; one researcher has stated that excess vitamin K may exacerbate periodontal disease.[34]

Nephrocalcin is found in kidney tissue and is believed to support calcium ion solubilization and inhibit crystal nucleation, thus reducing the risk of kidney stones.

Matrix Gla protein, or MGP, is found in many soft tissues, where it has at least one identified role, that of rejecting calcium deposition. Specifically, it is found in the skin and in the walls of arteries and veins, where it prevents the calcification of elastin fibers, thus reducing the risk of elasticity loss in these tissues. It is also found incorporated with underlying ground substance of the skin and cartilage (associated with chondrocytes), where it seems to play a role in the synthesis of glycosaminoglycans.[35] MGPs have also been identified in testes and sperm; their role there is not clear, but vitamin K deficiency has been shown to reduce testosterone production and sperm motility. One study that looked at primary prostate cancer cells versus metastatic cells found that "loss of MGP expression may be associated with tumor progression and metastasis."[36]

Note here the important roles of vitamins D and A in some of these VKDs:

- The active form of vitamin D (1,25[OH]D3) stimulates the synthesis of osteocalcin and MGP.[37]
- Vitamin A (retinoic acid) stimulates the synthesis of osteocalcin but inhibits that of MGP.[38]

Consequently vitamins K, D, and A work in concert and have interdependent actions. Thus, in order for vitamin K to perform its functions, the status of vitamins D and A must be optimized, so that VKDs are expressed adequately. It has also been established that the genetic effects of 1,25(OH)D3 are mediated by vitamin A through its nuclear receptor, which exert a permissive activation on the vitamin D nuclear receptor.[39]

GAS-6 protein (growth arrest-specific gene 6) is believed to play a role in platelet aggregation, cell growth, and apoptosis and has been shown to support the survival of cells in tissues such as arterial muscle, eye lens epithelium, brain, and possibly others. It is also involved in supporting adequate innate immunity (natural killer [NK] cells) and reducing the risk or severity of autoimmune cellular events.[40]

Modulation of Inflammation by Downregulation of Inflammatory Cytokines

Vitamin K may reduce inflammation by downregulating of IL-6 and PGE2 as follows:

- Metabolites of vitamin K, the 5- and 7-carbon carboxylic acid catabolites of vitamins K_1 or K_2 (MK-4 or MK-7), inhibit the release of IL-6. This was shown specifically for osteoblasts.[41]
- Vitamin K_2 (MK-4) has been shown to reduce the production of PGE2 by direct inhibition of the COX-2 enzyme.[42]

These actions of vitamin K may reduce the activity of any inflammatory/autoimmune diseases that are exacerbated by PGE2 and IL-6.[43] In osteoporosis, IL-6 and PGE2 have been shown to enhance bone resorption through activation of the RANKL

receptor, which in turn upregulates osteoclast differentiation.[44] This mechanism is considered essential to the effects observed from treatment with high doses of K_2 (MK-4) in reducing and reversing bone loss. Vitamin K_2 has also been shown to reduce the activity of rheumatoid arthritis by inhibiting the proliferation of the rheumatoid synovial cells.[45] A correlation has been found between vitamin K status (plasma vitamin K_1) and osteoarthritic disease activity in the hands and knees.[46] In the Framingham study, plasma vitamin K_1 was shown to inversely correlate with C-reactive protein (CRP), a marker of inflammation.

An elevated PGE2 should also be corrected by addressing the arachidonic acid/eicosapentaenoic acid (AA/EPA) ratio. This, in effect, modulates the substrates of the COX2 enzyme and would have an additional impact on PGE2 production when added to the effect of vitamin K_2 (MK-4) of inhibiting COX2. One study states the effect of the AA/EPA ratio on another inflammatory intermediate as follows: "nuclear factor kB is activated by arachidonic acid but not by eicosapentaenoic acid."[47]

Downregulation of Cell-Signaling Proteins (Produced Downstream of Mevalonate and HMG-CoA) Affecting Cell Differentiation and Apoptosis

Vitamin K_2 (MK-4) is believed to have an inhibitory effect in pathways downstream of mevalonate, the same pathways where statins and bisphophonates are believed to inhibit key enzymes (HMG-CoA reductase and protein farnesyl transferase, respectively). However, the actions of K_2 (MK-4) are not the same as those of pharmaceutical drugs, which have a direct enzyme inhibitory action. Instead, K_2 (MK-4) seems to work through a feedback inhibition effect on the mevalonate pathway by "mimicking" one of its downstream metabolites, the molecule geranylgeranyl pyrophosphate.[48,49] This mimicry occurs by means of the side chain of vitamin K_2 (MK-4), which is the molecule geranylgeranyl. This may be why K_2 (MK-4) has distinct effects compared with those of other forms of vitamins K_2 or K_1.

The inhibition of the mevalonate pathway has multiple effects on human physiology besides cholesterol inhibition since it also downregulates the synthesis of various geranylgeranylated proteins (rho, rab, rac) involved in cell proliferation, cell death, and survival, inflammation, and immune response.[50] Consequently when vitamin K_2 (MK-4) is supplied orally in large doses (many studies have used 45 mg and even 90 mg,[51] which are in the supraphysiological range), it exerts a "mass action" characterized by some researchers as "pharmacologic" in nature.

K_2 (MK-4) has been used as a drug in Japan and as a therapeutic nutrient in the United States for the prevention or reversal of osteoporosis, prevention or reversal of cardiovascular calcification, cancer prevention, and treatment support.

In conclusion, vitamin K as K_1 or K_2 is being revealed to have a plethora of actions and specific benefits for health maintenance and disease prevention or treatment.

Roles in Bone Health and Therapeutic Interventions for Osteoporosis

Bones undergo continuous remodeling by two opposing processes: (1) bone building by osteoblast cells and (2) bone breakdown (or bone resorption) by osteoclast cells. Vitamins K_1 and/or K_2 modulate bone metabolism through similar mechanisms, but vitamin K_2 has additional effects that vitamin K_1 cannot exert directly:

1. Vitamins K_1 and K_2 are cofactors for the activation (by carboxylation) of osteocalcin, which enables the proper deposition and binding of calcium in the bone matrix.
2. Osteoblasts' production of osteocalcin and collagen type I is increased by vitamin K_2 through modulation of the genetic expression of these proteins.[52]
3. Vitamin K_2 reduces osteoblasts' apoptosis (cell death)[53] and stimulates other bone blastic proteins, such as osteoprotegerin and osteopontin.[54]
4. Vitamin K_2 reduces osteoclasts' production from bone marrow cells[55] and induces osteoclasts' apoptosis, which in effect reduces the total number of osteoclasts. These metabolic effects are achieved through vitamin K_2's ability to downregulate inflammation (IL-6, PGE2) and cell proliferation while increasing apoptosis (through the geranylated proteins produced on the mevalonate pathway).[56] This would be beneficial only if the osteoclastic activity were excessively high.
5. Vitamin K_2 may reduce the accelerated bone resorption induced by menopausal hormonal loss[57] or corticosteroid treatment.[58,59]

The result of the combined actions of vitamins K_1 and K_2 is an optimization of calcium incorporation in the bone matrix and, at the same time, because of K_2 activity, a reduction of excessive bone breakdown (bone resorption). Bone resorption is a necessary process for optimal bone renewal, but it may be detrimental if it is excessive, as in the case of increased inflammation (PGE2, IL-6), increased metabolic signals from geranylated proteins (produced downstream of mevalonate), or deficiency of certain hormones (menopause/andropause: low estrogen, low progesterone, low testosterone).

Vitamin K Doses in the Physiologic Range

Some studies that tested interventions for bone health have used doses of vitamin K that can be considered physiologic—for example, 200, 500, and 1000 mcg of K_1.[31] The optimal physiologic range has not been completely defined for vitamin K_1 and less is known about that of vitamin K_2. The dose needed for complete bone osteocalcin activation is believed to be around 1000 mcg of K_1, but some individuals may need 2000 mcg.[60] This dose is 10 to 20 times higher than that needed for optimal clotting, which is in the range of 90 to 120 mcg.[61] In this dosage range, vitamin K exerts its effects in the metabolic pathways, the way the human body evolved to utilize this nutrient. Owing to very low consumption of leafy greens or liver, most people rarely ingest more than 100 to 200 mcg of vitamin K_1 and more than 50 mcg of vitamin K_2.[114] Vitamin K doses in the "normal" physiologic range would most likely be effective, as some studies have shown,[62] for the prevention of osteoporosis or osteopenia.

Vitamin K Doses in the Supraphysiologic Range

Therapeutic doses of vitamin K_2, such as 45 mg of K_2 (MK-4) or 5 and 10 mg of K_1, have been used for aggressive intervention in attempts to reverse already established osteoporosis or osteopenia or to reduce the rapid bone loss typical of menopause without hormone replacement therapy (HRT) or due to corticosteroid treatment. This approach most likely takes advantage of a "mass action" effect of vitamin K in certain biochemical pathways. These high doses of vitamin K could not be attained by any realistic diet.

Most of the studies using a very high daily dose of K_2 (MK-4) (e.g., 45 mg) done in Japan with the drug version of K_2 (MK-4), Glakay, have shown a significant effect on bone mineral density (BMD). The differences in BMD changes between the treatment and placebo groups for BMD were as follows: +1.1%, +5.2%, and +7.5% after 6, 12, and 24 months, respectively. Some studies also reported a reduced fracture rate (FR) by as much as 80%. Some

studies have shown that vitamin K can reduce the FR even when BMD is not affected.[63]

However, in two recent studies conducted in Holland and the United States, where the investigators used the same K_2 (MK-4) material from Japan (Glakay), there was no effect on BMD.[64,65] At least the Dutch study found an increase in total bone mineral content as a result of this treatment as well as in bone strength (calculated value). Also puzzling is the fact that a Glakay 1996 postmarketing population survey done in Japan of 4000 people taking the same dosage of 45 mg/day of K_2 (MK-4) showed no effect on overall FR (however, a subgroup that had at least five fractures at baseline did show a fracture reduction of about 40%).[66] BMD was not assessed in this survey.

Only a few of the studies that used vitamin K_1 (in daily doses of 200 and 1000 mcg) have seen a higher BMD in the treatment group over placebo. However, others that used daily doses of 500 mcg, 1 mg, 5 mg, and 10 mg have found no effect on BMD, even though the doses of 5 mg and 10 mg were 5 and 10 times higher than the upper physiologic dose of 1 mg. None of the vitamin K_1 studies mentioned previously reported FR except the one using 5 mg, which showed an approximate 50% reduction despite no change in BMD.[62]

Interestingly, a few of these studies included multiple treatment groups in addition to placebo in an attempt to sort out the effect of vitamin K alone or vitamin D alone versus combination treatments that included vitamin K plus vitamin D or vitamin D plus calcium or all three together.[67,68] The results from all these studies clearly showed that combining vitamin K with vitamin D had a stronger effect than either one alone and that combining vitamin K with vitamin D and calcium had even stronger effects. Only one study added magnesium and zinc to the treatment group (taking vitamin K_1 = 1 mg, vitamin D = 320 IU, and calcium = 500 mg), and this is one of the only two studies using vitamin K_1 that showed a slower age-related decline in BMD in the treatment group.[69]

The potential reasons for some of the disappointing and conflicting results among all vitamin K studies may be explained by the following reasons but are not limited to them:

1. Incomplete support and insufficient doses of the nutrients essential to the specific actions of vitamin K on bone (such as vitamin D, calcium, vitamin A, and vitamin B6) as well as other aspects of bone metabolism, such as magnesium, zinc, manganese, vitamin B6, and omega-3 fatty acids. These complementary nutrients have synergistic and additive effects to vitamin K's actions, as discussed earlier under "Mechanisms of Action of Vitamins K_1 and K_2."
2. The bioavailability of the supplements given in different studies may vary widely: (e.g., the solubility and absorption of vitamins D and K, and the absorption of minerals, especially calcium, the absorption rates of which vary greatly depending on its form).[70]
3. The common diagnostic technique to measure BMD used in studies of vitamin K is not as sensitive in detecting the specific actions of vitamin K on bone as are other types of evaluations of bone health and bone quality, such as BU (bone ultrasound test of the heel), BMC (total bone mineral content), BG (bone geometry or size of various bone components, including height changes), or BS (bone strength, calculated from BMD, BG, height, and weight). By the nature of the measurement, BMD is thought to be unable to "give the complete picture" of bone status because it cannot distinguish architectural aspects of the bone quality.[71] These aspects of bone health influence its elasticity and resilience and are all important predictors of FR.

Vitamin K supplementation is believed to improve bone quality whether or not it shows effects on BMD.[72] Bone quality may be best reflected by assessments of BU, BMC, BG, and BS; this has been done in a few studies in addition to the measurement of lumbar and spinal BMD.[73,74] One interventional study with 45 mg of vitamin K_2 (MK-4) has shown an increase in both BMC and BG despite no effect on BMD. The treatment group also maintained their bone strength (calculated from BMD and BG) as compared with the placebo group, which showed an expected age-related decline in bone strength. Consequently, this study showed that vitamin K supplementation might reduce FR even though it did not affect BMD.[64]

Researchers estimate that vitamin K status (as assessed by undercarboxylated Oc [ucOc] in plasma) may correlate better with BU and FR than BMD.[63] Bone heel BU was found to have an accuracy and ability to discriminate osteoporotic patients similar to lumbar and spine BMD (by dual-emission x-ray absorptiometry, or DEXA), with potentially better prediction for FR. Consequently it may be useful to do a BU measurement (in addition to or instead of DEXA) in assessing the effects of vitamin K interventions in clinical practice. One study found that "ultrasound parameters were still significant independent predictors of vertebral fracture even after adjusting for BMD."[75] The BU test may give additional information to the BMD test, especially for patients who, for example, have increased their BMD after many years of bisphosphonate therapy (which reduces bone remodeling severely owing to its main mechanism of action of inducing osteoclast apoptosis).

Optimal Doses of Vitamins K_1 and K_2 for the Complete Activation of Osteocalcin

One study used escalating doses of vitamin K_1 (250, 500, 1000, and 2000 mcg) and measured the increase in the percentage of plasma Oc that was completely carboxylated. The results showed that, for that particular population, an intake of about 1000 to 2000 mcg of vitamin K_1 was sufficient and necessary to achieve close to complete carboxylation of plasma Oc, which means that it would be completely activated. Another study that used doses of 1mg of vitamin K_1 in one group and 45 mg of K_2 (MK-4) in another showed that both groups achieved close to complete carboxylation of Oc.[65] However, it is not clear whether a dose of K_2 (MK-4) lower than 45 mg could have achieved the same degree of carboxylation.

A study published in 2009 looked at the short-term effects (4 weeks) of a dose of 1500 mcg of K_2 (MK-4) on the percentage of ucOc in plasma.[76] The results showed a decrease in the percentage of ucOc from about 30% to 20%, which is still suboptimal. Another study showed that a dosage of 45 mg/day was sufficient to bring the ucOc down to about 4% (which may be close to the detection limits of current laboratory assessments).[65]

Effects of Average Levels of Vitamin K_1 Derived from the Diet

As discussed, a few studies have observed an inverse correlation between normal vitamin K_1 intake derived from the diet and FR and a direct correlation with BMD. The difference between dietary and supplemental vitamin K_1 is that the subjects with a high dietary intake of vitamin K_1 may have derived it from consuming a lot of green leafy vegetables—which in itself may improve bone health through its magnesium, calcium, potassium, and bicarbonate content—thus improving alkalinity. One important fact to consider is that average dietary vitamin K_1 intakes are typically too low (slightly below 100 mcg in the United States and Great Britain to slightly above 200 mcg in Holland) to satisfy the need for

completely carboxylating osteocalcin (which is believed to be in the vicinity of 1000 to 2000 mcg of K_1) or other VKDs that may be involved in bone metabolism. The average vitamin D status in the general population is deficient, which would further impair bone health.[77]

The Synergy and Necessity of Combining Vitamins K and D

Vitamin D is known to enhance Oc expression. It was also demonstrated in vitro that the active form of vitamin D (1,25[OH] D3) enhances the effect of vitamin K_2 on Oc.[78] Vitamin K cannot realize its potential to carboxylate Oc if Oc is not adequately expressed in the first place owing to low vitamin D status.[79]

None of the studies employing vitamin K_1 or K_2 supplementation optimized the vitamin D status (as assessed by plasma 25[OH]D3) with sun exposure or vitamin D supplementation. Most studies used insufficient doses of vitamin D in the range of 200 to 1000 IU, whereas some used an analog of an active form of vitamin D: 1-alpha-hydroxycholecalciferol (which has drug status in Japan). Many commercial laboratories have raised the upper limit of the reference range to include the whole "normal physiologic range." The upper limit of the new reference range of plasma 25(OH)D3 now corresponds to adequately sun-exposed individuals (the so called "lifeguard level"), which has effectively almost doubled the old upper limit of the reference range. The old limit was simply derived from a population that was not adequately exposed to sun.[80]

The studies that used slightly higher doses of vitamin D, such as 800 or 1000 IU, achieved some of the better results: (1) FR reduction of about 50% (with 5 mg K_1 and 800 IU of D3)[63] and (2) a BMD increase of 2.3% over baseline and a 7.35% increase over placebo when supplemented with 45 mg of K_2 (MK-4), 1454 mg of calcium, and 1000 IU of vitamin D2. They showed that the higher the baseline levels of 25(OH)D3, the higher the rate of BMD increase was in the treatment group. Also, the lower the baseline levels of 25(OH)D3 were, the faster the BMD decline was in the untreated group.

The reason this study used D2 was stated by the authors as lack of availability of vitamin D3 in Japan at that time (2005). Vitamin D2 compared to vitamin D3 is similar but not as effective. In fact, the researchers believed that had they used D3, the results might have been stronger, and a recently published paper shows that vitamin D3 was 87% more effective in raising blood levels of vitamin D and also resulted in a two- to threefold increase in vitamin D storage as compared with D2.[81]

One animal study, published in 1994 and funded by the drug company producing Glakay (K_2[MK-4])[155], demonstrated that vitamin K supplementation had no effect on the bone density in the vitamin D deficient rat group, but showed an increase in bone density in the group supplemented with vitamin D, which also ended up with 50% higher plasma levels of 25(OH)D3. However, no study attempted to raise plasma levels of 25(OH) D3 adequately, and it may be possibly because the doses necessary to achieve this, such as 2000 to 5000 IU of vitamin D3 per day, are still considered above the commonly accepted UL (upper tolerable limit).

Two study authors actually state in their papers that they purposely did not design the vitamin K studies with added doses of vitamin D above 400 IU because vitamin D3 supplementation at the level of 800 IU was able to show a reduction in bone fractures on its own and confounded the effects of vitamin K.[82] Unfortunately, owing to this reductionist study design, we have few studies investigating the full effects of synergistic combinations of nutrients at levels that occur in a natural and optimal human physiology and in evolutionary adequate diets with added sun exposure.

Studies Using Supraphysiologic Doses of Vitamin K_1

A few studies tested the hypothesis whether increasing vitamin K_1 intake to 5 to 10 mg (which is above the level attainable by an evolutionary diet), may have more pronounced effects on bone metabolism. These doses are clearly well above the 1- to 2-mg dose needed for complete activation of Oc and would most likely cause a significant amount of vitamin K_1 to be converted to K_2 (MK-4) in various tissues, including bone. The resulting vitamin K_2 (MK-4) would be expected to reduce inflammation and osteoclast activity and cause osteoclast apoptosis, similar to supplementing directly with very high doses of K_2 (MK-4).

Why Use 45 mg K_2 (MK-4) and Are There Any Potential Side Effects?

It is also not clear why the makers of Glakay picked the particular therapeutic dose of 45 mg of K_2 (MK-4) per day for most of their studies. No side effects have been observed so far from the usage of vitamin K_2 (MK-4) under the pharmaceutical drug name Glakay since it was introduced in Japan in 1995 or in the many studies that employed it (including the postmarketing survey of 4000 subjects published in 2005). However, it is conceivable that there could be side effects from supraphysiologic doses of K_2 (MK-4) that have not been detected so far because they would require more sophisticated testing than what was performed in these studies and in the population surveys. Here are some potential consequences of high-dose K_2 (MK-4) based on its conversions and mechanism of action:

1. Oxidative stress, which may be enhanced because of high intermediate K_3 metabolites formed from ingesting K_2 (MK-4).
2. Coenzyme Q10 production or the immune response may be diminished because K_2 (MK-4) inhibits the mevalonate pathway, similar to what was observed with statins, since they downregulate via the same pathway.
3. Unfavorable effects on bone may occur from excessive reduction of osteoclast cell numbers, because this may cause an excessive reduction in bone remodeling. In this respect, vitamin K_2 (MK-4) acts like a bisphosphonate (BP), so one cannot rule out that, in the long term, similar side effects may be discovered for vitamin K_2 (MK-4), as they have been for BP. However, unlike BP, K_2 (MK-4) is likely to have a more positive effect on bone because it stimulates Oc production and its activation, thus enhancing the bone-building process, rather than only reducing the bone-resorbing activity, as BPs do.

Special attention should be paid to patients who are on statin therapy, since this obviously inhibits HMG-CoA reductase and reduces all the downstream metabolites, including the one where K_2 (MK-4) exerts a feedback inhibition on geranygeranyl pyrophosphate (as also discussed under "Mechanisms of Action of Vitamins K_1 and K_2").

How Does K_2 (MK-4) Compare with Bisphosphonates and Does It Make Sense to Combine Them?

One Japanese study showed that combining K_2 (MK-4) supplementation with BP treatment showed an additive and synergistic effect, probably because of their complementary actions, such as bone building support by vitamin K and not just osteoclast apoptosis by BPs.[83,84] Another study showed that vitamin K_2 (MK-4) improved the effect of the BP in reducing FR significantly (slightly more than 50%) but had only a modest effect in improving BMD.

Overall, BPs seem to have a much stronger effect in increasing BMD than K_2 (MK-4). However, BPs seem actually to produce an increase in certain types of FR after long-term use.[85] Also, as discussed in Chapter 194, "Osteoporosis," although bisphosphonates increase BMD, such bones are less remodeled and seem to be less elastic and more brittle and therefore, with time, tend to become more vulnerable to fracture.

What Is the Potential of K_2 (MK-7) in Supporting Bone Health?

The amount of total vitamin K_2 (mix of various lengths) in a Western diet (from a sample Dutch population) (which may contain fermented cheese, fermented milk, and processed meats) averages 29 mcg/day (in a range from 1 to 128), from which K_2 (MK-7) represents an average of 0.4 mcg (in a range from 1 to 2.2) (Table 136-3). Vitamin K_2 intake is much higher in the Asian diet owing to its high content of fermented vegetables and soy-based fermented foods; it ranges from 35 to 247 mcg/day, of which K_2 (MK-7) can represent 50 to 100 mcg/day in those that consume natto.

K_2 (MK-7) is considered a candidate for supplementation to improve bone health because studies have shown a positive correlation between the levels of natto intake (a fermented soy and rice food) and various markers of bone health, such as the degree of carboxylation of OC, BMD, and FR.[86] However, the benefits of natto may not be attributable entirely to its vitamin K_2 content, as it also contains soy isoflavones, which may have a significant effect on bones in menopausal women that do not take hormonal replacement. Soy foods also contains minerals, and other nutrients.

A study supplementing adolescents with 45 mcg of K_2 (MK-7) reported a drop in undercarboxylated Oc from approximately 48% to 38%, clearly showing that the 45-mcg of dose of K_2 (MK-7) was not high enough to support the complete carboxylation of Oc.[87] Researchers chose this dose because it had enough of a safety profile to be proposed as a supplement for adolescents, as it is within the normal range of total dietary vitamin K_2 in Holland. However, dietary K_2 is a mix of various forms of vitamin K_2, of which K_2 (MK-7) may represent only a small percentage, depending on diet (high in Japan; low in Holland and the United States). This level of 45 mcg of a vitamin K_2 mix from a Dutch diet was found to best correlate with reduced arterial calcification and reduced risk of cancer in previous epidemiologic studies (discussed under "Role in Cardiovascular Health and Therapeutic Interventions for Reversing Arterial Calcification"). There is an ongoing study using 180 mcg of K_2 (MK-7) investigating its effect on bone and arterial health, with results due in 2011.[88]

A 6-week study showed that a dose of K_2 (MK-7)—147 mcg—was able to carboxylate Oc to a larger extent than an equimolar dose of vitamin K_1 (100 mcg).[89] However, at the end of this study, the percentage of ucOc was 23%, which is still higher than optimal.

The only conclusion that can be drawn from the comparison study with vitamin K_1 is that the optimal K_2 (MK-7) dose for Oc carboxylation is lower than the molar equivalent of K_1. There may be specific benefits to using a small amount of K_2 (MK-7) in a supplement regimen along with K_1 and K_2 (MK-4) because it converts slowly in the body to K_2 (MK-4). This provides an advantage, because K_2 (MK-7) could be a time-released source of K_2 (MK-4). In summary, vitamin K_2 (MK-7) may be best used in conjunction with the other forms of vitamin K at doses comparable with the traditional Japanese consumption values of up to 165 mcg/day.

Dental Support

Vitamin K status may be essential for oral health because it supports the activation of Oc and osteodentin, two functional proteins involved in tooth mineralization and dental bone metabolism. In addition, salivary glands have a high content of vitamin K, which suggest additional roles for it in oral health.

Increased Needs of Vitamin K in Bone Support for Children, Adolescents, Older Persons, Menopause, Andropause, Corticosteroid Therapy

Most vitamin K interventional studies have focused on preventing or reversing bone loss in postmenopausal women, but maximizing peak bone mass during childhood development is just as important. All populations (including adolescents) studied for plasma levels of ucOc were found to have nonoptimal levels, ranging from 7.5% to 50%, which indicates a widespread subclinical deficiency of vitamin K.[90] Since children's suboptimal intake of leafy greens and liver is unlikely to be easily corrected, vitamin K may have to be supplemented to achieve maximal bone mass and tooth health[91] as well as proper craniofacial development. Vitamin K may also help speed bone and cartilage healing, since it is also involved in boosting the production of collagen and glycosaminoglycans.[35]

Older persons may have an increased need for vitamin K_1 in order to have optimal activation (carboxylation) of Oc.[92] This may be associated with age-related suboptimal enzymatic function and/or increases in cortisol and overall inflammation. Corticosteroids have been shown to downregulate Oc expression, but vitamin K_2 (MK-4) supplementation at 45 mg was able to partially compensate for this effect.

Increased intake of vitamin K, especially K_2, may be especially helpful for women with insufficient estrogen due to menopause, ovariectomy,[93] anorexia, or excess exercise. When estrogen levels drop dramatically, it seems to cause the following changes (1) elevated osteoclast cell activity, (2) higher ucOc levels (probably due to reduced carboxylation efficiency needed for Oc carboxylation), and (3) increased cortisol levels.[94]

Will women who cannot or will not take HRT be able to maintain bone mass and reduce FR by implementing only an intensive nutritional approach as well as women on HRT? Only one Japanese study has compared the bone loss in three groups of menopausal women with that of women on placebo: group 1 took 45 mg of K_2 (MK-4) alone, group 2 took vitamin D in a drug form (an analog of active vitamin D3) alone, and group 3 took conjugated equine estrogen mix (CEE) 0.625 mg/day together with progestin (2.5 mg/day).[57]

After a year, the groups had the following changes in BMD: +0.23% for group 1 (with K_2), -0.47% for group 2 (with D3), +4% for group 3 (with HRT), and -2.87 for placebo. Only the result for group 3 was statistically significant in differing from placebo. So, the results of this study suggest that vitamin K_2 (MK-4) at 45 mg/day may at least forestall the bone loss typical of menopause. Had these investigators combined vitamin K treatment with adequate vitamin D and minerals, the results might have become significant, with a potentially larger increase in BMD. Also, it should be noted that this study used equine HRT. No studies have looked at the effects of vitamin K_2 treatment in comparison with—or ideally, in conjunction with—bioidentical HRT (BHRT), which for numerous reasons is superior, safer, and more effective than equine-based HRT. Combining vitamin K_2 and BHRT treatment is likely to produce better results, not only in terms of bone, but in the effects on overall health.

When it comes to compensating for the effects of estrogen deficiency on bone loss, therapeutic doses of vitamin K_2 may be

necessary, as opposed to just physiologic doses of vitamins K_1 and K_2, as a number of studies suggest. This is because estrogen loss causes an excessive upregulation of osteoclast expression and activity, which translates into elevated bone resorption.

Similarly, one study showed that for men with low testosterone due to leuprolide treatment, a daily treatment of 45 mg of vitamin K_2 (MK-4) was able to reduce the expected decrease in BMD.[42] It is conceivable that the same treatment may be helpful for other low testosterone states as well.

Important Complementary Interventions to be Implemented Along with Vitamin K Supplementation

Adequate vitamin K intake from food and/or supplements or therapeutic high-dose supplementation may achieve the best results if it is coordinated with the following steps:

- Correct low vitamin D status[80]
- Correct low vitamin A status as well as preventing hypervitaminosis A, which has been shown to cause an excessive increase in bone turnover and to reduce bone quality[95]
- Ensure an adequate intake of well absorbed minerals (Ca, Mg, Zn, boron) and vitamin B6[96]
- Initiate an optimal omega-3/omega-6 balance (limit arachidonic acid) in order to prevent excessive PGE2 formation)[97]
- Ensure a proper acid/alkaline balance (possibly by monitoring urine ph) through dietary balance and optimal minerals and potassium intake[98]
- Stress the skeleton with the right type of weight-bearing exercise
- Ensure adequate levels of anabolic hormones (estrogen, testosterone, DHEA, growth hormone)[99]
- Correct excessive catabolic hormones (cortisol, thyroid)

Role in Cardiovascular Health and Therapeutic Interventions for Reversing Arterial Calcification

Vitamin K influences many aspects of the cardiovascular physiology: blood clotting, calcification of tissues critical to cardiovascular function, hypertension, inflammation, and oxidative stress.

Effect of Vitamin K in Preventing, Retarding, or Reversing Calcification in the Cardiovascular System

Vitamin K is an important cofactor necessary for the physiologic process inhibiting inappropriate calcification of soft tissues that are not normally calcified, such as arterial/venous vessel walls, heart valves, skin (elastin fibers), cartilage (other than the normal growth-related mineralization), and kidneys.[100] Vitamin K mediates this defensive action by carboxylating various VKDs, such as MGP, and GAS-6, which enhances their ability to bind calcium ions and prevent their inappropriate deposition in tissues.

Oc is another vitamin K protein involved in calcification, but it has the opposite effect of MGP; it promotes calcium retention in tissues. Oc expression within the blood vessel walls is considered a pathologic manifestation of some of the vascular smooth muscle cells (VSMCs) changing into bone or "cartilage-like" cells. However, Oc expression within bone cells is obviously considered desirable.[101]

MGPs are also often found inside the arterial wall (right where calcification occurs) and have been identified as important players in preventing calcium deposition in those tissues.[102] MGP is also found in tissues such as skin, kidney, and cartilage. MGP, which contains five GLA residues, must be completely carboxylated and also phosphorylated in order to have maximum activity. Plasma circulating undercarboxylated MGP (ucMGP) fraction of MGP has been evaluated as a marker of arterial or other types of calcification.

The calcification that occurs in tissues of the cardiovascular system can be grouped in various types, based on their potential etiology and treatment. However, vitamin K status and vitamin K interventions may affect each type of calcification differently.

Intimal Calcification. This type of calcification occurs within the atherosclerotic plaque, adjacent to the intima, and is always associated with atherosclerotic disease. Interventions that address cardiovascular risk factors may help to prevent or reduce the rate of intimal plaque formation and calcification. Statins have shown some potential in retarding intimal and/or medial calcification, but not in the reversal of existing calcifications.[103]

One animal study showed that a very high dose of vitamin K_2 (MK-4) (1 or 10 mg/kg) "suppressed progression of arterial plaque, intimal thickening, pulmonary atherosclerosis, reduced total cholesterol and lipid peroxidation and did not promote coagulative tendencies."[104] For a 70-kg human, this would translate into 70 to 700 mg/kg per day, which is well above the physiologic range. However, it is possible that some benefits may be observed at much lower doses, but the corresponding human studies have not yet been done.

In vitro studies have shown that all forms of vitamin K_2 can reduce inflammation (PGE2). Vitamin K_1 intake was found to inversely correlate with CRP,[105] and vitamins K_1 and K_2 (MK-4) were shown to act as antioxidants.

Medial Calcification (or Monckeberg's Arteriosclerosis). This type of calcification occurs within the medial layer of the arterial wall surrounding elastin fibers and within transformed VSMCs as well as within the heart valves and vein walls. Unlike intimal calcification, this type of calcification is not associated with cardiovascular disease. It seems so common that one study found it present in 95% of men and women at autopsy.[106] It seems to progress slowly with aging and may be an important component of the age-associated increase in coronary artery calcification (CAC). One human study[107] has shown a clear potential for vitamin K supplementation to slow down the progression of CAC.

Vitamin K deficiency causes MGP to be inadequately carboxylated, and thus incompletely functional. This may lead to the following phenomena:

1. Calcium deposition around the elastin fibers inside the arterial wall, which causes them to lose elasticity. This, in turn, will lead to reduced arterial compliance and increased risk of essential hypertension. The same phenomena occur for the skin elastin fibers, which may be one reason why skin elasticity decreases with aging.
2. Some muscle cells of the medial layer in the arterial wall change phenotypically to "bonelike" tissue cells that resemble bone marrow or cartilage cells. These cells express osteocalcin and start to retain calcium.[108]
3. Calcium deposition in the vein walls and valves, which may lead to varicose veins and impaired return circulation to the heart.

Vascular Calciphylaxis. This type of calcification is associated with kidney disease and other factors, of which vitamin K deficiency may be an important mediator.

Supplementation with 1 mg of vitamin K_1 was sufficient to prevent a typical 3-year increase in arterial stiffness and pulse pressure observed in the groups ingesting "normal" levels of dietary vitamins K_1 and K_2.[108a] The average vitamins K_1 and K_2 intake is most likely deficient relative to the need to completely carboxylatate extrahepatic VKDs, including MGP proteins.

Anticoagulant therapy induces an extreme state of vitamin K deficiency, and studies have shown that it may increase arterial calcification by twofold to eightfold as well as aortic pulse pressure and heart valve calcification.[109] Unfortunately, for patients on this therapy, any extra intake of vitamin D and calcium may intensify the calcification effects caused by the anticoagulant.

Vitamin A and thyroid supplements are both modulators of MGP expression. Excess vitamin A has been shown to increase the risk of arterial calcification, which may be related to the fact that it downregulates MGP expression. Similarly, the thyroid hormone T3 is essential in supporting adequate expression of MGP, and it has been shown that MGP expression is reduced in hypothyroidism. For example, a 68% reduction in MGP expression was associated with a 33% increase in calcium content.[110] Estrogen deficiency reduces carboxylation efficiency. Vitamin B6 and manganese are cofactors for the carboxylation reaction, whereas excess vitamin E (specifically alpha-tocopherol) has been shown to interfere with vitamin K recycling (similar to warfarin), thus reducing its ability to carboxylate VKDs.[111] Other vitamins E and K interactions are discussed under "Vitamin K Interactions."

What is the Potential of Preventing or Reversing Arterial Calcification with Vitamin K Supplementation in Humans?

One human study tested whether supplementation with 500 mcg of vitamin K_1 over 3 years could slow the "normal" age-related progression in CAC (coronary artery calcification).[107] The CAC scores are typically a reflection of the combination of intimal and medial calcification. Supplementing with 500 mcg of vitamin K_1 reduced CAC progression by only 6%. This is a small reduction and not surprising, because the vitamin K_1 dose used was probably not high enough to support adequate carboxylation of the MGP proteins, which are involved in rejecting calcium deposition. Perhaps in addition to higher doses, vitamin K_2 supplementation may have complemented the reduction in CAC by affecting many of the processes contributing to the intimal and medial calcification, as explained earlier.

One of the most exciting newly discovered extrahepatic effects of vitamin K is its potential to actually reverse already established arterial calcification of the medial layer in the arterial wall. This potential has been demonstrated in a rat study from 2007 and has yet to be reproduced in humans.[109] In the first part of the study, rats were in a protocol designed to cause them to develop arterial calcification by treatment with warfarin, which causes a state of severe vitamin K deficiency. In the second part of the study, the hypothesis tested was whether a low dose or high dose vitamin K_1 or K_2 (MK-4) (100mcg or 2 mg/day) could reverse this calcification.

Warfarin was discontinued when the desired calcification level had been achieved. Vitamin K_1 or K_2 (MK-4) supplementation was given right after warfarin treatment was stopped. Both treatments of 6 weeks with 2 mg/day of vitamin K_1 and 2 mg/day of vitamin K_2 (MK-4) were able to reduce the baseline calcification buildup by 35%. The lower dose of 100 mcg/day of either K_1 or K_2 did not achieve the same; in fact arterial calcification progressed in spite of the fact that warfarin had being discontinued. Vitamins K_1 and K_2 (MK-4) were similarly effective.

The calcification reversal observed in this study is impressive, but the question is whether we can translate the effective animal dose into an equivalent one for a typical 70-kg human. The equivalent human dose would be 490 mg/day, which is in a highly supraphysiologic range.

The only other trials that studied highly supraphysiologic doses used around 45 to 90 mg/day of K_2 (MK-4) in humans to reverse osteoporosis or reduce hepatic cancer development; while one study with athletes supplemented with 10 mg of K_1.[31,42] Unfortunately the rat study previously discussed did not test any intermediate doses between 2 mg and 100 mcg/day per rat to see if arterial calcification reversal could be achieved at a dose in between these.

Some researchers propose that in order to achieve calcification inhibition and potentially reversal, the vitamin K level should be high enough to achieve a very high degree of MGP carboxylation. However, no study was designed to find the optimal dose of vitamin K_1 or K_2, alone or in combination, that would be able to completely carboxylate MGP.

A dosage of 1000 to 2000 mcg/day of vitamin K_1, which is typically able to carboxylate osteocalcin close to 100%, may also carboxylate MGPs to a large extent as well. Vitamin K_2 is needed for patients who do not adequately convert vitamin K_1 to K_2.

The conversion of vitamin K_1 to K_2 seems crucial for vitamin K to exert its role in preventing calcification. This was demonstrated by one study that gave warfarin plus either K_1 (WK_1) or K_2 (WK_2) to rats, knowing that warfarin blocks K_1 to K_2 conversion.[112] The doses of vitamin K_1 and K_2 were 1.5 mg/g diet, devised to be high enough to compensate for the arterial calcification effect of warfarin at 3 mg/g diet. Vitamin K_2 prevented calcification in the WK_2 group, while an equal dose of K_1 did not. This study was not designed to explore the possible benefits of giving vitamin K along with warfarin because the dose used canceled any anticoagulant effects from warfarin, but it proved the point that vitamin K_1 must be converted to vitamin K_2 in order to prevent arterial calcification.

A few epidemiologic studies have looked at the correlation between the intake of vitamin K_1 or vitamin K_2 and the risk of cardiovascular calcification (CC), coronary heart disease (CHD), and all-risk mortality (ARM).[113] In particular, three of the studies were done in Dutch populations, and all found strong correlations between vitamin K_2 intake and reduced CC, CHD, and ARM by as much as 20% to 40%, 32% to 41%, and 19%, respectively, while no correlation was found between intake of K_1 and the same risk factors. One study also found a reduction in CHD of 9% for every increase of 10 mcg of total vitamin K_2 intake, ranging from 17 to 42 mcg (mixed variety of forms).[114]

Thus, for an intake of 42 mcg (the upper end of the average diet content), the risk reduction would be around 38%. One could extrapolate that for a vitamin K_2 (mixed variety of forms) intake higher than 42 mcg, the CHD risk reduction may be much higher than 38% and then plateau. At a first glance, the lack of correlation found between vitamin K_1 intake and CVD risk reduction is surprising, since the average intake of vitamin K_1 in the study was in the range of 211 to 250 mcg, which is 7 to 8 times higher than the vitamin K_2 intake at an average of around 30 mcg. However, if we factor in the typical absorption rates from each type of vitamin K, we can estimate that the average amount of vitamin K_1 absorbed was 5% to 15% of 230.5 mcg, approximately 11.5 to 34.6 mcg, whereas the average amount of vitamin K_2 absorbed was probably close to 100% of 30 to 48 mcg. Thus, in actuality, the average amount of dietary K_2 absorbed was potentially 1 to 3.5 times higher than that of vitamin K_1 in this population.

Of course the correlation found between vitamin K_2 intake (from various types of K_2) and the reduction in CC, CHD, and ARM risks may not have been entirely due to the vitamin K_2 but to other associated food patterns and factors.[115]

To put things in perspective, since the K_2 (MK-7) contribution in the typical Dutch diet (as a sample of a mixed diet) was found to be very small (at around 0.4 mcg among a total K_2 mix of an

average of 29.1 mcg), the outcome of supplementing with much higher doses of vitamin K_2 (MK-7), such as 180 mcg of K_2 (MK-7) alone, may be very different than that from a normal dietary pattern of a mixture of forms of vitamin K_2 because they tend to have different metabolic routes.

The Japanese diets are the only ones providing significant amounts of K_2 (MK-7) at around 50 to 100 mcg (for example, one serving of natto [40g] provides 350 mcg of K_2 (MK-7). K_2 (MK-7) has been shown to convert in the body entirely to MK-4 very slowly (over 3 days). However, if the doses are excessively high, the conversion ability becomes saturated, and it accumulates in the body as K_2 (MK-7).

K_2 (MK-4) seems a good choice for supplementation, especially at higher doses, since K_2 (MK-4) is the preferred form of vitamin K_2 stored in the body and the form into which K_1 is converted. The K_2 (MK-4) contribution in the typical Dutch diet was found to be only 7 mcg out of an average of about 29 mcg/day, but it presumably would have been higher if the animal products had been derived from grass-fed meats. K_2 (MK-7) supplementation may present advantages over K_2 (MK-4) because it can act like a time-released source of K_2-MK-4 owing to the fact that it is slowly metabolized to K_2 (MK-4) over an average of 3 days. It would seem that the combination of these two forms of vitamin K_2 may be most similar to the dietary occurrence of vitamin K_2 and have a chance to have a positive effect on CC, CHD, and ARM. Given the data available so far, we can hypothesize that maintaining a high vitamin K status throughout life may partially or completely prevent or retard age-related increases in arterial medial calcification and stiffness. In fact, the term *age-related calcification* may be replaced with *vitamin K deficiency-related calcification* and treated as a reversible condition. It may be possible also to reverse vitamin K-related arterial calcification with high doses of supplemental vitamin K_1 and K_2, but this has not yet been documented.

Are There Benefits from Adding Vitamin K_1 or K_2 to Anticoagulant Treatments Such as Warfarin?

Whenever patients are on anticoagulant treatment, they are told to minimize and keep at constant levels vitamin K-containing foods such as green leafy vegetables. Most patients end up not eating enough vegetables in fear of counteracting their anticoagulant therapy. This is unfortunate since they would be obviously missing important benefits. Some studies have proposed and demonstrated that supplementing with a small dose of vitamin K_1 in the range of 100 to 500 mcg during anticoagulant therapy would help minimize the need for adjusting the dose of the anticoagulant in response to dietary variations of vitamin K.[116,117] One shortcoming of using vitamin K_1 in this scenario is that warfarin blocks the conversion of vitamin K_1 to K_2, which eliminates many of its benefits, especially in the extrahepatic tissues.

This strategy could be implemented with vitamin K_2 instead of vitamin K_1, although no studies have explored this yet. The advantages of using vitamin K_2 would be as follows: (1) it would bypass the warfarin block on vitamin K_1 to K_2 conversion and (2) a part of the ingested vitamin K_2 would bypass the liver to reach the extrahepatic tissues, such as arteries (K_2[MK-4], more so than K_2[MK-7]), where vitamin K_2 may partially compensate for the undesirable effects of the anticoagulant, such as tissue calcifications (in arteries, veins, and heart valves).

One study showed that the international normalized ratio (INR) was lowered from 2 to 1.5 when a dose of 130 mcg (200 nmol)/day of K_2 (MK-7) or 315 mcg (700 nmol) of vitamin K_1 was given in conjunction with acenocoumarol. This shows that vitamin K_2 (MK-7) is around three times more potent on a molar basis in counteracting the blood-thinning effect of anticoagulants that block vitamin K recycling.[89]

Will Therapeutic Doses of Vitamin K Increase Clotting and Thrombosis Excessively?

As discussed in detail later, K_2 (MK-4) at doses of 45 mg or lower or vitamin K_1 at around 1 mg may not increase clotting and thrombosis beyond correcting deficiencies of vitamin K, while they may also optimize the vitamin K-dependent anticlotting factors C, S, and Z. Should therapeutic doses of K_2 (MK-7) be used for cardiovascular benefits, there are not enough data to assess its effects on clotting at high doses, although it is known that it is typically converted slowly to K_2 (MK-4).

Effects on Cancer of Vitamins K_1, K_2, and K_3

Epidemiologic, interventional, and in vitro studies provide evidence that vitamin K plays a role in reducing the incidence and progression of cancer. The three different forms of vitamin K each seem to manifest distinct activities in vitro against cancer cells. Vitamin K_3 has been found to have the highest anticancer activity through multiple mechanisms, followed by vitamin K_2, whereas vitamin K_1 had the weakest effect. Vitamin K_3 was shown in vitro and in vivo to induce oxidative stress, generate hydrogen peroxide, and deplete glutathione, unlike vitamins K_1 and K_2. In fact, some studies showed an antioxidant activity for the latter.[118]

Most likely the human body derives a significant amount of vitamin K_3 from cleaving the side chains of vitamin K_1 or K_2, especially when these agents are ingested in supraphysiologic doses. One study found that urinary excretion of vitamin K_3 was significant 2 to 3 hours after vitamin K_1 ingestion, but plasma vitamin K_3 was not measured.[20] It was also estimated that the percentages of vitamin K_1 or K_2 (MK-4) or K_2 (MK-7) to K_3 conversion are around 5% to 25%. This is believed to occur in the intestinal cells and other extrahepatic tissues, possibly also in the liver. Any effect of oral vitamin K_1 on cancer could be attributed to its direct actions and also its partial conversion to K_3 and K_2. Similarly, any effect on cancer from oral vitamin K_2 could be attributed to its direct actions and also its partial conversion to K_3.

Vitamin K_3 is cytotoxic to cancer cells through oxidative effects and various other mechanisms of action. In vitro studies with vitamin K_3 have shown an inhibitory effect against breast, endometrial, urologic, and prostate cancer as well as leukemia and squamous cell carcinoma.[2] Unfortunately, K_3 is also toxic to normal cells, especially red blood cells, which is why it is no longer used as a provitamin in humans. This profile would most likely qualify vitamin K_3 as a chemotherapeutic agent, but since it is not a patentable molecule, there are not enough studies to achieve FDA evaluation. Currently, vitamin K_3 is only allowed to be used for research purposes in humans; in animals, it is used as a vitamin K precursor to vitamin K_2.

Many studies have observed a synergistic benefit from combining vitamin K_3 with vitamin C (in the intravenous and oral forms) for reducing the rise of prostate-specific antigen in prostate cancer patients[119] and also with all trans-retionoic acid (ATRA) for the treatment of leukemia.[2] Vitamin K_3 has also been shown to inhibit DNA polymerase and angiogenesis[120] and to act as a radiation sensitizer.

Oral and intravenous vitamin K_3 has been used in studies for the treatment of various cancers (leukemia, lung, prostate, and bladder) with and without chemotherapy; such treatment has resulted in improved survival and reduced cancer growth but not complete cures.[2]

One epidemiologic study of a Dutch population found a reduced risk of overall cancer incidence and mortality by 14% and 28%, respectively, for the upper quintiles of vitamin K_2 intake, whereas no correlation was found with the intake of vitamin K_1.[121] The risk reduction was most pronounced for lung and prostate cancer. These results are strikingly similar to the correlations found for vitamin K_2 intake and reduced risk of cardiovascular calcification in the Dutch epidemiologic studies. Considering that the average intake of vitamin K_2 in the population studied is in the range of 26 mcg (first quintile) to 42 mcg (fourth quintile), the results are surprising and warrant future interventional studies with doses of vitamin K_2 (MK-4) in that range and above.

Vitamin K_1 and Cancer

Very few studies have investigated the effects of oral supplementation with vitamin K_1 on cancer, but those that have been done include the following:

1. Oral supplementation with 5 mg of K_1 for 4 years, along with 800 IU of vitamin D3 and 1500 mg of calcium, resulting in an approximate 75% reduction in all types of cancer in postmenopausal women. This was a randomized controlled trial designed to observe the effect of vitamin K_1 plus vitamin D and calcium on bone density; the cancer findings were incidental.[63]
2. A number of phase I/phase II trials investigated the effect of oral supplementation with 40 mg (20 mg twice daily) of K_1 in patients with hepatocellular carcinoma. All studies found improved survival rates, temporary disease stabilization, and reduced tumor growth and invasion.[2]
3. A recent study used both an oral dose of 40 mg/day of vitamin K_1 in one group and incremental intravenous doses of vitamin K_1 (from 40 mg to 1000 mg) in small groups of patients with unresectable hepatocellular carcinoma and distant metastases. All doses, oral and intravenous, were tolerated without toxicity. A small percentage of patients, 3 out of the group of 23 who received oral vitamin K_1 and 3 out of the group of 27 who received intravenous vitamin K_1 had tumor shrinkage, while 16 of each group had tumor stabilization (according to computed tomography). Also, 3 and 6 patients of the oral and intravenous groups, respectively, had a reduction in the tumor marker alfa fetoprotein (AFP).[122] In vitro testing of tumor cells extracted from the subjects in this study has shown that vitamin K_1 induced an inhibition of cell growth through "phosphorylation of JNK and c-Jun and caspase-mediated apoptosis." Even though the authors were aware of the evidence for the efficacy of vitamin K_2 (MK-4) in this type of cancer, they stated that they chose vitamin K_1 instead because "it is the only form of vitamin K available clinically in the U.S." Also, the study authors stated that the dose of 40 mg was chosen based on "how many tablets of the drug Mephyton (5mg K_1) were the patients willing to swallow comfortably."

Vitamin K2 and Cancer

In vitro studies have identified an anticancer activity for vitamin K_2 against liver, colon, leukemia, lung, stomach, lymphocyte, osteosarcoma, epidermoid, glioma, hepatoma, and breast cancer cell lines. Some of the anticancer mechanisms that have been indentified for vitamin K_2 are induction of apoptosis, cell cycle arrest (at G1/S transition), cell differentiation, reduction of cell proliferation and angiogenesis (due to inhibition of COX2), inhibition of signaling for tumor growth, and activation of the PXR genes. Many of these actions are not shared by vitamin K_1, which may be because of vitamin K_2's specific side chain, the molecule geranylgeranyl.

Interventions with oral doses of 20 to 135 mg (but most frequently with 15 mg three times daily) of K_2 (MK-4) have led to improved survival rates for hepatocellular carcinoma, with a slower progression and reduced recurrence rates (especially when patients were infected with the hepatitis C virus).[123] The combination of K_2 (MK-4) treatment with an angiotensin converting enzyme (ACE) inhibitor decreased the recurrence of hepatocellular carcinoma.

Since none of the studies employing high doses of vitamin K_1 or K_2 investigated any lower doses of vitamin K, such as 1 mg or any dose in between 1 and 40 mg of K_1 or 1 and 45 mg of K_2 (MK-4), the minimum dose that would achieve the same effect is not clear, nor, most importantly, is it known at what point no further benefit can be achieved by increasing the dose.

Some promising responses have been obtained from using high doses of K_2 (MK-4) (45 mg) for patients with leukemia or myelodysplastic syndrome (MDS), with an improvement of anemia and thrombocytopenia and sometimes complete remission.[124] The effect was even more pronounced for the group who were also given vitamin D3.

Vitamin K status, measured by the percent uncaboxylated osteocalcin in serum, was found to correlate with advanced-stage and high-grade prostate cancer.[125] As discussed later, this biomarker of vitamin K status can be considered a marker not only for bone health but also for risk prediction for other conditions where vitamin K plays an important role.

In using vitamin K supplementation for general health and for cancer therapy, it is important to keep in mind that, in advanced stages of certain cancers, thrombosis is abnormally activated. This is mediated through unclear mechanisms that may be unique to each cancer's strategy to promote its survival and metastasis. Upregulation of clotting factors and other VKDs, as mentioned, may have an important role in this pathologic process. McCann et al point out that in some specific cancer cases, warfarin treatment has been shown to improve survival rates.[29]

In utilizing vitamin K for cancer risk reduction or treatment, the patient should be evaluated first for coagulation/thrombosis status to make sure that he or she is not in a state where the cancer process is upregulating that status.

In addition, for therapeutic effects, the vitamin K_2 (MK-4) form may be a better choice than vitamin K_1 in implementing a therapy with supraphysiological doses. The dose in the vicinity of 45 mg has a good safety record and the most evidence for efficacy. High doses of vitamin K_2 (MK-4) were found not to increase clotting or platelet aggregation while actually reducing thrombotic tendencies. On the contrary, vitamin K_1 was shown to increase thrombotic tendencies at very high doses. This and the fact that the overall efficacy of vitamin K_1 against cancer is weaker compared with K_2 (MK-4) make vitamin K_2 (MK-4) the overall better candidate for therapeutic doses in cancer treatment and prevention in high-risk patients.

Effects on Various Other Conditions: Insulin, Kidney Stones, Skin Elasticity, Cystic Fibrosis, Brain Protection, Hemorrhage, Joint Health, and Inflammation after Laser Therapy

The optimization of vitamin K status with diet and/or supplements, as well as therapeutic doses of these two vitamers, may have many additional benefits to those previously discussed. These additional effects can be inferred from the presence of VKDs in

many tissues, even though all their roles have not been precisely identified. In addition, observing vitamin K deficiency states or inducing them in laboratory experiments for various tissues has provided many clues on vitamin K's potential to alleviate various pathologic processes.

Vitamin K has a complex role in the clotting processes supporting both the coagulation and anticoagulation/balancing pathways. Its deficiency may lead to increased risk of hemorrhage in various conditions: excessive menstrual, gum, or nosebleeding and increased risk of hemorrhage in infants born and breastfed by vitamin K-deficient mothers.[61,126]

Vitamin K deficiency may have many other consequences:

1. Improper cartilage maturation due to excessive growth plate mineralization[127]
2. Accelerated age-related degeneration of the intervertebral discs (increased calcified/uncalcified cartilage ratio)[128]
3. Reduced glucosamine and glycosaminoglycan synthesis, which affects the health of many tissues in the body: joint cartilage, tendons, ligaments, the dermal layer of the skin, the lining of the gastrointestinal tract, as well as the walls of the and blood vessel and veins[35]
4. Suboptimal skin health, elasticity, and overall appearance due to the following consequences of vitamin K deficiency:
 - Increased skin collagen breakdown.
 - Risk of calcification of the elastin fibers, which are a major determinant of skin elasticity.
 - Thinning of the skin ground substance layer. MGPs are found in the dermis, and control collagen expression as well as glycosaminoglycan biosynthesis (collagen and glycosaminoglycans are both components of the supporting structure of the dermis).
5. Impaired insulin secretion and increased insulin resistance[129]
6. Increased risk of kidney stone formation[130]
7. In animal studies (rats), vitamin K deficiency was shown to cause suboptimal energy production, a 10% reduction in muscle creatine kinase, and a 20% reduction in the alkaline phosphatase of the intestinal mucosa, which may be due to structural mitochondrial alterations[131]
8. Inadequate antioxidant protection of the brain
9. Increased severity of cystic fibrosis. Supplementation with 1 mg of vitamin K_1 was shown to be useful in compensating for the carboxylation defects that are characteristic of cystic fibrosis[132]
10. Reduced testosterone production[133]

Other observed benefits: Topical application of vitamin K_1 was shown to reduce laser treatment-induced redness (inflammation).[134] As described, it would seem that a topical cream containing vitamin K might influence skin physiology positively.

INTERACTIONS WITH OTHER VITAMINS

Interactions with Vitamins E, A, and D

These interactions and synergistic effects of vitamin K with vitamin D and vitamin A were discussed previously regarding their influence on the expression of VKDs: osteocalcin and MGP.

Vitamin E May Interfere with Vitamin K Metabolism When Administered in Very High Doses

Supplementation with high doses vitamin E, such as 800 to 1200 IU of alpha-tocopherol, has been shown to impair blood clotting by interfering with the vitamin K-dependent carboxylation of prothrombin.[111] This is thought to be mediated by a metabolite of oxidized vitamin E called tocopheryl quinone. Another study in rats suggested that high doses of vitamin E may impair the conversion of vitamin K_1 to K_2.[135] This is thought to be due to the competition that can occur between vitamin K_1 and excess vitamin E for a specific cytochrome P450 enzyme responsible for the first step in the conversion of vitamin K_1 to K_2.

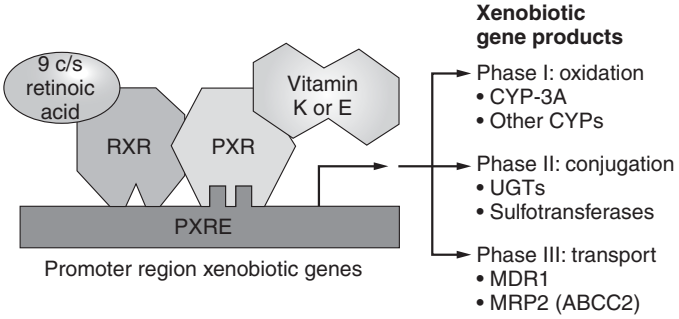


FIGURE 136-4 Xenobiotic receptor activation by vitamin E or vitamin K. (From Traber MG, Frei B, Beckman JS. Vitamin E revisited: do new data validate benefits for chronic disease prevention? Curr Opin Lipidol. 2008;19(1):30-38. Review.)

Reviews also point out that excessive doses of vitamin E may upregulate the expression of metabolizing enzymes responsible for both vitamin E and vitamin K clearance.[135] The reverse may be also true when supraphysiologic doses of vitamin K are administered, especially when the individual's vitamin E status is marginal. Trauber [136] estimates that 90% of the population does not even meet the recommended daily intake (RDI) of 15 IU/day. High doses of either vitamin E or vitamin K can activate the xenobiotic pathways (via the PXR nuclear receptor) twofold to tenfold. Figure 136-4 shows the interaction between vitamins A, E, and K in activating the PXR nuclear receptor. Landes et al. comment on this phenomenon as follows: "the organism handles such supranutritive dosages of vitamins like potential harmful xenobiotics."[137] One should keep in mind that the PXR-activated metabolic pathways are also involved in the clearance of many pharmaceutical drugs.

Since vitamin K seems to play an important role in reducing cardiovascular calcification, the interference by excess vitamin E (of various forms) on vitamin K metabolism may be one of the reasons why a few meta-analytic studies have found increased risk of cardiovascular events in populations that supplemented with alpha tocopherol in excess of 400 IU. The effects of excess vitamin E may be most relevant when vitamin K status is marginal, which is very common. To put things in evolutionary perspective, an analysis by Cordain of the nutritional content of a typical Paleolithic diet found that the average intake of alpha-tocopherol was around 19 IU for a 2200-Kcal diet.[138] However, the average total content of the other forms of vitamin E in that diet (such as beta-, gamma-, or delta-tocopherol) has not been estimated, but it is known that they have many metabolic roles that are distinct from those of alpha-tocopherol. At an intake of alpha-tocopherol above 100 IU, certain metabolic pathways may be pushed beyond the range of "normal physiology."

Interactions with Pharmaceutical Drugs

Anticoagulants Based on Vitamin K Antagonism

Anticoagulants, such as warfarin or coumarin, interfere with vitamin K activation and recycling (see Figure 136-3). Specifically, they inhibit the enzymes epoxide reductase and quinone

reductase. It has been estimated that the body reuses the same vitamin K molecule in the range of 100 times before it metabolizes it for excretion through bile or urine. When an anticoagulant is present, vitamin K recycling is greatly reduced. Anticoagulants also interfere with vitamin K activity in extrahepatic tissues, and studies have shown them to increase the risk of osteoporosis and fracture as well as to delay fracture healing; they may also contribute to arterial or heart valve calcification and hypertension.[139,140] If the total amount of vitamin K from food and supplements is increased by 100 mcg/day, it will most likely require an adjustment in anticoagulant dose. Consequently, vitamin K intake from food and supplements must be closely monitored with this therapy. See the previous discussion about the potential benefits of supplementing with a small dose of vitamin K_2 along with the anticoagulant therapy.

Anticoagulants with Mechanisms of Action Independent of Vitamin K Metabolism

Vitamin K does not interfere with the action of blood thinners such as heparin, antiplatelet agents (clopidrogel, abciximab, tirofiban, and eptifibatide), direct thrombin inhibitors (hirudin, argatroban), or thrombolytic agents (clot-dissolving proteolytic enzymes).[141]

Aspirin and Salycilates Interfere Slightly with Vitamin K Metabolism

Aspirin (acetylsalicylic acid) and salicylates exert most of their blood-thinning effect by reducing platelet aggregation via the inhibition of COX enzymes and potentially other mechanisms. In addition, these compounds have a mild anticoagulant action by inhibiting vitamin K recycling (similar to that of warfarin but a lot milder).[142] Aspirin has been shown to increase bone loss and impair fracture healing, and although the mechanisms have not been elucidated, this could certainly be due in part to its mild anti–vitamin K effect.

Antibiotics Interfere with Vitamin K Metabolism

Antibiotics may increase the need for vitamin K supplementation because (1) they may kill gut bacteria that normally produce vitamin K_2 in the intestinal tract, (2) they may interfere with vitamin K activation and recycling (similar but milder than anticoagulants like warfarin), (3) they may inhibit the activation of various proteins (carboxylation) by vitamin K.[143] Examples include broad-spectrum cephalosporins such as cefamandol, moxalactam, and cefoperazone.

Anticonvulsant Drugs

Anticonvuslant drugs induce vitamin K deficiency. Supplementation of rats on phenytoin with very high doses of K_2 (MK-4) (30 mg/kg body weight) prevented BMD reduction.[144]

Butylated Hydroxytoluene Interferes with Vitamin K Metabolism

Butylated hydroxytoluene (BHT), a preservative still used in some packaged foods and topical creams, inhibits vitamin K epoxide reductase by as much as 20%, which is similar to warfarin's mechanism of action. This may be relevant to the metabolism of vitamin K in the skin when BHT is applied topically, and could, for example, increase the risk of calcification of the elastin fibers, thus decreasing skin elasticity.

VITAMIN K STATUS BIOMARKERS

The majority of the ingested vitamin K_1 is metabolized and excreted (through bile and urine) within 12 to 24 hours. Consequently, fasting plasma vitamin K_1, although offered by many commercial labs, is not a good marker of vitamin K status because it is mostly determined by the previous day's intake of vitamin K_1 and is also not affected by vitamin K_2 intake. Fasting plasma vitamin K_1 is only useful as an approximate estimation of the amount of vitamin K_1 ingested in the day prior to the blood drawing. This may be useful in monitoring patients on anticoagulants in conjunction with the typical coagulation-related tests such as the INR and prothrombin time.

A complete assessment of vitamin K status should reflect the degree of vitamin K sufficiency for all physiologic functions in the body that require vitamin K_1 and/or K_2 for their optimal activity. Unfortunately, such a complete assessment is not available at this time, partly because there are so many VKDs in the body that are carboxylated by vitamin K, and researchers predict that new ones may still be uncovered in future research. Also, many of vitamin K's functions and physiologic effects are unrelated to its carboxylation effect.

Unlike other fat-soluble vitamins, vitamins K_1 and K_2 have not been found to be stored in excess anywhere in the body. Even after long-term dosing, such as a few years, supplementation with supraphysiologic doses of vitamin K_1 or K_2 (10 or 45 mg respectively), apparently no toxic storage levels or effects have been observed. Every molecule of vitamin K is reused multiple times through a recycling mechanism before it is excreted, and perhaps that is why there is no need to store large amounts of it in the tissues.

Prolonged intake of a significant dose of vitamin K has been shown to have a cumulative effect in improving functional markers of vitamin K status. For example, it has been shown to cause a progressive increase over many months of the percentage of carboxylated osteocalcin (Oc) and increased levels of total Oc (the sum of carboxylated plus uncarboxylated Oc).

Currently Available Tests for Vitamin K Status

Vitamin K deficiency results in the appearance of undercarboxylated VKDs (ucVKDs) in the plasma and various tissues and organs throughout the body. It is also conceivable, although not yet completely demonstrated, that if the vitamin K intake reaches a high enough level, all VKDs in the body would be close to 100% carboxylated; consequently all levels of ucVKDs would be close to zero.

Typical biochemical markers of vitamin K status used in studies are plasma levels of ucVKDs or their normalized values. However, one should keep in mind that plasma levels of any one type of ucVKD or carboxylated VKD (cVKD) do not always correlate with their total amounts found throughout the body.

The following vitamin K status tests have been used in studies: plasma undercarboxylated prothrombin (PIVKA II, which stands for proteins induced by vitamin K absence or vitamin K antagonism by anticoagulant drugs), plasma or urine ucOc, and plasma undercarboxylated matrix GLA protein (ucMGP). Of all the tests mentioned, only PIVKA II is available from many commercial laboratories in the United States, whereas plasma levels of ucOc are available from only one specialty laboratory.

It is important to note that as vitamin K intake increases, clotting-related VKDs (such as prothrombin synthesized in the liver) are carboxylated with higher priority than the extrahepatic VKDs (such as Oc and MGP). This is an example of the "triage theory" presented by McCann and Ames in their review.[29] There they present evidence for the concept that evolutionary pressure may have led to prioritizing nutrient allocation in the order of

importance for the "survival of the species." In this case, clotting is obviously more important for survival than bone or arterial health, so the carboxylation of the clotting-related proteins is prioritized.

For example, one study has shown that for patients on a small dose (1 mg) of warfarin, PIVKA II started decreasing when vitamin K_1 intake was around 100 mcg, whereas ucOc plasma levels did not start decreasing until vitamin K_1 intake reached around 300 mcg/day.[117]

Consequently PIVKA II may decrease significantly and approach zero for vitamin K_1 intakes in the lower range of the average intakes, whereas ucOc levels may not approach zero until vitamin K intake is much higher. One landmark study showed that the percentages of ucOc levels may approach zero when intakes of vitamin K_1 are in the range of 1000 to 2000 mcg.[60] No studies have found an equivalent amount of vitamin K_2 that can achieve the same decrease in percentage of ucOc, which corresponds to an almost complete carboxylation of Oc. Suggestions for possible biomarkers of vitamin K status:

1. PIVKA II is the inactive form of prothrombin, and it is a sensitive marker of vitamin K_1 status at very low intakes (for example, in the vicinity of 100 mcg of K_1/day).

It is not clear how PIVKA II levels are affected by vitamin K_2 (in various forms) compared with vitamin K_1. One study showed that the INR was lowered similarly by a lower amount of vitamin K_2 (MK-7) as compared with vitamin K_1.[89] Consequently, patients taking supplements and foods containing various forms of vitamin K (such as K_1, MK-4, MK-7) should be very closely monitored for changes in INR.

2. Plasma ucOc level is a test currently available only from one commercial lab in the United States specializing in nutrition status-related tests (Metametrix). Some studies have also measured the normalized value of ucOc relative to total osteocalcin (called %ucOc = ucOc/total Oc, or the ratio OCR = ucOc/iOc, iOc with meaning "intact or carboxylated osteocalcin").

The plasma levels of ucOc and its normalized ratios, %ucOc and OCR, have good sensitivity for a wide range of vitamin K_1 and/or K_2 intakes. The upper threshold of sensitivity seems to be achieved for a vitamin K_1 intake in the range of 1000 to 2000 mcg. However, ucOc measurements may not be adequately sensitive for patients on anticoagulant therapy or with very low vitamin K intakes (which represents an alarming 60% to 70% of the population).

The measurement of both PIVKA II and ucOc may give a good approximation of vitamin K status with good sensitivity over a wide range of vitamin K intakes even though they reflect only a few facets of the vitamin K status.

It should be noted that even if a patient has a considerably high intake of vitamin K_1 (around 1000 to 2000 mcg/day) and a corresponding low ucOc level, this does not rule out a deficiency of vitamin K_2 if one were to consider vitamin K_2 a conditionally essential nutrient. This is especially important for certain patients who are older and have genetic polymorphisms or certain severe conditions such as advanced osteoporosis and/or arterial calcification, cancer, multiple sclerosis, or rheumatoid arthritis.

Oc has an established role in bone metabolism and studies have revealed significant direct correlations between ucOc or %ucOc and fracture risk and bone density.[145]

However, the ucOc marker may be useful for the management of diseases besides the ones related to bone because it conceivably correlates with the percentage of carboxylation of other extra hepatic VKDs in the body.

For example, one study found a positive correlation between plasma levels of %uOc and the risk of prostate cancer.[121]

It is important to note that average populations deemed "apparently healthy" were found to have an average of 15% to 50% ucOc. Specifically, one study found teenage girls to have an average %ucOc of 21.9%.[146] This is considered by many researchers a sign of subclinical vitamin K deficiency, which may have various detrimental consequences for bone development, cartilage, brain, and the nervous system, since vitamin K is so critically involved in the physiology of all these tissue and organs. This is just one example why the RDI for vitamin K is outdated.

3. ucMGP is currently assessed only in research laboratories but hopefully may be offered in the future by commercial labs because it has good potential in evaluating and devising nutritional interventions for patients at risk of or with existing arterial calcification.

Plasma levels of ucMGP were found to directly correlate with arterial calcium buildup and calcium scores, but only for patients with relatively low amounts of arterial calcium and in early stages of cardiovascular disease.[102] Thus, the plasma level of ucMGP is thought to be a good indicator of current mild buildup of calcium in the arterial wall and/or of future risk of arterial calcification.

If this test becomes commercially available in the future, it may be helpful in guiding clinicians to devise the appropriate vitamin K intake for each patient so as to maximally reduce the risk of further cardiovascular calcification and possibly even reverse it.

Since the ucMGP measurement is not yet offered from commercial labs, the best available surrogate marker for it is plasma ucOc or its normalized ratio, which may also predict to a certain extent current or future risk of arterial calcification. However, it is also important to keep in mind that when the ucOc level is close to zero, it may not necessarily mean that the level of ucMGP in the body is also the lowest possible or that vitamin K intake has reached a level high enough to support complete carboxylation of all MGPs in the body and thus is providing significant protection from arterial calcification.

Some researchers point to the fact that osteocalcin contains three GLA residues, whereas MGP contains five; therefore they hypothesize that the carboxylation of MGP may require a higher vitamin K intake than that of Oc. This may be another example of the triage theory presented by McCann and Ames in their review, discussed earlier.

In summary, until more vitamin K assessments are available, plasma ucOc is the best biomarker for guiding patients toward optimization of their vitamin K status with vitamin K_1 and/or K_2 from diet and supplements, although it is only a partial marker of vitamin K sufficiency in the body.

Warfarin causes, by design, an impairement in the carboxylation of various clotting proteins, but unfortunately it also affects all other extrahepatic VKDs. For example, one study found that a "minidose" of warfarin of 1 mg/day induced an increase in %ucOc from 8% to around 20%, and it will most likely increase ucMGP as well.[147]

By monitoring ucOc and ucMGP in addition to PIVKA II, along with standard clotting parameters (such as prothrombin time and INR) in these patients, it may be possible to find the appropriate dose of vitamin K_2 for each individual that may reduce to a certain extent the effects of warfarin on extrahepatic tissues. All this would be done while keeping the INR within the therapeutic range.

In interpreting tests that measure the levels of undercarboxylated VKDs, it is important to keep in mind that there are other factors, other than vitamin K, that may affect these results, as follows:

1. Deficiencies of vitamin B6 and manganese, as well as low sex hormone status (estrogen or testosterone), may reduce the carboxylation rate of VKDs.[3]

2. Factors that can lower the production of osteocalcin or MGP include low vitamin D and K status (including treatment with warfarin), excess or deficiency of vitamin A, corticosteroid therapy, hypothyroid state (defined as suboptimal T3 levels), and possibly high endogenous production of cortisol.[148]
3. Total plasma levels of Oc may be elevated by vitamin D supplementation and in states of increased bone turnover (e.g., during adolescence, after injury, or after menopause).

Since so many factors can influence the levels of osteocalcin, some researchers believe that the normalized values of ucOc (OCR and %ucOc), rather than absolute values of ucOc, may be a better indicator of vitamin K status. However, this is still under debate, and researchers who favor the absolute levels of uOc argue that ucOc may be released more easily from the bone matrix into the blood as compared with carboxylated Oc because carboxylation enhances its ability to bind calcium in the bone matrix. Thus, the plasma ratios of these two biomarkers may not correlate with their tissue ratios.

4. MGP expression is decreased in hypothyroidism, which will also affect the body's ability to reduce arterial calcification.

Other factors that may increase the need for vitamin K intake and affect the interpretation of the ucVKDs tests include genetic polymorphisms, aging, fat maldigestion and/or malabsorption, pharmaceuticals (antibiotics, antiepileptic drugs, aspirin) or excess vitamin E.

One should keep in mind that oxidative stress may impair the tissues' ability to recycle vitamin K in order to reuse it for carboxylation multiple times. Thus, the vitamin K status should be thought of based not only on vitamin K intake but also on how many times each vitamin K molecule can be recycled.

It is also important to note that during active cancer development, various clotting factors may become upregulated, including thrombin.

DOSING CONSIDERATIONS: PREVENTION VERSUS THERAPY

Current RDI versus Expanded Criteria for Defining Optimal Vitamin K Intake

The adequate intake (AI) of vitamin K, specifically for the K_1 form, is 90 mcg for women and 120 mcg for men, or 1 mcg/kg per day.[149] For vitamin K, the AI criterion was initially adequate blood clotting, because that was the only vitamin K role recognized at the time. However, this criterion has had to be expanded in light of the additional vitamin K roles discovered since. A new AI may have to be increased significantly in order to support the function of various tissues and organs affected by vitamin K status.

The evidence in support of a higher AI for vitamin K has been accumulating for more than 10 years and, as reviewed previously, vitamin K has numerous extrahepatic roles. Unfortunately, the study results available are far from giving definite answers regarding the level of vitamin K intake that would maximize each specific body function in which vitamin K plays a role.

Surveys have found severe population deficiencies of vitamin K_1, even relative to the current AI[150]:

1. Sixty to seventy percent of the U.S. population does not even meet the current AI (90 to 120 mcg) for vitamin K, which is already well below what may be necessary for optimal health.
2. The average intake of vitamin K_1 in United States was found to be 70 mcg/day for the younger and 120 mcg/day and the older population. Whereas intakes of vitamin K in the United Kingdom are similar to those in the United States, in other European countries, such as Holland, average vitamin K_1 intakes are significantly higher, at 246 mcg.
3. Some 5% to 15% of people have been found to have undetectable levels of plasma vitamin K_1.
4. The majority of vitamin K_1 consumed in the United States is derived from vegetable oils as opposed to vegetables. Owing to the high prevalence of hydrogenated and fried oils and storage in transparent bottles (which allows vitamin K to be destroyed), it is possible that the active amount of vitamin K_1 ingested may be even lower than previously estimated.

This widespread deficiency of vitamin K_1 is not surprising, since consumption of fruits and vegetables is deficient in the American diet.

Guidelines for Optimal Vitamin K_1 Intake and High-Dose Therapies

Preventative versus Therapeutic Strategies

As discussed, vitamin K_1 has multiple extrahepatic functions. The only function studied with escalating doses of vitamin K_1 was osteocalcin carboxylation.

From the results of that study, we can hypothesize that 1000 to 2000 mcg of vitamin K_1 may be the best preventive dose for the aspect of bone health. It has not been demonstrated whether there is definite benefit from using therapeutic doses higher than 1000 to 2000 mcg/day of vitamin K_1. One study showed that 5 mg/day of vitamin K_1 may significantly reduce fracture risk and cancer incidence of all types, but it did not include comparison groups taking any other doses between 1 and 5 mg.[63]

Based on the studies available, vitamin K_1 doses of 500 and 1000 mcg would most likely be helpful for a preventive effect on arterial calcification, although there is no proof of complete prevention at these doses. However, a dose in the range of 1000 to 2000 mcg of vitamin K_1 may be more effective for preventive indications, as it may be more likely to carboxylate MGP to a larger extent.

For reversal of existing arterial calcification, we can only consider a theoretical equivalent to the dose used in the animal study, which may be anywhere from of 14 to 490 mg per day of K_1 or K_2 (MK-4). However, since the animal study using 240 mg/kg body weight of vitamin K_1 showed increased "thrombotic tendencies," whereas K_2 (MK-4) showed the opposite, it would be best to use therapeutic doses of K_2 (MK-4) for this application and not K_1.

Another line of evidence that may help reveal what the optimal vitamin K_1 intake may be for humans comes from evaluating vitamin K_1 intake during evolution, as in the typical content of a Paleolithic diet. Studies have looked at many nutritional components of this type of diet.[138] Preliminary data suggest that Paleolithic humans were ingesting vitamin K_1 in the vicinity of 1000 mcg/day on average. This amount is also achievable in a modern diet if it were to include substantial portions of spinach or other combination of vegetables plus some vegetable oils at two to three meals per day, as indicated in Table 136-1.

It is likely not a coincidence that the Paleolithic levels of vitamin K_1 intake overlap with the amount of vitamin K_1 needed to completely activate Oc. Since vitamin K_1 was abundantly available and consumed through the majority of human evolution, it is conceivable that the vitamin K needed for basic survival was adequate and that reproduction-related functions were well supported. However, for longevity past reproductive age and disease reversal, vitamin K requirements may be higher and may involve all of its various forms.

There is no doubt that the best foundation for achieving optimal vitamin K status starts with a diet rich in leafy greens and including moderate amounts of vegetable oils and seeds (nonoxidized and nonhydrogenated). Supplementation with vitamin K_1 may be necessary only when diets are deficient and for therapeutic purposes. At the very least, the well-founded recommendation of consuming five to nine servings of fruits and vegetables per day would provide a substantial amount of vitamin K_1 in the range of 200 to 1000 mcg/day.

For those who fail to incorporate in their diet foods to provide vitamin K_1 of around 1000 mcg/day, supplementation may be the only way to achieve optimal vitamin K status. It should be noted that there is a significant difference between the bioavailability of vitamin K_1 derived from the diet (around 5% to 15%) compared with that from vitamin K_1 supplements, which is around 10% when encapsulated with 85% cellulose and close to 80% when encapsulated with emulsifiers.[151]

Currently, vitamin K_1 supplements are typically found as part of multivitamin formulations in the range of 100 to 1000 mcg per daily serving and in bone support formulas and stand-alone vitamin K formulas around 500 to 1000 mcg/day. Vitamin K_1 has also been added in amounts of 200 to 500 mcg to stand-alone vitamin D formulas in order to compensate for the tendency of vitamin D to increase calcification in arterial and other tissues in subjects who are vitamin K deficient.

Aging, poor conversion of K_1 to K_2 due to genetic polymorphisms or other metabolic factors affecting vitamin K activation or action, and the need for treatment support of severe conditions (such as cancer, autoimmune diseases, and arterial calcification, or simply menopause and andropause) may require higher doses of vitamin K_1 and additional vitamin K_2.

Guidelines for Optimal Vitamin K_2 Intake and High-Dose Therapies

Preventive versus Therapeutic Strategies

Is Vitamin K_2 Useful or Necessary to Take in Addition to Vitamin K_1? Currently there is no AI set for vitamin K_2 because this nutrient is not recognized as a vitamin in the true sense. Another factor may be because it was always assumed that adequate vitamin K status (as defined by optimal clotting at 90 to 120 mcg), can be easily achieved from foods and/or supplements. However, new research has uncovered enough evidence for recommending a certain preventive amount of various forms of vitamin K_2, whereas much higher doses may be needed for specific clinical interventions.

Average vitamin K_2 intakes have been evaluated by a few epidemiologic studies, such as for correlations with cardiovascular disease risk and cancer risk in Dutch populations or osteoporosis risk in Japanese populations.[152] The average intakes of Vitamin K_2 reported by these studies were around 29 mcg (range of 1 to 128) for Western diets and 35 to 247 mcg for Asian diets. Also, see Table 136-3 for an example of a detailed distribution of the various forms of vitamin K_2 from one survey. It is important to keep in mind that Western populations have a particularly high consumption of cheese, hence the high contribution of K_2 (MK-4), K_2 (MK-8), and K_2 (MK-9), while the Japanese have a particularly high consumption of fermented soy, hence the high contribution of K_2 (MK-7).

For some metabolic situations, ingesting preformed vitamin K_2 (from diet and/or supplements) may be much more therapeutic than just ingesting vitamin K_1 and relying on the body or the bacteria in the gut to convert it to vitamin K_2. Also, vitamin K_2 may be essential for the gut cells, as there is no evidence that the gut cells convert vitamin K_1 to K_2 (see Figure 136-2). This may be because there was no evolutionary need for it, since the gut cells were always exposed to high amounts of vitamin K_2. Since vitamin K_2 is known to reduce inflammation and cancer risk in general, it may be beneficial for exerting these effects in colon cells.

Consequently vitamin K_2 may be conditionally essential for certain organs and certain individuals who have difficulty converting K_1 to K_2 because of age-related changes or those who need intensive intervention for certain disease states, who have genetic polymorphisms, or who are taking drugs like warfarin.

Another clue to the human need for preformed vitamin K_2 may be grounded again in an evolutionary perspective of the Paleolithic diet. The vitamin K_2 content of the Paleolithic intake has not been estimated as yet, but it is very likely higher for several reasons:

- The modern human's gut flora may be often impaired owing to therapeutic antibiotic use or antibiotics ingested within animal foods and dairy.
- Existing gastrointestinal bacteria cannot produce adequate amounts of K_2 (MK-n) from a low intake of vitamin K_1.
- The GI tract of the Paleolithic human was most likely populated with a variety of bacteria producing a fair amount of long-chain vitamin K_2 (MK-n)s. Vitamin K_1 intake was high, which served as a substrate for intestinal bacteria to produce abundant quantities of K_2 (MK-n). Fiber was also abundant, which supports gastrointestinal bacteria.
- The only significant dietary sources of long chain MK-ns for modern humans are cheeses and sauerkraut (in Europe and the United States) or fermented vegetables (kimchi) or soy fermented foods (such as natto, mostly in Asia).
- It is also unlikely that Paleolithic humans were ingesting any purposely fermented foods, but they may have eaten partially "spoiled" (thus naturally fermented) foods. Dairy foods were probably not often consumed, and neither were grains, legumes, or soy foods.[138]
- The modern content of K_2 (MK-4) in meats may be low because animals are fed mostly corn and not grass.

The only type of long-chain vitamin K_2 (MK-n) commercially available is K_2 (MK-7). The main reason to supplement with K_2 (MK-7) may be to provide a sustained delivery of vitamin K_2 through its slow conversion to vitamin K_2 (MK-4), since its average plasma half-life is around 3 days).

Supplementing with Vitamin K_2 for Prevention

When supplementing with vitamin K_2 for prevention, the dose that would be most appropriate is in the range of 40 to 250 mcg/day of a mix of various vitamin K_2 forms. The lower level of 40 to 50 mcg/day of vitamin K_2 was found to correlate with significant benefits. These levels may be comparable but potentially lower than what humans were ingesting in Paleolithic times from grass-fed animal foods plus what was derived from their intestinal bacteria (probably less than 100 mcg).

If the supplementation goal is to compensate for the poor K_1 to K_2 conversion, then a dose closer to 1 mg/day of vitamin K_2 may be more appropriate, considering that the Paleolithic intake of vitamin K_1 was around 1000 mcg, which may convert to a similar amount of K_2 (MK-4) inside various tissues. K_2 (MK-7), may be added in at around the same dose of about 50 mcg/day.

If the supplementation goal is a major therapeutic intervention for cancer, osteopenia, osteoporosis, osteoarthritis, or a

history of fracture, arterial calcification, or autoimmune diseases (such as multiple sclerosis or rheumatoid arthritis), a pharmacologic dose may be used in the range of more than 1 to 2 mg and possibly up to 45 to 90 mg/day (the dose used in the drug form Glakay in Japan). It is not known whether doses of K_2 (MK-4) lower than 45 mg may be just as effective because they simply have not been studied. A dose lower than 45 mg K_2 (MK-4) may be sufficient, especially if the patient is on statin therapy, since they both inhibit metabolites downstream of HMG-CoA/mevalonate, but this needs to be investigated. The 45 mg of K_2 (MK-4) should be administered in divided doses, ideally three times daily for optimal utilization. Although all these studies used exclusively K_2 (MK-4) (in the form of Glakay), it may be a good idea to add or substitute a part of it with a small amount of K_2 (MK-7). This combination could provide a more sustained therapeutic effect.

Currently, vitamin K_2 supplements are becoming more prevalent and the doses commonly available are as follows:

- K_2 (MK-4) is available in doses of approximately: 45 mcg, 1 mg, 15 mg, and 45 mg. It is also available in liquid form for easier titrating.
- K_2 (MK-7) is available in doses of approximately 20, 50, and 100 mcg.

Potential Side Effects of High Doses of Vitamins K_1, K_2, and K_3

No upper level of toxicity (UL) has been established for vitamin K_1, even though it belongs to the family of fat-soluble vitamins, which all have a UL because of their typical tendency to be stored and accumulated in various organs. This may be because vitamin K_1 is rapidly metabolized out of the plasma and the majority is excreted via bile and urine (50% and 20%, respectively) within a day, with complete excretion of the rest in about 3 days. No evidence has been found so far of toxic accumulation anywhere in the body.

Is It Safe to Take Vitamin K at Levels Higher Than AI (Adequate Intake)?

Will such very high intakes increase clotting excessively? Some studies suggest that once the liver clotting factors are maximized (by complete carboxylation), no amount of excess vitamin K_1 or K_2 can increase clotting performance any further.[153]

Whenever supplementation with vitamin K is initiated, most people will experience an increase in clotting factors because a large proportion (60% to 70%) of the population has a vitamin K intake below the optimal clotting requirement. However, vitamin K also supports the activation of anticlotting proteins that keep overall clotting tendencies in an optimal range (proteins C, Z, S). One study looked at the effects of supplementing postmenopausal women with 45 mg of K_2 (MK-4) and found that although clotting markers increased, the anticlotting activity increased as well; thus the clotting balance was maintained.[154]

One study looked at the effects of supplementing rabbits with very high doses of vitamin K_1 or K_2 (MK-4) (250 mg/kg) and found no increases in clotting factors or platelet aggregation. However, the investigators also looked at thrombogenic activity (defined as the time to develop a clot in a specific wound in the aorta), which was increased for vitamin K_1 treatment and decreased for vitamin K_2 (MK-4) treatment as compared with placebo. This study has also demonstrated that the different thrombogenic effects may be due to the side chains of vitamins K_1 and K_2 (MK-4), phytol and geranyol respectively, through an unknown mechanism.

Numerous 2- to 3-year studies have employed doses of 45 mg and even 90 mg of vitamin K_2 (MK-4) for various interventions and none have reported clotting or thrombotic abnormalities.

In regard to vitamin K_1, there are only a few short-term studies that supplemented with vitamin K_1 doses from 500 mcg up to 10 mg, and they have not reported clotting or thrombogenic abnormalities. However, because the study discussed previously found increased thrombogenic tendencies with K_1 (although at very high supraphysiologic doses of 250 mg/kg), it may not be prudent to prescribe more that 1000 to 2000 mcg of vitamin K_1 per day.[153] A level of 1000 mcg vitamin K_1 per day may be considered intrinsically safe because it could be normally derived from diets high in leafy greens, seeds, oils, and some organ meats.

There have been no long-term studies published so far that used K_2 (MK-7) supplements for more than 8 weeks. K_2 (MK-7) has been consumed traditionally in Japan (by approximately 42% of the population) at average levels of 58 mcg/day, with the upper reference range up to 165 mcg/day. This level of K_2 (MK-7) is typically derived from consuming an average of 350 mcg per serving of natto (one to three times per week). No clotting problems have been reported at this level of intake; however, natto food also contains nattokinase, which has antithrombotic effects.

Could Supraphysiologic Doses of Vitamin K_1 or K_2 Have Any Side Effects?

Vitamins K_1 and K_2 partially convert temporarily to vitamin K_3 in intestinal and other cells. Vitamin K_3 supplementation was shown to increase red blood cell lysis and to cause excessive oxidative stress as well as nonspecific binding of thiols from large and small molecules in the blood. Doses of vitamin K_1 and K_2 higher than 1 to 2 mg/day have not been evaluated for periods of time longer than 2 to 3 years in humans with appropriate health assessments, such as measuring oxidative stress and DNA damage. These studies have not reported any side effects, but their health assessments may not be enough proof of safety.

Specifically, very high doses of vitamin K_1 or K_2 (MK-n) could theoretically give rise to unusually high levels of vitamin K_3 in the few hours following their ingestion. The studies that used the 5-, 10-, or 40-mg doses of vitamin K_1 or 45 mg of K_2 (MK-4) have not reported plasma or urinary levels of vitamin K_3.[31,63]

One must also keep in mind the physiologic burden that supraphysiologic doses of vitamin K may impose on the various pathways it activates for its recycling and detoxification: quinone reductase and glucuronidation. Quinone reductase may generate excessive hydrogen peroxide and superoxide radicals.

Some researchers have expressed a concern for the potential stimulatory effect that large doses of vitamin K may have on bacterial overgrowth in the gastrointestinal tract, since vitamin K is involved in the energy production of certain bacteria, similar to the way in which coenzyme Q10 affects mitochondrial energy. Another researcher commented on the possibility of excess vitamin K potentially supporting periodontitis.[34]

The Japanese studies that used 45 to 90 mg of K_2 (MK-4) have not noted any side effects. However, knowing that high doses of vitamin K_2 (MK-4) inhibit the pathways downstream of mevalonate on the HMG-CoA pathway, the potential for side effects cannot be ignored.

As mentioned, at high doses, both vitamin E (all forms) and vitamin K activate the xenobiotic pathways twofold to tenfold because the body perceives that "supranutritional amounts of these vitamins might be considered as foreign."

In conclusion, whereas no UL exists currently for vitamin K_1 or K_2 (whether MK-4 or MK-7), because higher doses of these vitamins are

being used by populations at large, with or without a clinician's supervision, there is a need for better standards in monitoring the potential side effects that these supraphysiologic doses may have. Clinicians should also attempt to find the lowest effective dose of vitamin K_1 or K_2 for each particular clinical situation by using synergistic therapies, so that the potential for unknown side effects may be reduced.

SUMMARY

Optimizing Vitamin K Status and Therapies Through Diet and Supplements

The current paradigm shift in vitamin K knowledge is very similar to that of vitamin D, for which there is also a big discrepancy between the fast-accumulating new research and the outdated RDA/UL and therapeutic guidelines.

Many researchers who performed recent reviews of vitamin K_1 and K_2 call for establishing a higher AI and for more research to be done in order to further clarify vitamin K physiology and provide more evidence for clinical applications. However, they are far from a consensus on what the new AI for vitamin K should be and on what doses of vitamin K_1 and/or K_2 may be used effectively and safely for therapeutic purposes. As a side note, it is puzzling that some researchers called a daily dose of 1000 mcg of K_1 "pharmacologic," because this is realistically achievable with a diet very rich in leafy greens. Similarly, other researchers consider that 100 mcg/day of K_1 is a "normal" intake that could be increased only with supplements.

It certainly makes sense to recommend acquiring as much vitamin K as possible from one's diet in a balance of all forms: K_1, K_2 (MK-4), and some long-chain K_2 (MK-n) from fermented foods. Another aspect to address is the health of the intestinal tract, so that some K_2 (MK-n) can be derived from intestinal bacterial production. In that respect, avoidance of unnecessary antibiotic treatments and favoring grass-fed animal products would be helpful.

Vitamin K may be supplemented for two major purposes:

1. For complementing the patient's dietary deficiencies and correcting any physiologic deficiency of various forms of vitamin K: K_1, K_2 (MK-4), K_2 (MK-7). In most cases, it makes sense to supplement with all three forms of vitamin K.
2. For therapeutic purposes, where any combination of the three available supplemental forms of vitamin K may be used to achieve a pharmacologic-like action (as discussed in "Mechanisms of Action of Vitamins K_1 and K_2"). This application is experimental and the patient must be closely monitored for potential side effects and dose adjustments.

Another important aspect to consider is the dose distribution of vitamin K intake throughout the day. For example, a once-a-day high dose of vitamin K_1 or K_2 in the range of 10 to 15 mg may not be metabolized properly and may be more likely to have unwanted side effects. One has to keep in mind that in order for vitamin K_1 supplementation to realize some of its physiologic roles in extrahepatic tissues, it may have to be cleaved to form K_3 by the intestinal cells or convert peripherally to vitamin K_2 in various tissues and organs. This enzymatic reaction may very likely be saturable at intakes slightly above 1 to 2 mg.

It's important to consider the impaired absorption of vitamin K in individuals with pancreatic and biliary insufficiency, short bowel syndrome, and inflammatory bowel conditions (including celiac disease). For these cases, a sublingual delivery in an emulsified or liposomal formulation may have the best chance for absorption.

Dietary fat stimulates biliary and pancreatic secretions, so it would be best to incorporate a reasonable amount of fat (for example, 30 g) with the meal ingested at the same time as a vitamin K supplement.

In natural foods, vitamin K_1 is bound in the thykaloid membranes of chloroplasts, whereas vitamin K_2 may be dissolved in the fat of dairy or animal tissues. Also, mechanical processing, such as blending, juicing, or cooking may further enhance vitamin K_1 bioavailability from food.

The bottom line is that vitamin K_1 or K_2 requirements may vary between individuals based on their particular genetics, health status, and dietary habits. Ideally (only theoretical at this time), vitamin K status should be at the level that supports maximal activity for all vitamin K-related functions. Therapeutic supplementation with supraphysiologic doses of vitamin K has great potential for the reversal of severe diseases through complex effects. Patients should be monitored for various side effects and interactions with other pharmaceutical drugs, such as statins and bisphosphonates, and through specific vitamin K status tests and other tests relevant to vitamin K action pathways, as discussed under "Status Biomarkers and Commercially Available Assessments."

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CHAPTER 137

Vitamin Toxicities and Therapeutic Monitoring

Joseph E. Pizzorno, ND

CHAPTER CONTENTS

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INTRODUCTION

When nutrients such as vitamins are being used at high doses for pharmacologic effects, the physician must be vigilant for possible toxicity or side effects. In general, vitamin therapy is virtually "nontoxic" and the small risk of developing any toxicity can be further reduced by careful monitoring of the patient. The physician should also be aware of toxicity resulting from self-administered vitamins. The primary signs and symptoms of vitamin toxicity are listed in Tables 137-1 and 137-2, which are complemented by a more detailed discussion of toxicity and guidelines for monitoring select vitamins.

VITAMIN TOXICITY

Lipid-Soluble Vitamins

Vitamin A

Although vitamin A deficiency is a much greater problem than vitamin A toxicity, particularly in developing nations, both clinical and subclinical toxicities have been associated with excessive intakes of preformed vitamin A. Many cases of hypervitaminosis A involve ingestion of a large quantity at one time by young children, who, along with the elderly, are more susceptible to toxicity.[1,2] Acute toxicity is thought to occur when, within a short period of time, adults ingest more than 100 times the recommended daily allowance (RDA) and children ingest more than 20 times the RDA. However, in addition to acute toxicity, chronic intakes of high-dose vitamin A have also been associated with harm.[3] The most recognized among these is an adverse effect on bone, with observational studies suggesting an increased risk of osteoporosis and fracture. Unfortunately, assessment of vitamin A toxicity is limited by the lack of sensitive laboratory markers.

Adverse reactions to acute toxicity in children can occur with intakes as low as 1500 international units per kilogram daily (IU/kg/day),[4] and they are usually transient. Symptoms of acute hypervitaminosis A in children given 100,000 to 300,000 IU include diarrhea, headache (possibly resulting from elevated intracranial pressure), nausea, vomiting, occasional dizziness, and fever as well as a transient bulging of the fontanelle in infants. In adults, symptoms of toxicity may also include blurred vision and lack of muscular coordination.[5] Chronic vitamin A excesses can precipitate alopecia, arthralgias, anemia, erythema, skin peeling, thickened epithelium, and fatty liver as well as heart, kidney, and testicular defects and hypercholesterolemia. Other less commonly reported symptoms include dysphagia due to vertebral hyperostosis, and intrahepatic cholestasis.[6] Interestingly, in a small number of case reports of dysphagia, none of the patients reported vitamin A supplementation despite high serum retinol levels, suggesting an impairment of vitamin A metabolism rather than excessive intake.[7] Usually most of the untoward effects of excess vitamin A intake are resolved with cessation of its use.

Of all the reported adverse effects, bone abnormalities have received the most attention, with excessive intake of vitamin A suggested to have a lasting detrimental effect on bone by inducing osteoporosis.[8,9] However, the data are mixed and may be confounded by other variables, particularly vitamin D status.

One 9.5-year study involving almost 35,000 postmenopausal women with hip and other fractures found little evidence of an increased risk of fracture with higher

TABLE 137-1 **Toxic Dosages and Side Effects of Lipid-Soluble Vitamins**

VITAMIN	TOXIC DOSAGE	TOXIC SIGNS AND SYMPTOMS
Carotenoids	Long-term: none	No apparent toxicity, even at large doses (250 mg/day); synthetic form poses a risk for heavy smokers or asbestos-exposed persons not taking other antioxidants.
Vitamin A	Short-term:	
	Infants: 75,000-300,000 IU	Anorexia, bulging fontanelle, hyperirritability, vomiting.
	Adults: 2-5 million IU	Headache, drowsiness, nausea, vomiting.
	Long-term:	
	Infants: 18,000-60,000/day	Premature epiphyseal bone closing, long bone growth retardation.
	Adults: 100,000 IU/day	Anorexia, headache, blurred vision, loss of hair, bleeding lips, cracking and peeling skin, muscular stiffness and pain, severe hepatic damage and enlargement, anemia, teratogenesis.
Vitamin D	Short-term: 1000-3000 IU/kg	Anorexia, nausea, vomiting, diarrhea, headache, polyuria, polydipsia.
	Long-term: >40,000 IU/day	Hypercalcemia (unlikely).
Vitamin E	Long-term: >800 IU/day	Severe weakness, fatigue, exacerbation of hypertension, potentiation of anticoagulants. α-tocopherol used alone may increase disease risk.
Vitamin K	Long-term: none	Phylloquinone (K1), unlike menadione (K3), is not associated with side effects when given orally. Caution is in order with anticoagulant medications.

TABLE 137-2 **Toxic Dosages and Side Effects of Water-Soluble Vitamins**

VITAMIN	TOXIC DOSAGE	TOXIC SIGNS AND SYMPTOMS
Ascorbic acid	Short-term: usually >10g	Nausea, diarrhea, flatulence.
	Long-term: >3 g/day	Increased urinary oxalate and uric acid levels in rare cases, impaired carotene utilization, chelation and resultant loss of minerals.
Biotin	Long-term: >10 mg/day	No reported side effects from oral administration at therapeutic doses.
Folic acid	Long-term: 15 mg/day	Abdominal distention, anorexia, nausea, sleep disturbances May pose increased cancer risk (see text).
Niacin	Short-term: >100 mg	Transient flushing, headache, cramps, nausea, vomiting.
	Long-term: 3-7 g/day	Anorexia, abnormal glucose tolerance, increased plasma uric acid levels, gastric ulceration, liver enzyme elevations.
Niacin-amide	Long-term: >2000 mg/day	Same as for niacin.
Pantothenic acid	Long-term	Occasional diarrhea.
Pyridoxine	Short-term	No acute effects have been noted at therapeutic dose.
	Long-term: 300 mg/day	Sensory and motor neuropathies.
Riboflavin	Long-term	No toxic effects have been noted.
Thiamine	Long-term	No toxic effects noted for humans after oral administration.
Vitamin B_{12}	Long-term	No side effects from oral administration have been reported.

intakes of vitamin A or retinol. There was also no evidence of a dose-response relationship in hip fracture risk with increasing amounts of vitamin A or retinol from supplements. Furthermore, the results showed no association between vitamin A ingestion from food and supplements or food only and the risk of fractures of any kind.[10] Similar results were published in the *American Journal of Clinical Nutrition* in 2009. This was a large observational study that included over 75,000 participants from the Women's Health Initiative. Retinol and vitamin A intake were not significantly associated with either hip or total fracture incidence among postmenopausal women. However, women in the highest quintile of retinol and vitamin A intake who also had a low intake of vitamin D did have a modest (15%-20%) increased total fracture risk.[11] A smaller study that enrolled Spanish postmenopausal women did find an independent risk for osteoporosis among those with the highest intake, but this risk was magnified when combined with low vitamin D levels.[12] The interaction between high vitamin A and low vitamin D levels appears biologically plausible, as vitamin A may antagonize some of vitamin D's actions, including calcium absorption.[13] This may be relevant not only to bone health but possibly to susceptibility to respiratory infection as well.[14] A 2007 review of the bone effects of vitamin A concluded that the poor sensitivity of laboratory markers and assessment of dietary intake may contribute to the conflicting findings; it suggested that future studies incorporate superior analytic techniques, specifically stable-isotope-dilution methodology.[15] Although serum retinol is often employed to screen for vitamin A toxicity, it is thought to have poor sensitivity because it is subject to homeostatic control over a wide range of intakes as well as hepatic concentrations, and thus does not necessarily represent liver stores.[16] Additionally, many clinical factors interfere with its accuracy. One alternative is the measurement of fasting retinyl ester concentrations. When more than 5% to 10% of circulating vitamin A is in the form of retinyl esters, it may indicate either hepatic storage capacity or the capacity of the retinol-binding protein has been exceeded. Unfortunately, elevated retinyl esters do not necessarily indicate impaired liver function and are not sensitive to subclinical toxicity.[15,17]

Although expensive and not widely available, stable isotope dilution techniques appear to correlate well with values determined by liver biopsy and may emerge as the best marker of total vitamin A stores in both deficiency and toxicity. Indeed, variations of this method may be used to determine the intake needed to maintain target body storage levels. In animal models they have shown 100% sensitivity for the diagnosis of hypervitaminosis A.[18,19] Although the deuterated retinol dilution method has been validated in both children and adults to give a quantitative estimate of internal stores, it needs further verification among diverse populations and greater accessibility.[20] When large doses of vitamin A are being given, careful monitoring is necessary. Rather than sudden ingestion of large doses, a gradual stepwise increase in dosage is indicated, with an evaluation of symptoms made before the dosage is increased. Usually, the first symptom of hypervitaminosis to be recognized is frontal headache. If signs or symptoms appear, supplementation should be discontinued until they disappear. Levels of liver enzymes should be determined periodically to check for hepatic damage. Typically, levels of aspartate transaminase are the first to be affected.[1,2,21,22] Patients whose liver function is compromised by viral hepatitis, protein-energy malnutrition, cirrhosis, or hemodialysis seem to be the most vulnerable to vitamin A toxicity and to require close monitoring.[4] Vitamin A levels during pregnancy must be carefully assessed because both deficiency and excess can bring about undesirable results. Supplementation above the RDA is not warranted in pregnant or potentially pregnant women. According to one large observational study published in the *New England Journal of Medicine*, women consuming greater than 10,000 IU of vitamin A during pregnancy (specifically during the first 7 weeks after conception) had a 1 in 57 risk for having a child born with a birth defect.[22a]

It is the opinion of this author that much if not most of the problem of vitamin A toxicity, except at very high dosages, is likely due to the high prevalence of vitamin D deficiency.

Carotenoids

Carotenoids appear to be without toxic effects at the therapeutic doses customarily used. The only effect of large dosages is an apparently benign yellowing of the skin. Although carotenoid toxicity is limited, there is concern that some individuals have difficulty converting carotenoids to vitamin A and may be more prone to vitamin A deficiency.[23-25]

Several large, widely publicized therapeutic trials with synthetic beta-carotene have found that it appears to raise the risk of lung cancer in heavy smokers. It may also pose an increased risk for gastric cancer, particularly among smokers and those exposed to asbestos.[26] However, several factors complicate the interpretation of these results. The significance of these trials is fully discussed in Chapter 69.

Vitamin D

Significant advances have been made in understanding the role and importance of vitamin D in human health. Deficiency is now known to be widespread, with suboptimal levels much more prevalent than toxicity. The use of 25-OH vitamin D is widely accepted as a reliable biomarker, with most indicators suggesting that a level of 75 to 110 nmol/L is sufficient, although some studies indicate that even higher levels may be optimal.[27,28] The upper limits of 25-OH vitamin D are not clearly established, although levels less than 250 nmol/L are considered safe.[29] Therapeutic strategies should target 25-OH vitamin D levels rather than a specific supplemental dose, as the effect of supplementation on serum levels varies considerably between individuals. Doses between 2000 IU and 4000 IU will bring the majority of individuals within the range of 75 to 110 nmol/L.[27] Nevertheless, some will require higher dosing, and this is also a consideration for individuals with less functional vitamin D receptor polymorphisms. Doses as high as 40,000 IU per day have not been associated with toxicity.[28] However, very high single doses (500,000 IU in a single annual dose) have been associated with an increased risk for fracture and falls in a temporal pattern, with the highest risk in the period after administration.[30] Thus, lower doses given more frequently (i.e., more physiologically) are preferred. Despite ongoing controversy, vitamin D3 appears to be more potent and to produce greater storage than D2.[31]

Granulomatous diseases, such as sarcoidosis, warrant special concern because these individuals are more susceptible to hypercalcemia. Although many have low levels of 25-OH vitamin D (which appears to increase the risk for sarcoidosis), they also have elevated levels of 1,25 dihydroxyvitamin D and thus require careful management.[32] Apparently there is overconversion of 25-OH vitamin D3 to 1,25(OH)2-vitamin D3 by macrophages in granulomatous disease.[33]

Vitamin E

Although for many years observational studies found vitamin E supplementation to be safe, several controlled trials have been published suggesting harm with supplementation. For example, in a large meta-analysis of randomized placebo-controlled trials in which participants were given between 50 and 800 IU natural or synthetic vitamin E per day, supplementation was found to reduce the risk of ischemic stroke by 10% but to increase the risk of hemorrhagic stroke by 22%.[34] Similarly, a meta-analysis published in the *Annals of Internal Medicine* found that supplementation with more than 400 IU vitamin E increased all-cause mortality.[35]

Although the use of synthetic versus natural vitamin E may explain some of the increase in adverse effects, the natural form of vitamin D (d-alpha tocopherol) used in many clinical trials is not without risk. For example, supplementation with natural vitamin E at 400 IU per day was associated with an increased risk of heart failure among patients with diabetes or vascular disease.[36]

An explanation that appears more plausible is that despite the physiologic benefits of alpha-tocopherol, high-dose supplementation depletes other forms of naturally occurring vitamin E, such as beta- or gamma-tocopherol, which have greater physiologic significance. For example, in an observational study of elderly patients, higher plasma levels of beta-tocopherol were associated with a reduced risk of developing Alzheimer's disease, whereas other forms of vitamin E were only marginally significant.[37] The use of both gamma- and alpha-tocopherol in patients with the metabolic syndrome was shown to be superior to either used alone. Moreover, in vitro and in vivo evidence indicates that alpha-tocopherol not only failed to demonstrate anticancer properties but also blocked the anticancer effects of gamma-tocopherol.[38,39] Gamma-tocopherol is actually more prevalent than the alpha form in the U.S. diet as well as in many plant seeds, although the vast majority of trials and available products use alpha-tocopherol.[40] Thus, it may not be "vitamin E" that has the harmful effects mentioned above but rather the isolated use of alpha-tocopherol. Additional factors are likely to have an influence as well, such as age and vitamin C intake.[41] Genetics are also likely to play a role, as diabetic patients with the haptoglobin 2-2 genotype are more likely to receive benefit from supplementation.[42] Unfortunately, most laboratory evaluations of vitamin E's toxicity are based on alpha-tocopherol plasma or serum levels and thus may not be helpful in determining toxicity.

Vitamin K

Large doses of the synthetic water-soluble vitamin K_3 (menadione) administered to infants may cause hemolytic anemia, hyperbilirubinemia, hepatomegaly, and possibly death. Adults with glucose-6-phosphate dehydrogenase deficiency may show hemolytic reactions.[43] The natural vitamin K_1 (phylloquinone) and the menaquinones (MK-4, MK-7) do not appear to cause toxicity when given orally unless huge doses (e.g., 200 mg) are given.[44] Dr. Bruce Ames, professor of biochemistry and molecular biology, has provided compelling evidence for the triage theory; that given a suboptimal intake, vitamin K is shunted to basic functions necessary for survival at the expense of less essential functions, which are likely to be associated with aging and chronic disease. Given that many individuals have suboptimal vitamin K intake, supplementation with menaquinones has the potential to reduce the incidence of chronic disease.[45]

All forms of vitamin K can interfere with some anticoagulant medications, such as warfarin (Coumadin) and should be used with caution. Given that the menaquinones may have greater potency than vitamin K1, an upper limit of 50 mcg/day (MK-7) has been proposed for those patients on anticoagulant therapy.[46] However, the longer half-life of MK-7 (compared with other forms of vitamin K) may help to maintain a more stable international normalized ratio while also protecting these patients from the arterial calcification and osteoporosis for which they are at increased risk.[47]

Water-Soluble Vitamins

Ascorbic Acid

Vitamin C has been reported to have perhaps the lowest toxicity of all vitamins. Diarrhea and intestinal distention or gas are the most common complaints when it is consumed at higher dosages. It has been shown that high doses of vitamin C

- Increase the urinary excretion of calcium, iron, and manganese
- Increase the absorption of iron
- Raise urinary oxalate or uric acid levels, but only in a small subgroup of the population (This may vary with the form of vitamin C, as ester-C has been shown to reduce oxalate levels in a crossover study.[48])
- Alter many routine laboratory parameters (e.g., serum vitamin B_{12}, aminotransferases, bilirubin, glucose, stool occult blood)
- Cause nausea, edema, and dry mouth or skin when used intravenously, all considered minor[49]

The clinician must take these effects into consideration when supplementing with megadoses of vitamin C. Also, the ability of oral vitamin C to increase plasma levels is limited, with intravenous administration of vitamin C having been shown to raise levels 70-fold higher.[50] Even at the high plasma levels documented with intravenous therapy, toxicity does not appear to be a significant concern.

One concern with high dosages of vitamin C often cited in the medical literature is the development of calcium oxalate kidney stones. As mentioned above, various forms of ascorbic acid may negate this effect, as demonstrated with ester-C versus ascorbic acid. Additionally, in vitro oxidation of ascorbic acid to oxalic acid during storage or analysis is thought to be a common confounder in these studies. Nonetheless, 500 mg/day may be a reasonable limit for those prone to stone formation.[51] With regard to intravenous administration of vitamin C, less than 0.5% of a 100-g dose was converted to oxalic acid in individuals with normal renal function, much less than might be expected from such a large dose.[52]

A second, more theoretical concern about vitamin C relates to its excess use in progressive inflammatory diseases such as rheumatoid arthritis and Crohn's disease. It is theorized that available surplus vitamin C may interact with metal ions, eliciting a prooxidant consequence.[53] Alternatively, more recent data suggest that vitamin C may chelate metal ions, actually reducing their ability to generate reactive oxygen species, and animal models suggest that megadosing may reduce inflammation.[54,55] Although no clinical information is available to clarify this concern, it may be prudent to consider limiting the megadosing of vitamin C in patients with unresponsive or worsening chronic inflammatory conditions and to be cautious about giving large doses of vitamin C to patients with known conditions of iron or copper excess. This may also be relevant to the dietary intake of iron. For example, high dietary heme intake among women taking more than 500 mg vitamin C per day was found to increase the risk of lung cancer, whereas high zinc intake reduced the risk.[56]

There have been reports that abrupt cessation of high-dose vitamin C intake leads to "rebound scurvy, which has also been reported to occur after birth in the babies of pregnant women who have been taking high doses. However, other studies do not support the existence of rebound scurvy under these conditions. Although some experts question the existence of rebound scurvy, it is better to err on the side of caution. At this time a safe recommendation to pregnant women would be a daily dosage of 500 mg vitamin C.

Folic Acid

Although generally considered safe, caution should be exercised in supplementing with folic acid in the presence of a vitamin B_{12} deficiency. Although folic acid will correct a macrocytosis, it will not correct the underlying neurologic degeneration caused by vitamin B_{12} deficiency. Additionally, high folic acid levels appear to accentuate the toxicity of low vitamin B_{12}.[57,58]

High-dose folic acid (15 mg/day) has been used without adverse effects in several studies. For example, when given as 5-methyltetrahydrofolate to postmenopausal women, it significantly reduced their blood pressure and homocysteine levels and improved their insulin sensitivity.[59] Folic acid given at 5 mg/day with vitamins B_{12} and B_6 was found to reduce subclinical atherosclerosis among individuals with a fasting homocysteine level greater than 9.0 µmol/L when given over 3 years. This was a randomized placebo-controlled trial with over 500 participants, and no difference in adverse effects between groups was cited.[60] A meta-analysis also found that folic acid supplementation reduced the risk of stroke in primary prevention, especially when continued for a longer period of time.[61]

A very important placebo-controlled randomized trial, published in 2008, found that folic acid given at 5 mg/day over 3 years reduced the recurrence of colorectal adenomas; the recurrence rate in the placebo group was twice as high as in the folic acid group. Additionally, none of the patients who received folate was found to have histologically aggressive adenomas or carcinoma at their final endoscopy.[62] This study is particularly relevant because concerns have been raised that both low and high folate levels may increase the risk of cancer.[63,64] For example, in two previous trials, folic acid given at 1 mg/day was associated with more advanced colorectal lesions as well as an increased risk of prostate cancer.[65,66] It is possible that the high folic acid content of fortified foods can be a confounding variable when a low dose of 1 mg/day is used. Additionally, there is most likely a difference between synthetic folic acid and the more natural reduced and methylated forms, primarily 5-methyl tetrahydrofolate.

Finally, a serum folate level greater than 45.3 nmol/L is often used to define elevated levels, but it is arbitrarily chosen because of technical difficulties in analysis rather than a functional toxicity.[67]

Niacin

The acute side effects of niacin (nicotinic acid) are well known. The most common and bothersome is the skin flushing that typically occurs 20 to 30 minutes after the niacin is taken. Long-term consequences of niacin therapy include gastric irritation, nausea, and liver damage. In an attempt to combat the acute reaction of skin flushing, several manufacturers began marketing "sustained-release," "timed-release," and "slow-release" niacin products. These formulations allow the niacin to be absorbed gradually, thereby reducing the flushing reaction. However, although these forms of niacin reduce skin flushing, they have actually proved to be more toxic to the liver, particularly the slow-release products. One study strongly recommended that the use of slow-release niacin be restricted because of the high percentage (78%) of patient withdrawals from the study because of side effects; 52% of the patients taking the sustained-release niacin had liver damage compared with none of the patients taking immediate-release niacin.[68] "Extended-release (ER)" niacin (Niaspan) appears to have similar toxicity as immediate-release niacin, with a 2008 review documenting that significant increases in liver enzymes with either extended- or immediate-release niacin are rare and that elevations leading to severe hepatotoxicity occur rarely, if at all.[69]

Niacin has also been shown to cause a 4% to 5% increase in fasting glucose and a 20% to 28% reduction in insulin sensitivity. For this reason it should be used with caution in diabetic patients and those at risk for diabetes. However, its cardiovascular benefit often significantly outweighs the risk, even in these patients. In a recent meta-analysis published in *Atherosclerosis*, nicotinic acid given alone or in combination was associated with a reduction in the risk of coronary events and stroke (approximately by 75%) as well as positive effects on the evolution of atherosclerosis when used at 1 to 3 g/day. The authors of this analysis also point out that it reduces low-density-lipoprotein cholesterol to a similar degree as statin medications, and is the only effective therapy for reducing lipoprotein (a).[70] When extended-release niacin was given to diabetic patients at 1000 to 1500 mg/day, it was associated with only a 0.3% increase in hemoglobin A1c compared with placebo, with a dose-dependent improvement in levels of triglycerides and high-density-lipoprotein cholesterol. However, increases in diabetes medications may have prevented a larger increase in hemoglobin A1c.[71] Given that improving high-density-lipoprotein cholesterol is a primary goal in diabetes, the use of nicotinic acid is often indicated for these patients.[72]

Side effects can occur with any form of niacin, including niacinamide. Although niacinamide does not cause the acute flushing of the skin, it can also cause liver damage and has not demonstrated the same benefit to lipid profiles as nicotinamide. Inositol hexaniacinate is an alternative form of niacin that may have very few side effects, but large, well-designed studies to document its benefit are lacking.[73]

TABLE 137-3 **Laboratory Tests for Vitamin Toxicity**

VITAMIN	LABORATORY MEASUREMENT
Vitamin A	AST, serum retinol, serum free retinyl esters, stable isotope dilution (preferred)
Vitamin D	Serum calcium, 25(OH) vitamin D
Niacin	AST, ALT
Vitamin C	Urinary oxalate and uric acid

ALT, Alanine transaminase; AST, aspartate aminotransferase.

Regardless of the form of niacin being used, periodic checking (at least every 3 months) of liver function is indicated when high-dose (i.e., 2 to 6 g/day) niacin, inositol hexaniacinate, or niacinamide therapy is being used. Niacin should be used with caution in patients with preexisting liver disease or elevation in liver enzyme values, gout, or peptic ulcers.

Pyridoxine

Vitamin B_6 is one of the few water-soluble vitamins that is associated with toxicity when taken in large doses or in moderate dosages for long periods, and it is known to cause a transient sensory neuropathy. Large doses of vitamin B_6 are currently being used for a wide variety of conditions.

Doses greater than 1000 mg/day can produce symptoms of nerve toxicity (tingling sensations in the feet, loss of muscle coordination, and degeneration of nerve tissue) in some individuals, with ataxia being the clinical hallmark of vitamin B_6 hypervitaminosis.[74] Long-term intake of dosages greater than 500 mg/day can be toxic if taken daily for several months.[75] There are also a few rare reports of toxicity occurring at chronic long-term dosages as low as 150 mg/day.[76-78] One animal study reports the increased possibility of nerve toxicity in individuals with renal failure who have uremia, owing to decreased pyridoxine excretion, which induces an increase in susceptibility to pyridoxine-induced neuropathy.[79] Because patients with renal failure are commonly given long-term pyridoxine therapy, caution is advised, and it is prudent to look for neuropathic signs in pyridoxine-supplemented uremic patients with renal failure.

Toxicity is thought to occur when supplemental pyridoxine overwhelms the liver's ability to add a phosphate group to produce the active form of vitamin B_6 (pyridoxal-5-phosphate, or PLP). As a result, it is speculated that pyridoxine is either toxic to the nerve cells or that it actually acts as an antimetabolite by binding to PLP receptors, thereby creating a relative deficiency of vitamin B_6. Doses should therefore be limited to 50 mg. If more than 50 mg is desired, then the doses should be spread throughout the day or the active form (PLP) could be used.

LABORATORY TESTS FOR VITAMIN TOXICITY

Only a limited number of routine laboratory tests are available for detecting vitamin toxicity. These are presented in Table 137-3.

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CHAPTER 138

Vitex agnus castus (Chaste Tree)

Donald Brown, ND, and Michael T. Murray, ND

Vitex agnus castus (family: Verbenaceae)
Common name: chaste tree

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GENERAL DESCRIPTION

Vitex agnus castus, also known as chaste tree, is a shrub with finger-shaped leaves and slender violet flowers. It grows in creek beds and on river banks in valleys and lower foothills in the Mediterranean and Central Asia. The plant blooms in high summer and, after pollination, develops dark-brown to black fruit the size of peppercorns. The fruit possesses a pepper-like aroma and flavor. The ripe, dried fruit of *V. agnus castus* is the part of the plant used in medicinal preparations today.[1]

CHEMICAL COMPOSITION

The fruit of *Vitex* contains essential oils, iridoid glycosides, and flavonoids.[2] The essential oils include limonene, 1,8-cineole, and sabinene.[3] The primary flavonoids are castican, orientin, and isovitexin. The two isolated iridoid glycosides are agnuside and aucubin (Figures 138-1 and 138-2).[4] Agnuside serves as a reference material for quality control in the manufacture of *Vitex* extracts, although the flavonoid casticin appears to be the most active component.

HISTORY AND FOLK USE

The genus name *Vitex* is derived from the word *vitilium*, which means "plaiting." The flexible but tough and hard branches were used to construct fences. Plinius, in the first century AD, made the earliest reference to the plant as *Vitex*. The species name *agnus castus* originates from the Latin *castitas* ("chastity") and the equating of the Greek *agnos* with the Latin *agnus* ("lamb").

The English name for *V. agnus castus*, "chaste tree," is derived from the belief that the plant would suppress libido in women who took it. In Greek cities, festivals in the honor of Demeter included a vow of chastity by the local women. The Roman Catholic Church in Europe developed a variation on this theme by placing the blossoms of the plant in the clothing of novice monks to supposedly suppress libido. Interestingly, another common name for *V. agnus castus*, "monk's pepper," derived from the fact that monks in southern Europe commonly used the fruit as a spice in their cooking.

PHARMACOLOGY

Vitex acts on the hypothalamic-pituitary axis. One observed effect is that it increases the production of luteinizing hormone (LH) (Figure 138-3), resulting in a corpus luteum–like hormonal effect that shifts the estrogen/progesterone ratio in favor of progesterone.[5] The ability of *Vitex* to increase or modulate the body's progesterone levels is therefore an indirect effect and not a direct hormonal action.[6]

Vitex also modulates the secretion of prolactin from the pituitary gland. In studies with rats, it was shown to inhibit prolactin release by the pituitary gland, particularly in conditions of stress. The mechanism of action appears to involve the ability of *Vitex* to directly bind dopamine receptors and subsequently inhibit prolactin release in the pituitary.[7,8] The flavonoid casticin appears to be responsible for this antihyperprolactinemia effect.[9] *Vitex* also possesses significant antioxidant effect.[10,11]

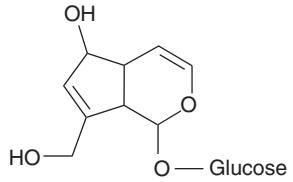


FIGURE 138-1 Aucubin.

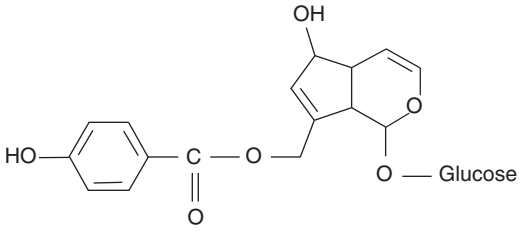


FIGURE 138-2 Agnuside.

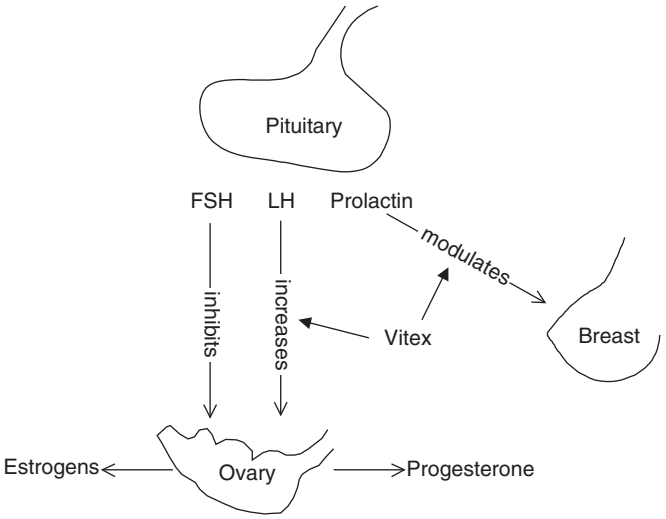


FIGURE 138-3 Effect of *Vitex* on pituitary hormone secretion.

CLINICAL APPLICATIONS

The causes of menstrual disorders are multifaceted and can vary greatly in their manifestations. Frequently, therapeutic interventions must be used on a trial-and-error basis over a number of menstrual cycles to determine their efficacy. Nutritional interventions like vitamin B_6, magnesium, and vitamin E, as well as evening primrose oil for cyclic mastalgia, have all shown greater efficacy when used over several months. This characteristic reflects the gradual balancing effect that many of these interventions have on the female hormonal system. *Vitex* certainly fits this mold.

The majority of earlier clinical studies completed with *Vitex* were uncontrolled studies with large populations of female patients in European gynecology practices. *Vitex*, which has a Commission E Monograph in Germany, is commonly used in these practices as an initial intervention in a number of menstrual disorders, as follows:

- Anovulatory cycles
- Hypermenorrhea
- Hyperprolactinemia
- Infertility
- Mastalgia
- Polymenorrhea
- Premenstrual syndrome
- Secondary amenorrhea

Many of these conditions have been linked to corpus luteum insufficiency.

TABLE 138-1 **The Most Common Clinical Conditions in 1592 Women Diagnosed with Corpus Luteum Insufficiency**

DIAGNOSIS	NO. OF PATIENTS	PERCENTAGE OF TOTAL
Hypermenorrhea	418	26.3
Polymenorrhea	369	23.2
Persistent anovulatory bleeding	216	13.6
Secondary amenorrhea	202	12.7
Dysmenorrhea	186	11.7
Anovulatory cycles	175	11.0
Involuntary sterility	145	9.1
Oligomenorrhea	69	4.3
Menorrhagia/metrorrhagia	66	4.1
Irregular menstrual cycles	32	2.0
Primary amenorrhea	1	0.1

Corpus Luteum Insufficiency

Corpus luteum insufficiency (also referred to as luteal phase defect) is a manifestation of suboptimal ovarian function. In laboratory terms, corpus luteum insufficiency is usually defined as an abnormally low progesterone level 3 weeks after the onset of menstruation (serum progesterone below 10 to 12 ng/mL). This state is normal during puberty and at menopause; however, it is usually considered abnormal in women between the ages of 20 and 40 years.[12]

Corpus luteum insufficiency points to abnormal formation of ovarian follicles, an abnormality that may be so pronounced that no secondary or tertiary follicles are produced, with a resulting lack of ovulation (anovulation). Corpus luteum insufficiency also leads to a relative deficiency of progesterone. Insufficient levels of progesterone may also result in the formation of ovarian cysts.

Corpus luteum insufficiency may give rise to a myriad of menstrual abnormalities. Table 138-1 lists the most common clinical conditions in 1592 women diagnosed with corpus luteum insufficiency. Foremost are hypermenorrhea (heavy periods), polymenorrhea (abnormally frequent periods), and persistent anovulatory bleeding. Secondary amenorrhea (lack of a period) may sometimes be observed in women with corpus luteum insufficiency.

Disturbances of other hormones may also be associated with corpus luteum insufficiency. One study found hyperprolactinemia in 70% of cases.[13] Also noted is an exaggerated response to the thyroid-releasing hormone test, which is associated with manifest or latent hypothyroidism.

Premenstrual Syndrome and Cyclic Mastalgia

Premenstrual syndrome (PMS) is one of the most common complaints found in gynecology practices. According to some estimates, 30% to 40% of menstruating women are affected by PMS.[14] Table 138-2 lists the different subgroups of PMS and the symptoms associated with them.

TABLE 138-2 **Subgroups of Premenstrual Syndrome (PMS)**

SUBGROUP	SYMPTOMS	PREVALENCE (%)
PSM-S	Anxiety Nervous tension	75-80
PMS-H	Irritability Fluid retention Weight gain Swollen extremities Abdominal bloating Breast tenderness	60-70
PMS-C	Increased appetite Craving for sweets Headache Fatigue Fainting spells	35-40
PSM-D	Depression Insomnia Forgetfulness	30-35

In a double-blind study, 170 women (mean age, 36 years) with a diagnosis of PMS were randomly assigned to receive either 20 mg of a *Vitex* extract (dried ethanolic extract [6-12:1]) or placebo once a day for three menstrual cycles. Twenty-three women were taking oral contraceptives (11 in the *Vitex* group and 12 in the placebo group) during the study period. At the end of the treatment period, women taking the *Vitex* extract had a significantly greater reduction in overall PMS symptom score than those taking placebo ($P < 0.001$). Five of the six self-assessment items indicated a significantly greater reduction for the *Vitex* group with the exception of the item listed "others and bloating," which was measured as unaffected by treatment with *Vitex*. The Clinical Global Impressions (physician's assessment) also showed a significantly greater reduction in PMS symptoms in the *Vitex* group than in the placebo group ($P < 0.001$). The overall response rate was 52% for the *Vitex* group compared with 24% for the placebo group.[15]

One study compared the efficacy of *Vitex* (3.5 to 4.2 mg/day of dried fruit extract) with vitamin B_6 (200 mg/day) in 175 women with premenstrual tension syndrome.[16] Although both agents were effective (the symptom scale decreased from 15.2 to 5.1 in the *Vitex* group and from 11.9 to 5.1 in the vitamin B_6 group), 24.5% of subjects reported excellent results for *Vitex*, compared with only 12.1% for B_6. However, more than twice as many women (12) reported side effects from *Vitex* than from vitamin B_6 (5).

Two double-blind placebo-controlled studies have been conducted in Chinese women. In one double trial in 67 women, *Vitex* reduced the premenstrual syndrome diary (PMSD) sum score from 29.38 at baseline to 4.28 at the third cycle in the treatment group.[17] In the other double-blind study comprising 208 women in the *Vitex* group, the mean total PMSD score decreased from 29.23 at baseline to 6.41 at termination (third cycle) for the treatment group and from 28.14 at baseline to 12.64 at termination (third cycle) for the placebo group.[18] A placebo effect near 50% was found in both studies.

Other studies with *Vitex* for PMS have been uncontrolled or clinical monitoring trials. A monitoring survey of gynecology practices in Germany examined the effect of *Vitex* on 1542 women with a diagnosis of PMS.[19] The patients' mean age was 34.7 years, with a range of 13 of 62 years. Additional diagnoses noted in these patients included corpus luteum insufficiency ($n = 1016$) and uterine fibroids ($n = 170$). Patients were instructed to take 40 drops per day of a *Vitex* liquid extract. The average duration of treatment was 166 days. The efficacy of treatment was assessed by both patients and their physicians. These assessments are listed in Table 138-3.

TABLE 138-3 **Efficacy of *Vitex***

OUTCOME	PERCENTAGE OF PATIENTS
Patient's Assessment	
Improved	57
Relieved	33
No change	4
No data	5
Physician's Assessment	
Very good/good	71
Satisfactory	21
Unsatisfactory	4
No data	3

In more than 90% of the patients, symptoms were completely relieved, with a report of side effects in only 2% (listed in Table 138-3). Only 17 of the 1542 women studied had to stop treatment because of side effects. Improvement in symptoms began after an average treatment duration of 25.3 days. After completion of the monitoring period, 562 patients continued taking *Vitex*. Similar results have been reported in three uncontrolled studies.[20-23]

Vitex has been shown to reduce cyclic breast pain (mastalgia) in many of the PMS studies. In a detailed review, data from randomized and nonrandomized studies regarding the efficacy and safety of *Vitex,* the authors concluded that *Vitex* can be considered a safe and effective agent in the treatment of mastalgia.[24] In one double-blind study of 97 patients suffering from cyclic mastalgia, the intensity of mastalgia, as measured by visual analog score, in patients treated with a liquid product combining *Vitex* with several homeopathic ingredients significantly decreased after one or two treatment cycles and remained reduced after the third cycle.[25] Not only the intensity but also the duration of pain improved on *Vitex* treatment. In the *Vitex* group, after two cycles 50% of patients did not have severe pain at all during menstrual cycle. Clinicians should expect it to take three or four cycles for *Vitex* to work for mastalgia as well.

Hyperprolactinemia

As mentioned previously, *Vitex* has shown a modulating effect on prolactin and is regarded as a useful agent for the treatment of hyperprolactinemia.[26] A double-blind placebo-controlled study examined the effect of *Vitex* on 52 women with luteal phase defects due to latent hyperprolactinemia. The daily dose of the *Vitex* extract was 20 mg and the study lasted for 3 months. Hormonal analysis was performed at days 5 through 8 and day 20 of the menstrual cycle before and after 3 months of therapy. After 3 months of therapy, 37 cases were available for analysis (20 placebo and 17 *Vitex*). Prolactin release was significantly reduced in the *Vitex* group. Both shortened luteal phases and deficits in progesterone production were normalized. No side effects were noted, and two women in the *Vitex* group became pregnant.[27]

Infertility and Secondary Amenorrhea

Twenty patients with secondary amenorrhea were enrolled in a 6-month study using *Vitex* liquid extract at 40 drops daily. Laboratory monitoring of progesterone, follicle-stimulating hormone (FSH), and LH values as well as Papanicolaou smears were

performed before the study and at 3 and 6 months. At the end of the study, data were available in 15 patients. The onset of menstrual cycles was observed with *Vitex* treatment in 10 of the 15 patients. The hormone values showed increased values for progesterone and LH, but FSH values either did not change or dropped slightly.[28]

A nonblinded uncontrolled trial studied the effect of *Vitex* on corpus luteum function in 48 infertile women between 23 and 39 years of age. The inclusion criteria were normal prolactin levels (<20 ng/mL), normal results in the prolactin and thyroid-stimulating hormone tests, and an abnormally low serum progesterone levels (<12.0 ng/mL on the twentieth day of the cycle). Treatment consisted of *Vitex* liquid extract 40 drops daily without any other medication for 3 months. Forty-five women completed the trial (3 were excluded because of concurrent hormone use). The outcome of therapy was assessed through evaluation for normalization of the midluteal progesterone level and correction (lengthening) of any preexisting shortening of the phases of the cycle. Treatment was deemed successful in 39 of the 45 patients. Seven women became pregnant, serum progesterone was restored to normal (>12 ng/mL) in 25 patients, and there was a trend toward normalization of progesterone levels in 7 patients.[29]

A double-blind, placebo-controlled study involving 89 women with infertility, luteal phase defect, or secondary amenorrhea looked at the effect off a liquid *Vitex* extract (32.4 mg) with homeopathic ingredients on progesterone, LH, and prolactin levels and conception rates over a 3-month span. Of the 66 women evaluated at the end of the study, 31 had normal hormone values. More importantly, 15 women (7 with amenorrhea, 4 with infertility, and 7 with luteal phase defect) conceived during the study.[30]

DOSAGE

The recommended daily dose of *Vitex* is a dried or liquid extract delivering the equivalent of 30 to 40 mg of the dried fruit a day.[31] *Vitex* is typically taken once in the morning before breakfast; it should be taken for at least three menstrual cycles to evaluate efficacy.

TOXICOLOGY

Human and animal studies have determined *Vitex* to be safe for most women of childbearing age. *Vitex* is not recommended for use during pregnancy,[32] and its use during lactation is being questioned owing to its possible dopaminergic actions, which might lead to a suppression of lactation. The safety of *Vitex* in children has also not been determined.

TABLE 138-4 **Side Effects from *Vitex* in 1542 Women**

SIDE EFFECT	NO. OF PATIENTS REPORTING
No information	7
Nausea	5
Gastric complaints	3
Acne	3
Changes in menstrual rhythm	2
Diarrhea	2
Erythema	2
Allergy	1
Weight gain	1
Giddiness	1
Heartburn	1
Hypermenorrhea	1
Pruritus	1
Alopecia	1
Cardiac palpitations	1

Data from clinical trials, postmarketing surveillance studies, surveys, spontaneous reporting schemes, manufacturers, and herbalist organizations indicate that the adverse events following *Vitex* treatment are mild and reversible.[33,34] The most frequent adverse events are nausea, headache, gastrointestinal disturbances, menstrual disorders, acne, pruritus, and erythematous rash. Side effects noted in one large population study are listed in Table 138-4.

DRUG INTERACTIONS

Because of theoretical interactions, some authorities suggest that *Vitex* be avoided by women taking oral contraceptives or on hormone therapy.[35] However, two clinical studies have found no adverse interactions in women taking oral contraceptive concomitantly with *Vitex*.[15,23] The potential dopaminergic action of *Vitex* also suggests that it should not be used concomitantly with dopamine antagonist drugs, such as haloperidol and metoclopramide.

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CHAPTER 139

Water: The Most Basic Nutrient and Therapeutic Agent

Herb Joiner-Bey, ND

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Pure water has been undervalued as a therapeutic tool because of a number of false assumptions and beliefs, according to Dr. Fereydoon Batmanghelidj. Conceptual fallacies in regard to the body's need for and use of water are as follows:

- Dry mouth is the only sign of water need.
- Water is merely a passive solvent with no chemical properties of its own.
- The human body can never become depleted of water because water is free and readily available.
- The water needs of the body can easily be met by any commercially prepared fluids.[1]

WATER AND THE HUMAN BODY

Water is the predominant compound in the human body. At birth, a baby's body is 78% water by weight. The average young adult is 70% water, and although the body's water content declines with age, water content remains at no less than 50% even in the geriatric individual. During youth, most cells with the exception of adipose cells are 90% water. In adulthood, two-thirds of body water resides within cells; the remainder resides in the extracellular spaces.[2] Even bone tissue is 22% water.

Water has numerous roles to play in human physiology[3]:

- Building material. Water molecules facilitate the folding of amino acid chains assembled on the basis of DNA genetic sequences and reinforce the structural integrity of proteins. Water molecules fill every space not occupied by other molecules in every nook and cranny of every cell.
- Solvent. The ionic nature of water molecules makes water an excellent solvent of ionic compounds: salts, glucose, amino acids, etc.[4] The tendency of water molecules to surround ions and molecules of solutes allows chemical agents to move freely to wherever they are needed.
- Reaction medium and reactant. The biochemical reactions that sustain life occur within the medium of water. Yet water is not just the medium in the background; it is also an active participant—a reactant in the hydrolysis of macromolecules such as proteins, carbohydrates, and fats. Water is also a by-product of the metabolism of food energy molecules that contain hydrogen: carbohydrates, proteins, and fats.
- Carrier for nutrients and waste products. Water is the transport medium that moves nutrients into cells and waste products out of cells and then out of the body. Water is also the most basic constituent of blood, indispensable to the function of the cardiovascular, respiratory, urinary, and nervous systems.[5]
- Thermoregulation. The electromagnetic bonds among water molecules give water a great capacity to absorb heat, hold heat, and resist temperature changes. This property allows water to support homeostasis by helping to maintain body temperature. In addition, the evaporation of water from the skin as perspiration releases heat sufficiently to maintain body temperature even when the surrounding atmospheric temperature is higher than body temperature.
- Lubricant. Water combines with molecules forming viscous substances that lubricate and protect tissue functions. Examples include the mucus of the respiratory and gastrointestinal mucous membranes, synovial fluid in joints, saliva, tears, etc.
- Shock absorber. Within the cell, water takes the structural configuration of a gel that maintains cellular shape and form. This property cushions tissues against the shock of movement and mild trauma. Water molecules have an affinity for the electronegative molecules of connective tissue matrix (e.g., chondroitin, keratin,

etc.), including the nucleus pulposus of the vertebral discs. It is the water molecules surrounding the compounds of the connective tissue matrix that provide the cushioning effect.

Causes of Dehydration

The most common are:
- Vomiting
- Diarrhea
- Blood loss
- Malnutrition
- Failure to replenish liquids lost from sweating and urination

THIRST: THE SENSE THAT CANNOT BE TRUSTED

The osmoreceptors in the hypothalamus are sensitive to only certain solutes in the blood (e.g., sodium) but insensitive to others (e.g., urea).[6] Thus, the osmoreceptors are not accurate gauges of blood solute concentration and water need at the cell level. The "thirst center" of the hypothalamus, triggered by osmosreceptor reaction to solute concentration, is distinct from the osmoreceptors.

Unfortunately for optimal hydration, the sense of thirst in the mouth (dryness) is quickly and easily satiated by small amounts of water, stimulating the moisture receptors within the mucous membranes of the mouth, throat, and upper gastrointestinal tract. Although thirst returns if the osmoreceptors and thirst center are not satiated, the body is caught in a game of catch-up that it can never win because it is never allowed to be in a continuous state of optimal hydration.

Signs and Symptoms of Dehydration

Clinical dehydration is a serious medical condition that must be treated immediately. Here are the indications to look for:
- Fatigue and weakness
- Headache
- Rough, dry skin
- Dry mucous membranes in the nose, mouth, or throat
- Nosebleeds (especially in dry interior air during winter)
- Dark, concentrated, strong-smelling urine produced in small quantities
- Irritability
- Irrational behavior
- Constipation
- Nausea
- Intestinal cramps
- Weak, irregular pulse
- Low blood pressure
- Shallow, rapid breathing

Sources of Water for the Body

Human beings derive their water intake from these basic sources:
- Beverages (70% to 80%)
- Foods with high water content (20% to 30%)
- Liberation of water molecules during oxidative metabolism of food sources[7]

Water Losses from the Body

Water exits the body via several portals:
- Skin—insensible perspiration (450 mL daily in temperate climates). Of course elevations in body temperature can lead to massive increases in water losses in the form of sweat.
- Kidneys—1 to 2 L of urine daily. Water loss via urine increases during hyperglycemia (diabetes mellitus) as well as in disorders involving antidiuretic hormone (vasopressin).
- Respiratory mucous membranes—breath (250 to 350 mL daily). Additional water loss occurs during respiratory infections, which trigger increased discharge of mucous secretions.
- Digestive system, including feces (200 mL daily). Dramatic water losses arise from disorders whose symptoms include vomiting and/or diarrhea.

Perspiration is hypotonic; that is, it has lower electrolyte content than plasma or extracellular fluid. This phenomenon means that sweating leads to more water loss than electrolyte loss. As the electrolyte concentration in the extracellular fluid rises, it draws water out of cells (intracellular fluid), leading to cellular dehydration. This state of hypertonic dehydration demands replenishment with hypotonic beverages, such as pure water. Water need supersedes salt need during endurance exercise.[8]

Factors That Influence Water Need

Water intake requirements vary according to individual needs and circumstances. Some of the factors that affect water need are
- Physical activity/exercise
- Metabolism
- Diet
- Ambient atmospheric temperature
- Humidity
- Health status

Ideal Water Intake

In units of liters per day, the water intake levels recommended by the U.S. Food and Nutrition Board, based on age and gender, are as follows[9]:
- Infants, 0.7 to 0.8 L
- Children
 - 1 to 3 years, 1.3 L
 - 4 to 8 years, 1.7 L
- Males
 - 9 to 13 years, 2.4 L
 - 14 to 18 years, 3.3 L
 - 19+ years, 3.7 L
- Females
 - 9 to 13 years, 2.1 L
 - 14 to 18 years, 2.3 L
 - 19+ years, 2.7 L
 - During pregnancy, 3.0 L
 - During lactation, 3.8 L

Hydration for Athletes and Laborers

The National Athletic Trainers' Association has published guidelines for athletic hydration. Here are some highlights of their recommendations that apply equally to "weekend warriors" and those involved in heavy physical labor[10]:
- Establish hydration protocols, accommodating sweat rate, rest breaks, fluid access, environmental factors, acclimatization state, exercise duration and intensity, and personal preferences.
- Make fluid-replacement beverages easily accessible in individual containers to permit easier monitoring of fluid intake.

- Ensure that athletic activity begins in a well-hydrated state. Pre-exercise hydration entails consuming 500 to 600 mL (17 to 20 fl oz) of water 2 to 3 hours before exercise and 200 to 300 mL (7 to 10 fl oz) of water 10 to 20 minutes before exercise.
- Replace fluids sufficiently to meet sweat and urine losses and maintain hydration by preventing at less than 2% body weight reduction. This need requires 200 to 300 mL (7 to 10 fl oz) every 10 to 20 minutes.
- Hydrate postexercise to correct any fluid loss, ideally within 2 hours after exercise. When rehydration must be rapid, compensate for urine losses during rehydration by drinking 25% to 50% more than sweat losses to assure optimal rehydration 4 to 6 hours after exercise.
- Be alert for signs and symptoms of dehydration—thirst, irritability, general discomfort, followed by headache, weakness, dizziness, cramps, chills, vomiting, nausea, head or neck heat sensations, and decreased performance.

PURE WATER VERSUS OTHER BEVERAGES

By definition, *osmosis* is the diffusion of water molecules from a place of relatively high concentration across a semipermeable membrane to a place of relatively low concentration. The amount of pressure that must be applied against this osmotic movement of water is called osmotic pressure. It is a measure of how vigorously water is attempting to cross the membrane. The differences in water concentration across membranes define the "water concentration gradient" across that membrane. Thus, the osmotic pressure is proportional to the concentration gradient. The higher the water concentration on one side of the membrane relative to the other side, the higher the osmotic pressure and the greater the vigor of movement of water molecules across the membrane. Any solutes dissolved in water outside the membrane decrease the water concentration gradient across the membrane and the vigor of water movement. If the concentration of solutes in the water outside the cell is less than the concentration of solutes within the cell, the concentration of water molecules will be greater outside the cell than within it. Therefore, water molecules will move by osmosis down their concentration gradient from the exterior to the interior and the cell will be hydrated.[11]

Conversely, if the concentration of solutes is higher in the exterior than the interior, water molecules are in higher concentration within the cell. Therefore, water molecules will move down their concentration gradient from the interior to the exterior; thus the cell becomes dehydrated.

Obviously, the beverage that has the least amount of solutes and therefore the highest osmotic drive to hydrate the body down to the cellular level is pure water. If anything is dissolved in water (coffee, tea, sugar, flavorings, colors, protein, etc.), osmosis is reduced. Body and cell hydration are therefore inhibited by the consumption of beverages containing solutes. Thus the basic principles of physiology indicate that pure water is the beverage of choice for optimal hydration of the body.[12]

WATER TEMPERATURE

According to the principles of traditional Chinese medicine, the consumption of cold food and drink is a bane of optimal health and wellness among Western people. The interior temperature of the body is higher than oral, axillary, or rectal temperature. For example, the interior temperature of the stomach is about 102° F and that of the heart is approximately 106° F. These warm temperatures are appropriate for the optimal physiologic functions and biochemical processes that sustain life. The ingestion of large amounts of cold food and beverages tends to inhibit these processes.

For this reason, it is prudent to ensure that water consumed is at room temperature or warmer.

SPECIAL NEEDS

Particular care must be taken to adequately hydrate people who, because of special circumstances, may need an even greater intake of water than recommended above. These persons include the following:

- Infants fed high-protein formulas (with caution not to overhydrate infants)
- Persons eating high-protein diets
- Patients suffering from disorders whose symptoms include fever, vomiting, diarrhea, respiratory discharges, and other types of water loss
- Patients taking diuretics
- People living in environments with high atmospheric temperatures

PHYSIOLOGY OF WATER METABOLISM

Oxygen Transport

In the alveoli and in tissue capillaries and connective tissue, water is the medium in which gas exchange occurs. Without the ready solubility of oxygen and carbon dioxide in water, gas exchange in living systems would not be possible. Oxygen diffuses from atmospheric air into the water of alveolar tissues and plasma before it associates with hemoglobin in red blood cells. After being carried to peripheral tissue capillaries, oxygen dissociates from hemoglobin into the water of plasma and connective tissue. Water carries oxygen into the cell through membrane aquaporins.[13,14]

Role of Water in Protein Structure and Function

The function of a protein is determined by its form—its three-dimensional shape. The unique sequence of amino acids, coded by human DNA, determines the shape or form of a protein. That sequence is determined by the sequence of the coding genes on chromosomal DNA that initiate the synthesis of that protein.[15]

Water molecules provide the environment that not only allows proteins to function but also supports their endeavors in unrecognized ways. In order to fulfill their respective missions, the amino acid strands of proteins must bend, twist, and contort their primary linear structure into secondary, tertiary, and quaternary forms. The hydrophobic and hydrophilic interactions between water and amino acid strands drive the conformational changes needed for proteins to realize their ultimate functional shapes. The final shape of a protein is determined by the manner in which water and amino acid strands are bonded to each other. As a lubricating agent, water facilitates the breaking and reestablishing of hydrogen bonds and other links between the various parts of protein. Once the appropriate bonding is in place, water molecules are critical to the continued integrity and stability of protein structure.[16] It can therefore be suggested that the DNA genetic code is arranged in a fashion that specifically anticipates the conformational interaction of water molecules required to finish protein-generating tasks.[17,18]

Cell Hydration and Cell Behavior

Because of the lack of routine techniques for measuring cell hydration and volume in patients, naturopaths and conventional practitioners alike often fail to consider cell hydration state during clinical assessment. This is an unfortunate oversight because of the effect of cell hydration state on the behavior of cells.

There is evidence that cell hydration state is an important determinant of protein and RNA turnover—anabolism and catabolism. It appears that hormones and amino acids modify protein turnover, partly by altering the cell hydration state, which alters cell volume. Changes in cell volume can serve as signals mediating hormone and amino acid effects, which control protein turnover. Increases in cell volume (swelling) inhibit protein catabolism and RNA degradation while stimulating the synthesis of protein, DNA, and RNA. Loss of cell volume (shrinkage) has the opposite effect on RNA, DNA, and protein. Consequently, cell swelling stimulates anabolic proliferative metabolism, while cell shrinkage has a catabolic and antiproliferative influence.[19,20]

In view of the protein catabolism that arises in disease states, researchers have proposed that cell shrinkage or loss of cellular volume caused by a loss of intracellular water volume, as is often seen in skeletal muscle and liver tissue, may be a common endpoint triggering protein catabolism in a variety of disease states.

CLINICAL APPLICATIONS

Hydration and the Elderly

Dehydration is one of the most common causes of hospitalization among persons over the age of 65. It has been estimated that one half of those admitted for clinical dehydration die within a year of admission.

There are many factors leading to clinical and subclinical dehydration among seniors:

- Lower body water percentage
- Lack of awareness of hydration needs
- Lack of mental clarity and attentiveness to personal needs
- Illnesses that accelerate water loss by inducing vomiting, fever, and/or diarrhea
- Decline of thirst sensation with age

Gradual total body dehydration is a hallmark of the aging process. In addition, the preponderance of body water shifts gradually with age from cell interiors to the exterior connective tissue. Even death itself is frequently linked to dehydration. Long-term chronic disease eventually wears the body down to the point where patients can no longer ingest water and food, ultimately succumbing to dehydration.

To make matters worse, our sense of thirst declines with age. Researchers have concluded that after water deprivation, "there is a deficit in thirst and water intake in healthy elderly men, as compared with younger men." This is true despite the fact that the antidiuretic hormone response is maintained.[21]

Chronic "subclinical" dehydration (or "hypohydration") contributes to the aging process. In its struggle for survival, the body shifts precious resources away from processes that increase longevity toward those needed for short-term survival.

Winter Hydration

The human body loses water in many ways during winter. Some are obvious; others are not:

- Exercising in cold weather mutes the experience of sweating in many people, deceiving them into thinking that their bodies are not losing much water.
- Cold air cannot hold as much moisture as warm air. Therefore winter air is drier than summer air. The drier air draws more water from the lungs as we breathe, so we exhale more moisture during winter months.
- Interior environments are usually very dry in the winter because of the use of dehumidifying heating methods. The decreased interior humidity increases water loss from the lungs and skin.
- When the body gets chilled, blood is shifted away from the periphery toward the interior organs to preserve vital heat. The shunting of blood to the interior increases renal arterial flow, glomerular filtration rate, and urine output. This effect is called cold diuresis.
- Cold weather increases body metabolism and the associated water needs required to maintain healthy body temperature.
- Respiratory illnesses of winter cause the body to generate large amounts of mucus in order to dispose of pathogens. The water in these discharges must be replaced.
- Intestinal influenza, with diarrhea and vomiting, requires additional water and perhaps electrolyte replacement.

Dehydration and Jet Lag

The cabin atmospheric pressure of modern passenger jets is equivalent to that found on land at an elevation of 8000 ft above sea level. Although the relative humidity of the Sahara Desert is typically 20% to 25%, the humidity of jet cabin air can be as dry as 1% to 10%. For these reasons, dehydration is a major factor in the experience of jet lag. People should keep thoroughly hydrated with pure water and avoid the other beverages offered by flight attendants. It is prudent to drink at least 8 ounces of pure water per hour.

Effect of Hydration State on Blood Flow

Whole-blood viscosity has been identified as an independent risk factor for atherosclerosis and cardiovascular events. The most dangerous time of day for heart attack is the last period of sleep and the first few hours in the morning after awakening. A number of factors may play a role in this trend; hydration state may be one of them. Overnight fasting from fluid intake increases blood viscosity and adversely affects blood flow (rheology) to major organs. Consumption of 200 mL of water under these circumstances helps normalize blood flow to major organs.[22]

Cognitive-Motor Function and Hydration State

In young adults, neither cognitive-motor function nor neurophysiologic function differs between people under water deprivation and controls. On the other hand, subjective ratings of mental performance during water deprivation point to increased fatigue as well as impaired alertness and the concentration needed to complete tasks. Healthy people tend to employ compensating mechanisms for increased fatigue and reduced alertness. Test of reaction time reveal significant gender differences in the response to dehydration. Water deprivation induces a prolonged reaction time in women but a shortened one in men.[23]

Multiple-Organ-System Effects of Chronic Subclinical Dehydration

The insidious effects of chronic hypohydration are wide ranging and staggering. Consider the following effects:

- Disintegration of cellular structure
- Impaired flow of nutrients into the cell due to compromised membrane protein channels and insufficient carrier solvent (water)

- Local tissue resistance to endocrine hormones due to faulty integrity and responsiveness of membrane receptors
- Chronic fatigue due to lack of enzyme-catalyzed energy production[24]
- Free radical damage to cell structures, including DNA, due to reduced enzymatic free radical scavenging
- Inadequate repair of nuclear DNA damage due to faulty enzyme repair activity
- Reduced production of key bioactive compounds, such as hormones, digestive enzymes, neurotransmitters, etc.
- Accumulation of toxins within cells
- Increased synthesis of histamine within the central nervous system[25]
- Chronically elevated levels of antidiuretic hormone (vasopressin)
- Chronically elevated levels of cortisol, with adverse effects on bone integrity, muscle mass, connective tissue, blood pressure, and immunity[2]

Subclinical Dehydration (Hypohydration): The Missing Diagnosis

Water cures nothing except dehydration. However, once dehydration has been corrected at the cellular level, healing is possible. This is because hypohydration at the cellular level is a major contributing factor to many ailments. Based on years of research with inmates of an Iranian prison, Dr. Fereydoon Batmanghelidj has proposed a new paradigm of disease and healing. It states that the suffering associated with many disorders is triggered or worsened by dehydration.

The reason for this effect is that, under the stress of dehydration, the body takes desperate measures to conserve water. Part of this effort involves the synthesis and release of histamine. It appears that histamine release activates other systems designed to save body water. Antidiuretic hormone decreases water loss in urine. Histamine and kinin compounds influence the escape of water from capillaries into connective tissue. Decreasing blood water content decreases blood volume and increases plasma sodium concentration, activating the renin-angiotensin system and vasopressin to elevate blood pressure.[4,5,26]

A key concept of Dr. Batmanghelidj's new paradigm is based on his years of clinical observation and practice with only the simplest crude healing tools at his disposal. He writes, "Chronic cellular dehydration painfully and prematurely kills. Its initial outward manifestations have until now been labeled as diseases of unknown origin."

Recurrent noninfectious conditions associated with pain and discomfort in various parts of the body, which cannot be explained by other identifiable causes, can be interpreted as expressions of water deficits at the sites of the tissue manifesting symptoms.[4,27]

COMMON CONDITIONS IMPROVED BY WATER

On the basis of empiric experience, the scope of application of water as a therapeutic tool is immense. The only caveat is that kidney filtration must be intact and healthy to allow the excretion of water and accompanying toxins. The following is a list of disorders in which water therapy is indicated:

- Coronary heart disease
- Peptic ulcers
- Arthritis
- Hypertension
- Low back pain
- Intermittent claudication
- Fibromyalgia
- Migraine headache
- Hangover headache
- Constipation
- Colitis
- Obesity
- Edema of unknown origin
- Chronic fatigue syndrome

A few of these are considered in more detail below.

Coronary Heart Disease and Fatal Myocardial Infarction

It has been known for some time that high blood and plasma viscosity, high hematocrit, and high blood concentrations of fibrinogen are correlated with coronary heart disease and atherosclerosis. Remarkably, even high "normal" levels of these parameters are considered independent risk factors.[16,24,26-33] These factors have also been linked to intermittent claudication.[31] High hematocrit has been associated with tachycardia, the magnitude of heart tissue damage from myocardial infarction, reduced oxygen transport, and reduced blood supply to heart tissue.

Based on this evidence, researchers at the Heart Institute of Loma Linda University analyzed lifestyle data to determine what influence the consumption of pure water and other beverages would have on the risk of fatal heart attack.

Compared with those who drank two or fewer glasses of pure water daily, men who drank five or more had only 46% of the risk of having a fatal heart attack and women had only 59% of the risk. Even more remarkable, compared with those who drank two or fewer glasses of fluids other than pure water (e.g., tea, soft drink, juice, etc.), women who drank five or more had 147% greater risk and men had 46% greater risk. Moreover, these relative risk relationships held regardless of adjustments for any other factors. In essence, the consumption of pure water decreases the risk of fatal heart attack; consumption of other beverages increases the risk.[25]

According to the researchers, failing to drink enough water can be as harmful to heart health as smoking. Just by increasing pure water intake, one can reduce the risk of death from heart attack by one half. This amount of benefit is greater than that gained by ceasing smoking, reducing cholesterol, exercising, or maintaining ideal body weight. Thus, increasing one's intake of pure water could be the cheapest and simplest method of reducing fatal heart attack risk imaginable.

Peptic Ulcers and Dyspepsia

These conditions were the first that brought hidden, subclinical dehydration to the attention of Dr. Batmanghelidj in the Iranian prison. Thousands of cases successfully treated with water therapy lend credence to this modality. Chronic inflammation of the stomach and duodenum, with heartburn and acid reflux, are prime indications for water intervention. The concept here is not farfetched when the function of the intestinal organs is understood. The gastrointestinal mucous membranes must produce sufficient mucus to protect themselves from damage from digestive acid and enzymes. All of these secretions are water-based. Hypohydration inhibits both digestion and membrane protection. In addition, water deficits reduce the volume of bicarbonate-containing fluids released from the pancreas. This deficit results in a failure to properly neutralize stomach acid, leading to duodenal ulcers.[34]

Asthma and Allergies

Histamine is a prime mediator of allergy and asthma. It is generated in the central nervous system when the body is dehydrated. It is also released by mast cells located on the mucous membranes of the respiratory and gastrointestinal tracts. Histamine works with the immune system, facilitating the movement of white blood cells to sites of microbial invasion.

Of particular note is the new scientific light being shed on exercise-induced asthma. Studies indicate that dehydration during exercise can increase the intensity of asthma symptoms in persons subject to asthmatic attacks. Dehydration can increase spasms of the bronchial smooth muscle because of overly dry airway membranes. Dehydration of mucous membranes occurs before the asthmatic athlete even begins training. Dehydrated asthmatics begin exercise with reduced hydration capacity; therefore, a pathologic respiratory state occurs more rapidly. Researchers have concluded that "Exercise induced asthma is an exaggerated airway response to airway dehydration." Airway narrowing from exercise in elite athletes and otherwise healthy subjects is now considered a physiologic response to pathologic changes in airway cells resulting from "dehydration injury."[35] These changes also occur in healthy subjects exercising intensely for long periods and breathing cold air, dry air, or both.[36]

In order to minimize the risk of asthmatic attacks during exercise, it is imperative for the athlete to be in a state of optimal hydration before training begins and for good hydration status to be maintained throughout the exercise and during recovery. Pure water can be a very dear friend to an asthmatic.

Migraine Headache

As with allergies and asthma, histamine is believed to be a contributing factor in migraine headache.[37] Hypohydration induces the central nervous system to increase its synthesis of histamine. Thus, optimal hydration should minimize histamine synthesis as well as associated migraine headache. Anecdotal clinical evidence is mounting in support of pure water as a helpful adjunct to other natural approaches.

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CHAPTER 140

Zingiber officinale (Ginger)

Michael T. Murray, ND

Zingiber officinale (family: Zingiberaceae)
Common name: ginger

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GENERAL DESCRIPTION

Ginger is an erect perennial herb with thick tuberous rhizomes (underground stems) from which the aerial stem grows to a height of 2 to 4 ft. Grasslike alternate leaves 6 to 12 in. long and 0.75 in. wide shoot off from the aerial stem. Wild ginger produces a beautiful flower, but cultivated ginger rarely flowers.

Although ginger is native to southern Asia, it is now extensively cultivated throughout the tropics (e.g., India, China, Jamaica, Haiti, and Nigeria). Jamaica is the major producer, with exports to all parts of the world amounting to more than 2 million pounds annually.

The knotted and branched rhizome, commonly called the root, is the portion of ginger used for culinary and medicinal purposes. Extracts and the oleoresin are produced from dried unpeeled ginger, because peeled ginger loses much of its essential oil content.[1,2] Ginger oil is produced from the fresh ginger via steam distillation.

CHEMICAL COMPOSITION

The following compounds have been isolated from ginger:[1,2]

- Starch (up to 50%)
- Protein (about 9%)
- Lipids (6% to 8%) composed of triglycerides, phosphatidic acid, lecithins, and free fatty acids
- A protease (2%)
- Volatile oils (1% to 3%), the principal components of which are sesquiterpenes (bisabolene, zingiberene, and zingiberol) and various "pungent" principles, aromatic ketones, known collectively as gingerols vitamins (especially niacin and vitamin A)
- Resins

The pungent principles are thought to be the most pharmacologically active components of ginger. Gingerol and its derivatives can be found in concentrations as high as 33% in ginger oleoresin (Figure 140-1). The fresh oleoresin will have a higher percentage of the more pungent gingerol, because gingerol can be dehydrated during storage to form shogaol or have its fatty acid moiety cleaved to form zingerone (Figures 140-2 and 140-3). The oleoresin is made by extracting the oily and resinous materials with the aid of a solvent (alcohol, hexane, or acetone). Pharmacokinetic studies in humans show that the major pungent principles are absorbed after oral dosing and can be detected as glucuronide and sulfate conjugates in the blood.[3]

HISTORY AND FOLK USE

Ginger has been used for thousands of years in China for medicinal purposes. Chinese records dating from the fourth century B.C. indicate that it was used to treat the following conditions[1]:

- Stomachache
- Diarrhea
- Nausea

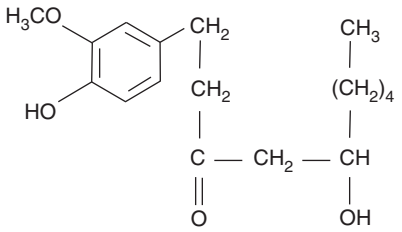


FIGURE 140-1 Gingerol.

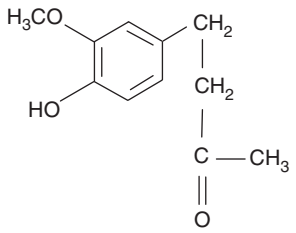


FIGURE 140-2 Zingerone.

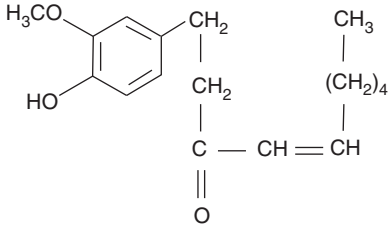


FIGURE 140-3 Shogaol.

- Cholera
- Hemorrhage
- Rheumatism
- Toothache

It was used by eclectic physicians in the United States in the late 1800s as a carminative, diaphoretic, appetite stimulant, and local counterirritant.[4]

Ginger is widely used as a spice, especially in Asian and Indian cuisine. It is also used in many baked goods, beverages (ginger ale), candy, liqueurs, and cosmetic products (perfumes, soaps, creams, etc.).

PHARMACOLOGY

Ginger possesses numerous pharmacologic properties; the following are the most relevant:

- Antioxidant effects
- Inhibition of prostaglandin, thromboxane, and leukotriene synthesis
- Inhibition of platelet aggregation
- Cholesterol-lowering actions
- Choleretic effects
- Cardiotonic effects
- Gastrointestinal actions
- Thermogenic properties
- Antibiotic activities

Antioxidant Effects

Ginger has shown antioxidant effects in experimental studies.[5] In a study in rats, ginger significantly lowered lipid peroxidation by maintaining the activities of the antioxidant enzymes superoxide dismutase, catalase, and glutathione peroxidase. The blood glutathione content was significantly increased in ginger-fed rats. To achieve a similar effect with vitamin C, the dosage required was 100 mg/kg body weight.[6]

Ginger's strong antioxidant properties have led to its being investigated for preventing the development of rancidity in meat products.[7] Ginger has been shown to prolong the shelf life of fresh, frozen, and precooked pork patties. Because the use of many synthetic antioxidants is prohibited by law, ginger may one day be used commercially to extend the shelf lives of meats and other foods.

Effects on Prostaglandin and Leukotriene Metabolism

Numerous constituents in ginger have been shown to be potent inhibitors of prostaglandin and leukotriene synthesis through blocking of the cyclooxygenase enzymes.[8-13] The most potent components appear to be the pungent principles, although the aqueous extract has also demonstrated inhibition. Inhibition of prostaglandin and leukotriene formation could explain some of ginger's historic use as an antiinflammatory agent. However, ginger and its extracts also have strong antioxidant activities, and fresh ginger contains a protease with action that may be similar to that of other plant proteases (e.g., bromelain, ficin, papain) on inflammation.[1] Repeated ginger administration to mice augmented corticosteroid secretion, indicating that chronic ingestion may produce an antiinflammatory effect via this mechanism as well.[14]

Effects on Platelets and Fibrinolysis

Ginger, like garlic and onions, is an inhibitor of platelet aggregation.[11] However, ginger's effects may be far more powerful. In a comparison, an aqueous extract of ginger was shown to exert greater inhibitory effects on platelet aggregation than aqueous garlic and onion extracts.[15] Ginger was shown to produce a greater inhibition on thromboxane formation and proaggregatory prostaglandins. Ginger but not onion or garlic also significantly reduced platelet lipid peroxide formation. In another model, gingerol compounds and their derivatives were more potent antiplatelet agents than aspirin.[11]

The superiority of ginger over onions was also demonstrated in a controlled study.[16] Female volunteers given either 70 g raw onion or 5 g raw ginger demonstrated that ginger has a pronounced effect in lowering platelet thromboxane production, whereas onion actually produced a mild elevation (pooled results).

In addition to acting on platelets, ginger promotes fibrinolysis. In one study, administration of 50 g of fat to 30 healthy adult volunteers decreased fibrinolytic activity from a mean of 64.20 to 52.10 U.[17] Supplementation of 5 g of ginger powder with the fatty meal not only prevented the drop in fibrinolytic activity but actually increased the activity significantly.

Cholesterol-Lowering and Hepatic Effects

Ginger has been shown to significantly reduce serum and hepatic cholesterol levels in cholesterol-fed rats by impairing cholesterol absorption as well as stimulating cholesterol-7-alpha-hydroxylase, the rate-limiting enzyme of bile acid synthesis.[18-20] In addition, ginger has been shown to increase bile secretion.[21] Therefore, ginger works to lower cholesterol by promoting excretion and impairing absorption.

Cardiotonic and Hypotensive Properties

Gingerol has shown potent cardiotonic activity (positive inotropic and chronotropic effects) on isolated guinea pig left atria.[22,23] These effects are a result of acceleration of calcium uptake by the

sarcoplasmic reticulum. Gingerol was the first substance shown to produce these effects.

Individuals with heart problems or high blood pressure are probably better off using fresh ginger rather than a dried preparation. This recommendation is based not only on the fact that gingerol is the more potent cardiotonic but also on the demonstration that shogaol has a blood pressure–elevating effect in animals.[24] Gingerol is found predominantly in fresh ginger, whereas shogaol is rarely found in dried ginger.

Analgesic Effects

Ginger has demonstrated analgesic effects in experimental studies in animals.[25] This effect is thought to be a result of inhibition by shogaol of the release of substance P, much like that by capsaicin, the pungent principle of red pepper *(Capsicum frutescens)*.

Gastrointestinal Smooth Muscle Effects

Another aspect of ginger is its ability to simultaneously improve gastric motility and exert antispasmodic effects. This action is consistent with its use as a gastrointestinal tonic. A lipophilic ginger extract was shown in one study to enhance gastric motility, as evidenced by increased intestinal transport of a charcoal meal fed to rats,[26] and various fat-soluble components of ginger, such as galanolactone, demonstrated antagonism of serotonin receptor sites.[27] This latter mechanism may be responsible for ginger's antispasmodic effects on visceral and vascular smooth muscle.

In a human study, 1000 mg of dried ginger did not affect lower esophageal sphincter (LES) pressure at rest or esophageal contractile amplitude and duration when swallowing, but caused more relaxation of the LES (after 90, 150, and 180 minutes, when swallowing) and decreased the esophageal contraction velocity, which may produce the expulsion of gastric gas or have an antiflatulant effect.[28] Ginger has also been shown to inhibit serotonin-induced diarrhea and exert antiemetic effects in experimental models.[29,30]

Via inhibition of prostaglandin production, ginger also prevents the slow-wave dysrhythmias produced by acute gastrointestinal hyperglycemia.[31]

Ginger accelerates gastric emptying and stimulates antral contractions in healthy volunteers.[32] Oral ginger extract was also shown to improve gastroduodenal motility in the fasting state and after a standard test meal in healthy human volunteers.[33]

Antiulcer Effects

Ginger has demonstrated significant antiulcer effects in a variety of animal models.[34-36] Ginger prevents ulcer formation due to ethanol, indomethacin, aspirin, and other common ulcerogenic compounds. The pungent principles appear to be responsible for this effect. In one study, roasted ginger inhibited ulcer formation in three gastric ulcer models, but dry ginger had no such effect.[37]

A methanol extract of the dried powdered ginger rhizome, fractions of the extract, and the isolated constituents, gingerol and shogaol were tested against 19 strains of *Helicobacter pylori*—a bacterium associated with peptic ulcers and gastric cancer. The methanol extract of ginger rhizome inhibited the growth of all 19 strains in vitro with a minimum inhibitory concentration range of 6.25 to 50 mg/mL. One fraction of the crude extract, containing the gingerols, was active and inhibited the growth of all strains with a minimum inhibitory concentration range of 0.78 to 12.5 μg/mL.[38]

Thermogenic Properties

Ginger is noted for its apparent ability to subjectively warm the body and has historically been used as a diaphoretic. In animal studies, ginger has been shown to help maintain body temperature and to inhibit serotonin-induced hypothermia.[29,39]

Crude extracts and the pungent components of ginger have been shown to increase oxygen consumption, perfusion pressure, and lactate production in the perfused rat hind limb.[40] These effects signify increased thermogenesis. Gingerol is the most potent thermogenic component of ginger. A human study demonstrated that consuming a ginger sauce (containing unspecified amounts of ginger principles) with a meal had no significant effect on metabolic rate.[41] However, there were two problems with this study: (1) the concentration of gingerol in the preparation used was probably low or zero and (2) the effective concentration range of gingerol for its thermogenic effects is quite narrow.

Given ginger's historic use as a "warming" substance, these scientific investigations appear to support its use as a diaphoretic and thermogenic aid, although confirmation in humans is still lacking.

Antibiotic Activity

Ginger, shogaol, and zingerone have been shown to be strongly inhibitory against *Salmonella typhi*, *Vibrio cholerae*, and *Trichophyton violaceum*, whereas aqueous extracts at 2.5%, 5%, and 25% concentrations have been shown to be effective against *Trichomonas vaginalis*.[42] Ginger and its pungent principles were also demonstrated to possess significant antifungal activity against pathogenic yeast.[43]

Anticancer Effects

Ginger extracts and some pungent constituents present in ginger have exhibited antitumor activity in experimental models of carcinogenesis.[44]

CLINICAL APPLICATIONS

Ginger is widely used as a condiment for its unique flavors, but from the previously described pharmacology, it obviously has important medicinal effects as well. In general, like many other culinary herbs and spices such as garlic and onions, ginger provides many health-promoting effects. Specifically, ginger provides benefit to many body systems, including the digestive, hepatobiliary, and cardiovascular systems.

Historically, the majority of complaints for which ginger was used concerned the gastrointestinal system. A clue to ginger's efficacy in alleviating gastrointestinal distress is offered in several double-blind studies on motion sickness, hyperemesis gravidum, and postoperative nausea and vomiting. Human studies have also shown a positive effect in arthritis and migraine headaches. These studies are discussed below.

Motion Sickness

Ginger was first shown to be effective in treating motion sickness by Mowrey and Clayson[45] in 1982. In their study, ginger (940 mg) was shown to be far superior to dimenhydrinate (Dramamine) 100 mg in relieving symptoms of nausea and vomiting. Since this initial study, several better-designed follow-up studies have evaluated the effectiveness of ginger as a motion sickness medication.

The appearance of motion sickness trials using ginger prompted an interest in ginger by the National Aeronautics and Space Administration, which subsequently funded a study at Louisiana State University. This study compared ginger, both fresh and dried powdered, with scopolamine by measuring the number of head movements experimental subjects could make in a rotating chair until they reached an endpoint defined as motion sickness short of vomiting. Ginger was not shown to produce any protection against motion sickness in this model or in two additional protocols (vestibular stimulation only and combined vestibular-visual stimulation).[46] However, in a double-blind trial, perhaps a more "real life" test, ginger (1 g) given to naval cadets unaccustomed to sailing in heavy seas was shown to reduce the tendency to vomiting and cold sweating in comparison with a placebo.[47]

Mowrey and Clayson[45] proposed that the anti–motion sickness effects of ginger were due to local gastrointestinal tract effects rather than to central nervous system effects. Although ginger's mechanism of action in alleviating gastrointestinal distress has yet to be fully elucidated, there is evidence to support this hypothesis. Ginger has been shown to partially inhibit the excessive gastric motility characteristic of motion sickness.[46] To further support a gastric versus a central nervous system mechanism of action, one study clearly demonstrated that neither the vestibular system nor the oculomotor system, both of which are critical in the occurrence of motion sickness, was influenced by ginger (1 g).[48] However, in a double-blind crossover placebo-controlled study, ginger (1 g) was shown to significantly reduce induced vertigo but not nystagmus.[49]

It has been hypothesized by others that ginger ameliorates the nausea associated with motion sickness by preventing the development of gastric dysrhythmias and the elevation of plasma vasopressin. To test this hypothesis, 13 volunteers with a history of motion sickness underwent circular vection, during which nausea (scored 0 to 3, i.e., none to severe), electrogastrographic recordings, and plasma vasopressin levels were assessed with or without ginger pretreatment in a crossover double-blind randomized placebo-controlled study.[50] Circular vection induced a maximal nausea score of 2.5 and increased tachygastric activity and plasma vasopressin. Pretreatment with ginger (1000 and 2000 mg) effectively reduced nausea, tachygastric activity, and vasopressin release induced by circular vection.

The overall effectiveness of ginger in motion sickness has yet to be definitively determined. Issues that the studies have raised include the variability in the quality of commercial ginger preparations and the time required for ginger to produce its effects. Commercial preparations vary widely in chemical composition and often contain adulterants, and in the ginger study conducted at sea, ginger reduced symptoms of cold sweating and vomiting only at the end of 4 hours. In other words, it appears that ginger may prove to be more effective when well-defined preparations are given at least 4 hours before motion is experienced.

Nausea and Vomiting

Ginger's antiemetic action has been studied in hyperemesis gravidum, the most severe form of pregnancy-related nausea and vomiting. This condition usually requires hospitalization. In a double-blind randomized crossover trial, ginger root powder at a dose of 250 mg four times a day brought about a significant reduction in both the severity of the nausea and the number of attacks of vomiting in 19 of 27 patients in the early stages of pregnancy (<20 weeks).[51]

Another natural approach to nausea and vomiting of pregnancy is vitamin B_6. In one double-blind study, 138 women were given either 500 mg of ginger or 10 mg of vitamin B_6 three times daily for 3 days.[52] Subjects graded the severity of their nausea using visual analog scales before treatment and recorded the number of vomiting episodes in the previous 24 hours and again during three consecutive days of treatment. The ginger and vitamin B_6 significantly reduced the nausea scores from 5 to 3.6 and 5.3 to 3.3, respectively and the number of vomiting episodes from 1.9 to 1.2 and 1.7 to 1.2, respectively. There was no significant difference between ginger and vitamin B_6 for the treatment of nausea and vomiting during pregnancy. However, in another study, ginger was shown to be more effective.[53] In that study, 70 women were randomized to receive either ginger 1 g/day or vitamin B_6 40 mg/day for 4 days. Subjects graded the severity of their nausea using a visual analog scale and recorded the number of vomiting episodes in the 24 hours before treatment and during 4 consecutive days while taking treatment. Compared with baseline, the decrease in scores of posttherapy nausea in the ginger group was significantly greater than that for the vitamin B_6 group. In the ginger group, 29 of 35 women reported an improvement in nausea symptoms compared with 23 of 34 women in the vitamin B_6 group. These results indicate that ginger is more effective than vitamin B_6 for relieving the severity of nausea and is equally effective for decreasing the number of vomiting episodes in early pregnancy.

In a placebo-controlled study, 70 women with nausea and vomiting of pregnancy were randomly assigned to receive either oral ginger 1 g/day or an identical placebo for 4 days.[54] Subjects graded the severity of their nausea using visual analog scales and recorded the number of vomiting episodes in the 24 hours before treatment, and again during 4 consecutive days during treatment. At a follow-up visit 7 days later, the number of vomiting episodes had decreased significantly in the ginger group; 28 of 32 in the ginger group had improvement in nausea symptoms, compared with 10 of 35 in the placebo group.

In a double-blind study comparing ginger with dimenhydrinate, 170 pregnant women with the symptoms of nausea and vomiting in pregnancy were randomly allocated to take one capsule of ginger twice daily (one capsule contained 0.5 g of ginger powder) while the patients in group B received the identical capsule of 50 mg dimenhydrinate twice daily. Results showed that ginger is as effective as dimenhydrinate in the treatment of nausea and vomiting during pregnancy and has fewer side effects. In particular, there was a statistically significant difference in the side effect of drowsiness after treatment in diphenhydramine group compared with the ginger group (78% versus 6%, respectively).[55]

These clinical results and those reported by others,[56-60] along with the safety and the relatively small dose of ginger required and the problems (e.g., teratogenicity) with antiemetic drugs in pregnancy, support the use of ginger for nausea and vomiting in pregnancy. This recommendation is becoming a well-accepted prescription even in orthodox obstetric practices.

Ginger appears to be very safe for use during pregnancy. In a cohort study of women exposed to ginger during pregnancy, all of whom used it during the first trimester, the results indicated that there is no higher risk for major malformations with ginger use. In fact, the only statistical differences between the pregnancy outcomes of the ginger and the comparison groups were the numbers of low-birth-weight infants (<2500 g): only 3 in the ginger group compared with 12 in the comparison group.[54]

The antiemetic action of ginger has also been observed in women who had undergone major gynecologic surgery. In four double-blind studies, 1000 to 1500 mg of dried powdered ginger

root per day was shown to significantly reduce the incidence of nausea compared with placebo in a manner similar to the drug metoclopramide.[61-64]

Ginger also has shown good results in alleviating chemotherapy-induced nausea and vomiting. In one study, 60 chemotherapy cycles of cisplatin/doxorubicin in bone sarcoma patients were randomized to ginger root powder capsules or placebo capsules as an additional antiemetic to ondansetron and dexamethasone in a double-blind design.[65] Acute moderate to severe nausea was observed in 28 of 30 (93.3%) cycles in the control group as compared with 15 of 27 (55.6%) cycles in the ginger group. In a study in women receiving cisplatin for gynecologic cancers, the addition of ginger to a standard antiemetic regimen had no advantage in reducing nausea or vomiting in the acute phase of cisplatin-induced emesis; however, after the initial 24 hours postcisplatin, ginger was shown to be equal to metoclopramide.[66] In still another study, ginger provided no additional benefit in reducing the prevalence or severity of acute or delayed chemotherapy-induced nausea and vomiting when given with 5-HT3 receptor antagonists and/or aprepitant [Emend].[67]

Inflammatory Conditions

Ginger's ability to inhibit the formation of inflammatory prostaglandins, thromboxanes, and leukotrienes along with its strong antioxidant activities and protease component suggest a possible benefit in inflammatory conditions. To test this hypothesis, a preliminary clinical study was conducted in seven patients with rheumatoid arthritis, in whom conventional drugs had provided only temporary or partial relief.[68] One patient took 50 g/day of lightly cooked ginger, and the other six took either 5 g of fresh or 0.1 to 1 g of powdered ginger daily. All patients reported substantial improvement, including relief of pain, greater joint mobility, and decreased swelling and morning stiffness.

In the follow-up to this study, 28 patients with rheumatoid arthritis, 18 with osteoarthritis, and 10 with muscular discomfort who had been taking powdered ginger for periods ranging from 3 months to 2.5 years were evaluated. On the basis of their clinical observations, Srivastava and Mustafa[69] reported that 75% of the patients with arthritis and 100% of the patients with muscular discomfort experienced relief in pain or swelling. The recommended dosage was 500 to 1000 mg/day, but many patients took three to four times this amount. Patients taking the higher dosages also reported quicker and better relief.

Three double-blind studies with standardized and highly concentrated extracts of ginger provide additional support for the usefulness of ginger in osteoarthritis, although in one study ginger was effective only after 3 months of use.[70-72] In the largest of the three studies with the concentrated ginger extract, 261 patients with osteoarthritis of the knee were given either ginger extract or placebo twice daily, with acetaminophen allowed as rescue medication.[71] The primary efficacy variable was the proportion of responders experiencing a reduction in "knee pain on standing," with use of an intent-to-treat analysis. The percentage of responders experiencing a reduction in knee pain on standing was superior in the ginger extract group to that in the control group (63% versus 50%). Analysis of the secondary efficacy variables revealed a consistently greater response in the ginger extract group compared with the control group in the following mean values: reduction in knee pain on standing (24.5 versus 16.4 mm), reduction in knee pain after walking 50 ft (15.1 versus 8.7 mm), and reduction in the Western Ontario and McMaster Universities' Osteoarthritis Composite Index (12.9 versus 9 mm). Change in global status and reduction in intake of rescue medication were also numerically greater in the ginger extract group.

One evaluation looking at ginger's ability to reduce muscle pain consisted of two identical double-blind, placebo-controlled randomized studies with participants consuming either 2 g of either raw (study 1) or heated (study 2) ginger or placebo for 11 consecutive days.[73] Participants performed 18 eccentric actions of the elbow flexors to induce pain and inflammation. Pain intensity, perceived effort, plasma prostaglandin E(2), arm volume, range of motion, and isometric strength were assessed prior to and for 3 days after exercise. Raw and heat-treated ginger resulted in similar pain reductions 24 hours after eccentric exercise compared with placebo (25% and 23% reduction, respectively). In another study, a single 2-g dose of ginger did not attenuate eccentric exercise-induced muscle pain, inflammation, or dysfunction 45 minutes after ingestion, indicating that ginger's effects are likely more cumulative in reducing the day-to-day progression of muscle pain.[74]

It has also been reported that ginger is beneficial in migraine headache.[75] Given ginger's effects on platelets, eicosanoids, and serotonin inhibition, this recommendation makes sense.

DOSAGE

Many questions remain concerning the best form of ginger and the proper dosage. Most research studies have used 1 g of dried powdered ginger root. Practically speaking, this is a small dose. For example, ginger is commonly consumed in India at a daily dose of 8 to 10 g. Furthermore, although most studies have used powdered ginger root, fresh (or possibly freeze-dried) ginger root or extracts (concentrated for gingerol) at an equivalent dosage may yield even better results because they may deliver higher levels of gingerol as well as the active protease.

In the treatment of nausea and vomiting due to motion sickness or pregnancy or after surgery, a dosage of 1 to 2 g of dried powdered ginger may be effective. This would be equivalent to approximately 10 g or 1/3 oz of fresh ginger root, roughly a 1/4-in. slice. For inflammatory conditions like rheumatoid arthritis, the dosage should be double this amount.

For ginger extracts standardized to contain 20% gingerol and shogaol, an equivalent dosage in treating motion sickness or nausea and vomiting would be 100 to 200 mg. For other applications, the dosage is 100 to 200 mg three times daily.

TOXICOLOGY

Ginger does not appear to produce any toxicity problems when used at normal dosages. Although ginger extracts and several components in ginger have been shown to possess potent mutagenic activity, ginger also contains several equally potent antimutagenic substances.[76,77] The significance of this mutagenicity (the study was conducted in *Escherichia coli* and did not use the Ames test) has not been entirely determined, but the long history of ginger's use and the lack of carcinogenic or toxic effect in animals suggest that toxicity is not a problem.

In acute toxicity tests in mice, ginger extract administered as a lavage was tolerated up to 2.5 g/kg with no mortality or side effects during a 7-day trial period.[78] Increasing the dosage to 3 to 3.5 g/kg resulted in a 10% to 30% mortality rate. In comparison, 0.6 g/kg of aspirin produced mortality in 25%, stomach ulcers in 40%, and hypothermia in 60% of subjects.

Some individuals consuming high doses—more than the equivalent of 6 g of dried powdered ginger—alone on an empty stomach may experience some gastrointestinal discomfort. Administration of 6 g of dried powdered ginger has been shown to increase the exfoliation of gastric surface epithelial cells in human subjects.[79] This effect may cause some gastric distress and ultimately could lead to ulcer formation. Therefore, it is recommended that dosages consumed on an empty stomach be less than 6 g.

DRUG INTERACTIONS

Ginger may potentiate antiplatelet therapy.[80] However, ginger administration had no such effect in 12 healthy male subjects who received coumadin alone or with ginger. No changes in platelet aggregation, the international normalized ratio of prothrombin time, warfarin enantiomer protein binding, warfarin enantiomer concentrations in plasma, or S-7-hydroxywarfarin concentration in urine were seen.[81]

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SECTION 6

SPECIFIC HEALTH PROBLEMS

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This section is both a therapeutic handbook and a study of the origins and causes of disease. Each disease is thoroughly discussed, with particular emphasis on the biochemistry of the altered physiology leading to the symptomatology and pathology. We also discuss, as appropriate, the aspects of genetics and lifestyle leading to the disorder. Finally, we present a comprehensive therapeutic regimen using relatively natural and nontoxic therapies.

Although we believe this to be the most effective way to present the material, we are extremely concerned that it could continue to promote the disease orientation of the current dominant medical system. We can only offer the following suggestion: Always treat the patient, not the disease!

All recommendations made here should be considered in the context of the whole patient. Our purpose is to help our patients to become well, not to simply alleviate symptoms and allow the true cause(s) of their disease to continue unabated. We therefore recommend that readers carefully study Sections 1 and 4 be before reading this section, and that the psychological and spiritual reasons people may have for being sick always be considered.

ORGANIZATION

In general, each chapter is divided into the following five parts:

- Diagnostic summary—a brief list of the key diagnostic elements
- General considerations—a discussion of the underlying pathology and altered physiology
- Therapeutic considerations—a discussion of the correctable deficiencies and various natural therapies that may be used to treat the underlying pathophysiology
- Therapeutic approach—a concise therapeutic regimen
- References—thorough referencing of our discussion to aid those who seek further study of our treatment rationale

The section is arranged alphabetically by disease name. Please also use the Index to look for diseases, as some are addressed in other disease chapters or within a grouping; for example, depression is discussed in the chapter "Affective Disorders."

To aid us in the further development of this textbook, we welcome comments. In particular, we are greatly interested in well-documented successes, and failures, of the use of these procedures. We would also appreciate recommendations for therapeutic and diagnostic approaches not included here.

CHAPTER 141

Acne Vulgaris and Acne Conglobata

Michael Traub, ND, DHANP, FABNO, and Michael T. Murray, ND

DIAGNOSTIC SUMMARY

- Open comedones—dilated follicles with central dark, horny plugs (blackheads)
- Closed comedones—small follicular papules with (red papules) or without (whiteheads) inflammatory changes
- Superficial pustules—collections of pus at follicular opening
- Nodules—tender collections of pus deep in dermis
- Cysts—from nodules that fail to discharge contents to the surface
- Large deep pustules—from nodules that break down adjacent tissue, leading to scars

GENERAL CONSIDERATIONS

Acne vulgaris is characterized as a pilosebaceous disease with comedones, papules, and pustules, whereas acne conglobata is a more severe form, with cyst formation and subsequent scarring. The lesions occur predominantly on the face and, to a lesser extent, on the back, chest, and shoulders. It is more common in males, and onset is typically at puberty (somewhat later for the conglobata form).

Etiology

Acne is the most common of all skin problems. A key factor is genetics. It is inherited in an autosomal dominant pattern with incomplete penetrance. If both parents had acne, 3 of 4 children will have acne. If 1 parent had acne, then 1 of 4 of the children will have acne.[1]

The on sent of acne vulgaris usually reflects an increase in pilosebaceous gland size and sebum secretion due to androgenic stimulation. The severity and progression are determined by a complex interaction among hormones, keratinization, sebum, and bacteria.

The lesions begin in the upper portion of the follicular canal, with hyperkeratinization being the first microscopic change. This leads to blockage of the canal, resulting in dilation and thinning. Eventually a comedone is formed. The formation of open or closed comedones appears to be related to the degree of keratinization and the level of blockage of the duct.

Despite a large amount of purulent exudate in pustular and cystic lesions, the only bacteria commonly cultured are normal skin species. *Propionibacterium acnes* is believed to release lipases that hydrolyze sebum triglycerides into free fatty acid lipoperoxides, thus promoting an inflammatory cascade.

Acne-like lesions can occur in response to various compounds: corticosteroids, halogens, isonicotinic acid, diphenylhydantoin, and lithium carbonate. Exposure to various industrial pollutants also causes acne: machine oils, coal tar derivatives, and chlorinated hydrocarbons. Cosmetics, pomades, overwashing, and repetitive rubbing can produce acne.

Endocrinologic Aspects

Acne is considered to be an androgen-dependent condition, and androgen excess, either systemic or local, is associated with more severe forms of the disease. Androgens control sebaceous gland secretion and exacerbate the development of abnormal keratinizing follicular epithelium. Endocrine disorders producing excess androgens are important etiologic factors: idiopathic adrenal androgen excess, partial defect in 21-hydroxylase, and polycystic ovary syndrome. Free testosterone,

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dehydroepiandrosterone, dehydroepiandrosterone sulfate, and low sex-hormone-binding globulin levels have all been implicated.[2-4] The skin of acne patients shows greater activity of 5-α-reductase, the enzyme that converts testosterone to a more potent androgen, dihydrotestosterone.[5,6] This increased activity is independent of systemic levels of androgens and may explain the poor correlation between systemic levels of androgens and the severity of the acne lesions. Receptors for growth hormone and insulin-like growth factor (IGF-1) are present on the sebaceous gland and these hormones stimulate sebum production. Conditions of growth hormone excess (such as acromegaly) are associated with increased sebum production and acne. Insulin at high levels can interact with IGF-1 receptors. IGF-1 promotes expression of enzymes responsible for androgen biosynthesis and conversion. Elevated cortisol due to chronic stress thickens sebum. The stress of acne compounds this problem.

THERAPEUTIC CONSIDERATIONS

Effective treatment of acne is a significant clinical challenge. Success can be obtained only by the rigorous, comprehensive application of dietary, nutritional, and botanical interventions.

Diet

Although there is some controversy regarding diet in the etiology of acne, there is clear evidence of an association. In Western societies, acne vulgaris is a nearly universal skin disease afflicting 79% to 95% of the adolescent population. Among men and women older than 25 years, 40% to 54% have some degree of facial acne, and clinical facial acne persists into middle age in 12% of women and 3% of men. In contrast, epidemiologic evidence suggests that acne incidence rates are considerably lower in non-Western societies. For example, researchers found no cases of acne among the Kitavan Islanders of Papua New Guinea and the Ache hunter-gatherers of Paraguay.[7]

The exact diet for acne sufferers to follow has not been evaluated, but foods high in iodine should be eliminated and milk consumption limited.[8] Milk contains estrogens, progesterone, and androgens as well as glucocorticoids and IGF-1.[9] Trans fatty acids and high-fat foods should also be eliminated because they can disrupt sebaceous secretions and increase inflammation. The composition of the diet should be in the range of 45% protein, 35% carbohydrate, and 20% fat, as such a composition produces substantially less 5-α-reduction of testosterone and enhanced cytochrome P450 hydroxylation of estradiol, both therapeutic goals.[10] A high-carbohydrate diet (10% protein, 70% carbohydrate, and 20% fat) has the opposite effect. A diet that encourages a high insulin response chronically could promote acne by resulting in elevated levels of IGF-1.[11,12]

Sugar, Insulin, and Chromium

Many dermatologists have reported that insulin is effective in the treatment of acne, suggesting impaired cutaneous glucose tolerance, insulin insensitivity, or both.[13,14] The insulin was either given systemically (5 to 10 units two to three times a week) or injected directly into the lesion.

One study comparing the results of oral glucose tolerance tests in acne patients showed no differences from controls. However, repetitive skin biopsies revealed that the acne patients' skin glucose tolerance was significantly impaired.[15] One researcher of the role of glucose tolerance in acne coined the term *skin diabetes* to describe the disorder of acne.[16] Considering the known immunosuppressive effects of sugar (see Chapter 56), all concentrated carbohydrates should be strictly eliminated.

High-chromium yeast is known to improve glucose tolerance and enhance insulin sensitivity[17] and has been reported in an uncontrolled study to induce rapid improvement in patients with acne.[18]

NUTRIENTS

Vitamin A

Many studies have demonstrated that retinols, including oral vitamin A, reduce sebum production and the hyperkeratosis of sebaceous follicles. Retinol has been shown to be effective in treating acne when used at high and potentially toxic dosages (i.e., 300,000 to 400,000 IU/day for 5 to 6 months).[19]

Although dosages of vitamin A below 300,000 IU/day for a few months rarely cause toxic symptoms,[19] early recognition is important. Cheilitis (chapped lips) and xerosis (dry skin) generally occur in the majority of patients, particularly in dry weather.

The first significant toxic symptom is usually headache, followed by fatigue, emotional lability, and muscle and joint pain. Laboratory tests appear unreliable for monitoring toxicity, since serum vitamin A levels correlate poorly with toxicity, and serum glutamate oxaloacetate transaminase and serum glutamate pyruvate transaminase are elevated only in symptomatic patients. Of far greater concern is the teratogenicity of massive dosages of vitamin A. Women of childbearing age should use effective birth control during treatment and for at least 1 month after discontinuation.

Contraception counseling is mandatory, and two negative pregnancy test results are required prior to the initiation of vitamin A therapy in women of childbearing potential. The baseline laboratory examination should also include cholesterol and triglyceride assessment, hepatic transaminase levels, and a complete blood count. Pregnancy tests and laboratory examinations should be repeated monthly during treatment.

In the author's experience, vitamin A 150,000 IU daily in an emulsified form has prove to be a reliable and safe means of bringing acne under control.

Zinc

Zinc is also important in the treatment of acne. It is involved in local hormone activation, retinol-binding protein formation, wound healing, immune system activity, and tissue regeneration.

Zinc supplementation in the treatment of acne has been the subject of much controversy and many double-blind studies. Inconsistent results may be due to the differing absorbability of the various zinc salts used. For example, studies using effervescent zinc sulfate show efficacies similar to those of tetracycline, with fewer side effects from chronic use,[20] whereas those using plain zinc sulfate have shown less beneficial results.[21] The majority of patients required 12 weeks of supplementation before good results were demonstrated, although some showed dramatic improvement immediately.

In another study, 66 patients with inflammatory acne were given zinc gluconate (30 mg elemental zinc) or placebo for 2 months.[22] On the basis of the number and severity of lesions, an "inflammatory score" was attributed to each patient. In the placebo group the inflammatory score dropped from 58 to 47 in the 2-month period, whereas in the treatment group the score dropped from 49 to 27. Physicians rated 24 of 32 patients in the zinc group as responders compared with only 8 of 34 in the placebo group.

At least two additional double-blind studies with zinc gluconate provide additional support,[23,24] but unfortunately there have been no studies to date using better absorbed forms of zinc, such as zinc picolinate, citrate, acetate, or monomethionine.

The importance of zinc to normal skin function is well recognized, especially in light of the zinc-deficient syndrome acrodermatitis enteropathica. Zinc is essential for retinol-binding protein and thus for serum retinol levels.[25] Although low levels of zinc increase 5-α-reduction of testosterone, high concentrations significantly inhibit this reaction.[26] Serum zinc levels are lower in 13- and 14-year-old males than in any other age group.[27]

Vitamin E and Selenium

Serum vitamin A levels in rats on vitamin E-deficient diets remain low regardless of the amount of oral or intravenous vitamin A supplementation given. Serum levels return to normal after vitamin E is restored to the diet. Vitamin E has been shown to regulate retinol levels in humans.

Male acne patients have significantly decreased levels of erythrocyte glutathione peroxidase, which normalizes with vitamin E and selenium treatment. Acne in both men and women improves with this treatment,[28] probably owing to inhibition of lipid peroxide formation; it suggests the use of other free radical quenchers.

Pyridoxine

Women with premenstrual aggravation of acne often respond to vitamin B_6 supplementation, reflecting its role in the normal metabolism of steroid hormones.[29] In rats, a vitamin B_6 deficiency appears to cause an increased uptake of and sensitivity to testosterone.[30] However, this observation has never been replicated.

TOPICAL TREATMENTS

Various topical gels, ointments, and creams containing natural products are available to treat acne. The goal of these preparations is the same as that of benzoyl peroxide (i.e., to reduce both the bacterial level and inflammation). Although there are many choices, the most popular formulas are those with tea tree oil azelaic acid, vitamin C, or nicotinamide

Tea Tree Oil

Melaleuca alternifolia, or "tea tree," is a small tree native to only one area of the world: the northeast coastal region of New South Wales, Australia. The leaves, the portions of the plant that are used medicinally, are the source of a valuable therapeutic oil.

Tea tree oil possesses significant antiseptic properties and is regarded by many as the ideal skin disinfectant. This claim is supported by its efficacy against a wide range of organisms (including 27 of 32 strains of *P. acnes*)[31] and its good penetration and lack of irritation to the skin. The therapeutic uses of tea tree oil are based largely on its antiseptic and antifungal properties.

In a study conducted at the Royal Prince Hospital in New South Wales, a 5% tea tree oil solution demonstrated similar beneficial effects as 5% benzoyl peroxide in acne, but with substantially fewer side effects.[32] However, this 5% tea tree oil solution is probably not strong enough for moderate to severe acne. Stronger solutions (up to 15%) should provide even better results. Numerous studies have shown that tea tree oil is extremely safe for use as a topical antiseptic, but it can occasionally produce contact dermatitis.

Azelaic Acid

This naturally occurring nine-carbon dicarboxylic acid has exerted much pharmacologic activity, including antibiotic activity against *P. acnes*. Clinical studies with 20% azelaic acid cream have shown it to produce results equal to those achieved with benzoyl peroxide, tretinoin, and oral tetracycline.[33] It has been shown to be effective in all of the different forms of acne. In order to achieve benefits, azelaic acid must be applied to affected areas twice daily continuously for a period of at least 4 weeks. Treatment must usually be continued for at least 6 months to maintain the benefits produced after the first month.

One review article found a topical cream containing 20% azelaic acid to be as effective as 5% benzoyl peroxide, 4% hydroquinone cream, 0.05% tretinoin, 2% erythromycin, and 0.5 to 1 g/day of oral tetracycline in ameliorating comedonal, papulopustular, and nodulocystic acne but less effective than oral isotretinoin at a dose of 0.5 to 1 mg/kg per day in reducing conglobate acne. The authors suggested that the few side effects of topical azelaic acid and lack of overt systemic toxicity made it a better choice for chronic use than other agents. The lower incidence of allergic sensitization, exogenous ochronosis, and residual hypopigmentation offers a clear advantage over conventional drugs.[34]

Vitamin C

Sodium L-ascorbyl-2-phosphate 5% lotion is a stable vitamin C derivative and highly effective antioxidant that has demonstrated statistically significant improvement when compared with vehicle in all of the parameters measured.[35]

Nicotinamide

Topical nicotinamide inhibits the release of lysosomal enzymes, vasoactive amines, and activity of *P. acnes* lipase. It is well tolerated, does not induce bacterial resistance, and has shown superior efficacy compared with 1% clindamycin gel for moderate inflammatory acne.[36]

PROCEDURAL TREATMENTS

There is a growing interest in the nonmedical treatment of acne. Traditional acne procedures include comedone extraction, intralesional injections, epidermal exfoliation (cryotherapy, peels, microdermabrasion). More recent procedures include the use of various types of lights and lasers. Blue light may be antiinflammatory, reducing the cytokine-induced production of IL-1 alpha in keratinocytes.[37]

OTHER CONSIDERATIONS

Psychological support may be necessary as depression is a common occurrence appearing twofold to threefold more often compared with the general population.[38] In 1948, Sulzberger and Zaidens stated, "There is no single disease which causes more psychic trauma and more maladjustment between parents and children, more general insecurity and feelings of inferiority and greater sums of psychic assessment than does acne vulgaris."[39]

Acne has always been associated with emotional stress, but it is possible that the emotional stress also plays a role in the disease progression. In the 1940s, dermatologists John H. Stokes and Donald M. Pillsbury first proposed a gastrointestinal mechanism for the overlap between depression, anxiety, and skin conditions

such as acne.[40] These doctors hypothesized that emotional states might alter the normal intestinal microflora, increase intestinal permeability, and contribute to systemic inflammation. They also noted that as many as 40% of those with acne have hypochlorhydria and hypothesized that less than adequate stomach acid would set the stage for migration of bacteria from the colon toward the distal portions of the small intestine, as well as an alteration of normal intestinal microflora. The remedies these authors discussed as a means to cut off the stress-induced cycle included administration of Lactobacillus acidophilus cultures long before they were known as probiotics. Many aspects of this gut-brain-skin unifying theory proposed by Stokes and Pillsbury have recently been validated. The ability of the gut microflora and oral probiotics to influence systemic inflammation, oxidative stress, glycemic control, tissue lipid content and even mood itself, may have important implications in acne.[41] Probiotic supplementation is often indicated, given the common use of antibiotics to treat acne.



THERAPEUTIC APPROACH

Acne is a multifactorial disease requiring an integrated therapeutic approach in order to avoid supplement toxicity during treatment. Patients should be checked for treatable causes and underlying hormonal abnormalities before specific therapies are initiated.

The most effective acne medication is isotretinoin (Accutane), a derivative of vitamin A. It is approved only for severe and recalcitrant nodular acne. Concern over the safety and widespread use of this drug is growing. Specifically, reports of intracranial hypertension, depression, and suicidal ideation with isotretinoin use have prompted an examination of its serious and life-threatening potential. A warning was added to its product label for signs of depression and suicidal ideation, and a U.S. Food and Drug Administration–mandated registry is now in place for all individuals prescribing, dispensing, or taking isotretinoin. This registry aims to further decrease the risk of pregnancy and potentially dangerous adverse effects during a course of isotretinoin therapy.

Diet

Eliminate all refined and concentrated carbohydrates and limit high-fat and high-carbohydrate foods. Avoid foods containing trans fatty acids and iodine.

Supplements

- Vitamin A: 150,000 IU/day for 3 months (please read cautions above)
- Vitamin E: 400 IU/day
- Vitamin C: 1000 mg/day
- Zinc: 30 to 45 mg/day (picolinate form may be best)
- Selenium: 200 mcg/day
- Chromium: 200 to 400 mcg daily or brewer's yeast 1 tablespoon twice a day
- Probiotic: 5 to 10 billion live bacteria a day

Physical Medicine

- Sun or ultraviolet lamp
- Fruit acid peels
- Light therapy (blue and red light), intense pulsed light, laser, photodynamic therapy, fractionated light (for acne scars)

Topical Treatments

- Tea tree oil (5% to 15%) preparations
- Azelaic acid (20%) preparations
- Nicotinamide gel (4%)
- Thorough daily cleansing with calendula soap
- Expression of comedones with comedo extractor

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CHAPTER 142

Affective Disorders

Peter B. Bongiorno, ND, LAc, and Michael T. Murray, ND

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DIAGNOSTIC SUMMARY

Depression

The official definition of clinical depression, according to the American Psychiatric Association in its *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, is based on the following eight primary criteria:

- Poor appetite with weight loss or increased appetite with weight gain
- Insomnia or hypersomnia
- Physical hyperactivity or inactivity
- Loss of interest or pleasure in usual activities or decrease in sexual drive
- Loss of energy and feelings of fatigue
- Feelings of worthlessness, self-reproach, or inappropriate guilt
- Diminished ability to think or concentrate
- Recurrent thoughts of death or suicide

The presence of five of these eight symptoms definitely indicates clinical depression; the individual with four is probably depressed. According to the *DSM-IV*, the symptoms must be present for at least 1 month to be called depression. Clinical depression is also referred to as *major depression* or *unipolar depression.*

Dysthymia

Like clinical depression, dysthymia is diagnosed according to *DSM-IV* criteria. In order to be officially diagnosed as dysthymic, a patient must be depressed most of the time for at least 2 years (1 year for children or adolescents) and have at least three of the following symptoms:

- Low self-esteem or lack of self-confidence
- Pessimism, hopelessness, or despair
- Lack of interest in ordinary pleasures and activities
- Withdrawal from social activities
- Fatigue or lethargy
- Guilt or ruminating about the past
- Irritability or excessive anger
- Lessened productivity
- Difficulty in concentrating or making decisions

Manic Phase

- Mood is typically elation, but irritability and frank hostility are not uncommon.
- Signs and symptoms include inflated self-esteem, grandiose delusions, boasting, racing thoughts, decreased need for sleep, psychomotor acceleration, weight loss due to increased activity, and lack of attention to dietary habits.

Seasonal Affective Disorder

- Regularly occurring winter depression frequently associated with summer hypomania

INTRODUCTION

Affective disorders are disturbances in mood. In this context, mood is a prolonged emotional tone dominating an individual's outlook. Normal, typically transient moods (e.g., sadness, grief, elation) are a part of everyday life, making the demarcation between "normal" and "pathologic" often difficult to determine. Depression and mania, either alone or in alternation, are the most common affective disorders, with depression alone being much more common.

In order to separate states of depression that alternate with mania from the more common types of depression (i.e., those uncomplicated by mania), the terms *unipolar* and *bipolar* are commonly used. A unipolar depressive suffers from depression alone, whereas the bipolar depressive suffers from either mania alone or mania alternating with depression. Many nutritional, environmental, and lifestyle factors are discussed in this chapter, and it is important to recognize that they have a much broader scope of clinical application than simply depression and mania. This chapter is really a compilation of many chapters that address factors associated with mood disturbance.

As the biochemistry of mood and behavior have become better understood, many conditions once thought of as having a psychological or sociological etiology are now being shown to have a physiologic or biochemical basis as well. There appear to be at least eight factors that modify the functional state of the brain, thus affecting mood and behavior:

- The individual's genetic makeup
- The particular age of neuronal development, which results in age-specific variability
- The functional plasticity of the brain during development, which contributes to the functional and structural shaping of the system
- The motivational state, affected by various biological drives, which channels behavior toward specific goals by setting priorities or prejudicing the context of particular types of incoming information
- The availability of memory-stored information and related processing strategies
- The environment, which can adjust the incoming information, depending on its momentary significance
- Disease or lesion of the brain, which can cause aberrant functional states
- Conditions of the metabolic/hormonal system or the internal biochemical environment of the central nervous system (CNS)

This chapter focuses on the nutritional, environmental, and lifestyle factors that contribute to affective disorders as well as specific therapies used to alter brain neurotransmitter levels.

There is a spectrum of clinical depression that ranges from mild feelings of depression to the serious consideration of suicide. Mild depression is also known as *dysthymia*. This term, coined in the 1980s, replaced the term *depressive neurosis,* which was used in the 1950s, and the term *depressive personality,* which was used in the 1970s.

DEPRESSION

Approximately 20 million Americans suffer true clinical depression each year, and more than 30 million Americans take antidepressant drugs or anxiolytics. The World Health Organization predicts that depression will become the second most burdensome disease in the world in the coming decade, with the greatest burden of disease in North America and the United Kingdom.[1] The obvious question is: Why are so many people depressed? From a nonphysiologic standpoint, several basic theoretic models of depression attempt to answer this question.

- The "aggression-turned-inward" construct, which, although apparent in many clinical cases, has no substantial proof.
- The "loss model," which postulates that depression is a reaction to the loss of a person, thing, status, self-esteem, or even a habit pattern.
- The "interpersonal relationship" approach, which uses behavioral concepts (e.g., the person who is depressed uses depression as a way of controlling other people, including doctors). This can be an extension and outgrowth of such simple behaviors as pouting, silence, or ignoring something or someone. It fails to serve the need, and the problem worsens.
- The "learned helplessness" model, which theorizes that depression is the result of habitual feelings of pessimism and hopelessness.
- The "biogenic amine" hypothesis, which stresses biochemical derangement characterized by imbalances of biogenic amines.
- The analytical (or adaptive) rumination hypothesis, whereby the ruminative cognitive processes of a person with depression facilitate the solution of complex social problems.

Although the more physiologic biogenic amine model of depression is now the dominant medical model of depression, there is much value to counseling, especially in clear cases of psychological etiology. Of the various psychological theories of depression, the one that may have the most merit is the learned helplessness model developed by Martin Seligman. During the 1960s, Seligman discovered that animals could be trained to be helpless. His animal model provided a valuable clue to human depression as well as serving as the research model to test antidepressant drugs.[2]

The Learned Helplessness Model

Seligman's early experiments were performed on three groups of dogs. The first group of dogs received an escapable electrical shock. The dogs could turn off the shock by simply pressing a panel with their noses. This group of dogs would thus have control. The second group of dogs was "yoked" to the first group. They got exactly the same shocks as the first group but could not turn off the shock. The shock would cease only when the "yoked" dog in the first group would press its nose to the panel. Thus, the second group of dogs had no control over the degree of shock they received. The third group of dogs received no shocks at all.

Once the dogs had gone through this first part of the experiment, they were placed in a "shuttle box," a box separated in the middle by a small barrier that the dogs could jump over. The dogs would be electrically shocked but could escape the shock simply by jumping over the barrier to the other side. Seligman hypothesized that the first and third groups would quickly figure this out but that the second group would have learned to be helpless in that they would believe nothing they could do would matter. Seligman thought that the dogs in the second group would simply lie down and accept the shock.

As predicted, the first and third groups of dogs learned within seconds that they could avoid the shock by jumping over the barrier, whereas the dogs in the second group would simply lie down and not even make an effort to jump over the barrier, although they could see the shockless side of the shuttle box. Seligman and his colleagues went on to show that many humans react in an identical fashion to the animals in these experiments.

The adoption of Seligman's model was revolutionary in psychopharmacology, because it became an effective experiment to test antidepressive drugs. Basically, when animals that had learned to be helpless were given antidepressant drugs, they would unlearn helplessness and start exerting control over their environment. Researchers discovered that when animals learned to be helpless, it resulted in an alteration of brain monoamine content. The drugs would restore proper monoamine balance and alter the animals' behavior. Researchers also discovered that when animals with learned helplessness were taught how to gain control over their environment, their brain chemistry also normalized. The alteration in brain monoamine content in the animals with learned helplessness mirrors the altered monoamine content in human depression.

Although most physicians look quickly to drugs to alter brain chemistry, helping patients to gain greater control over their lives actually produces even greater biochemical changes. One of the most powerful techniques to produce the necessary biochemical changes in the brains of depressed individuals is to teach them to be more optimistic.

Outside the laboratory setting, Seligman discovered that the determining factor on how a person would react to uncontrollable events, either "bad" or "good," was their explanatory style—the way in which they explained events. Optimistic people were immune to becoming helpless and depressed. However, individuals who were pessimistic were extremely likely to become depressed when something went wrong in their lives. Seligman and other researchers also found a direct correlation between an individual's level of optimism and the likelihood of developing not only clinical depression but other illnesses as well.[2] In one of the longer studies, patients were followed for a total of 35 years. Optimists rarely got depressed, but pessimists were extremely likely to battle depression and other psychological disturbances.

THERAPEUTIC CONSIDERATIONS

Modern psychiatry focuses on manipulating neurotransmitter levels in the brain rather than identifying and eliminating the psychological factors responsible for producing the imbalances in serotonin, dopamine, gamma-aminobutyric acid, and other neurotransmitters. Although the use of antidepressants may be important in treating severe depressive illness and threatened suicide, antidepressants have not been shown to work any better than placebo in cases of mild to moderate depression, the most common reason for prescription medication.[4] In fact, 25% of patients taking antidepressants do not even have a diagnosable psychiatric problem.[5] So, the bottom line is that millions of people are using antidepressants for a problem they do not have, and for the people who do have a diagnosable condition, these medications generally do not work. This is a clear mandate to consider natural medicine therapeutics for these mood disorders.

Depression can often be due to an underlying organic or physiologic cause (Box 142-1). Identification and elimination of such an underlying cause should be the primary therapy. In this spirit, the depressed individual needs a comprehensive clinical evaluation.

The basic clinical approach to a person suffering from depression is to ascertain which nutritional, environmental, social, and psychological factors are involved in the disease process. After the diagnosis of depression has been made, it is important to rule out the simple organic factors that are known to contribute to the depression:

- Nutrient deficiency or excess
- Drugs (e.g., prescription, illicit, alcohol, caffeine, nicotine)
- Hypoglycemia
- Stress and feelings of being overwhelmed
- Hormonal derangement
- Allergy
- Environmental factors
- Microbial factors

Each factor is discussed later. Regardless of whether there is an underlying organic cause, counseling is always recommended for the depressed individual.

BOX 142-1 Organic and Physiologic Factors That May Underlie Depression

Preexisting physical condition
- Diabetes
- Heart disease
- Lung disease
- Rheumatoid arthritis
- Chronic inflammation
- Chronic pain
- Cancer
- Liver disease
- Multiple sclerosis

Prescription drugs
- Antihypertensives
- Antiinflammatory agents
- Birth control pills
- Antihistamines
- Corticosteroids
- Tranquilizers and sedatives
- Premenstrual syndrome
- Stress/low adrenal function
- Heavy metals
- Food allergies
- Hypothyroidism
- Hypoglycemia
- Nutritional deficiencies
- Sleep disturbances

Counseling

Although many counseling techniques are useful, the one with the most merit and support in the medical literature is cognitive behavorial therapy (CBT). In fact, CBT has been shown to be as effective as antidepressant drugs in treating moderate depression.[5,6] Although there is a high rate of relapse of depression when drugs are used, the relapse rate for cognitive therapy is much lower. People taking drugs for depression tend to stay on them for the rest of their lives. That is not the case with CBT, because the patient is taught new skills with which to deal with depression.[7]

Psychologists and other mental health specialists trained in cognitive therapy seek to change the way the depressed person thinks about failure, defeat, loss, and helplessness. Cognitive therapists employ five basic tactics.

First, they help patients recognize the negative automatic thoughts that flit through their minds when they feel the worst. The second tactic is disputing the negative thoughts by focusing on contrary evidence. The third tactic is teaching the patient a different explanation to dispute the negative automatic thoughts. The fourth tactic involves teaching patients to avoid rumination (the constant churning of a thought in the mind) by helping them to achieve better control of their thoughts. The final tactic is questioning depression-causing negative thoughts and beliefs and replacing them with empowering positive thoughts and beliefs.

Cognitive therapy does not involve the long, drawn-out process of psychoanalysis. It is a solution-oriented psychotherapy designed to help patients learn new skills and thus improve the quality of their lives.

A second useful technique is interpersonal therapy (IPT), which generally focuses on improving communication skills and

increasing self-confidence and self-esteem. Interpersonal therapy is often used with depression due to loss of a loved one, during life transitions (such as becoming a parent or changing careers), feelings of isolation, and relationship conflicts. A study of 233 women with a history of recurrent depression were given acute IPT once a week, twice a month, or once a month. Of these subjects, 112 achieved remission (as defined as a rating of less than 7 for 3 consecutive weeks on the Hamilton Depression Rating Scale [HDS]) with IPT alone. It was concluded that dosage was not a factor. Interestingly, the once-monthly frequency appeared to be as effective as the once weekly in preventing the recurrence of depressive symptoms. However, it was noted that the attrition rate for twice-monthly therapy was the lowest, raising the idea that patient preferences for treatment frequency may be a factor in determining effectiveness of treatment.[8]

Hormonal Factors

Many hormones are known to influence mood; however, it is beyond the scope of this text to address all of them. Instead, the focus is on the effects of the thyroid and adrenal hormones.

Thyroid Function

Depressive illness is often a first or early manifestation of thyroid disease, as even subtle decreases in available thyroid hormone are suspected of producing symptoms.[9,10] The link between hypothyroidism and depression is well known, but whether the thyroid hypofunction is a result of depression-induced hypothalamic-pituitary-thyroid dysfunction or of thyroid hypofunction, remains to be definitively determined. It is probably a combination. According to the American Association of Clinical Endocrinologists, one in ten Americans suffers from thyroid disease, and almost one half of these remain undiagnosed as hypothyroid. Many of these individuals may be susceptible to depression. Depressed patients should be screened for hypothyroidism, particularly if they complain of fatigue or have other symptoms suggestive of hypothyroidism.

Stress and Adrenal Function

Like that of the thyroid gland, dysfunction of the adrenal gland is closely associated with depression. Often this dysfunction is the result of stress—a major factor to consider in the depressed individual. The patient's level of stress and response to it can be measured with the adrenal stress index. This test measures the levels of cortisol and dehydroepiandrosterone in the saliva. The typical pattern found in depression is an elevated morning cortisol level and a decreased level of dehydroepiandrosterone.

That elevations in cortisol reflect a disturbance in the hypothalamic-pituitary-adrenal (HPA) axis is the basis of the dexamethasone suppression test (discussed later). Defects in HPA regulation seen in affective disorders include excessive cortisol secretion independent of stress responses, abnormal nocturnal release of cortisol, and inadequate suppression by dexamethasone.[11]

The CNS effects of increased endogenous release of cortisol mirror the effects of exogenous cortisol: depression, mania, nervousness, insomnia, and, at high levels, schizophrenia. The effects of glucocorticoids on mood are related to their induction of tryptophan oxygenase (Figure 142-1). This results in the shunting of tryptophan to the kynurenine pathway at the expense of serotonin and melatonin synthesis.[12]

Tests of Hypothalamic-Pituitary Function

The two tests widely used as aids in classifying psychiatric conditions are the dexamethasone suppression test (DST) and the thyrotropin-releasing hormone (TRH) test.[13,14] The basic function of these tests is to determine if the condition is a result of hypothalamic dysfunction and to categorize the psychiatric illness (e.g., severe major affective disorders versus severe psychotic disorders).

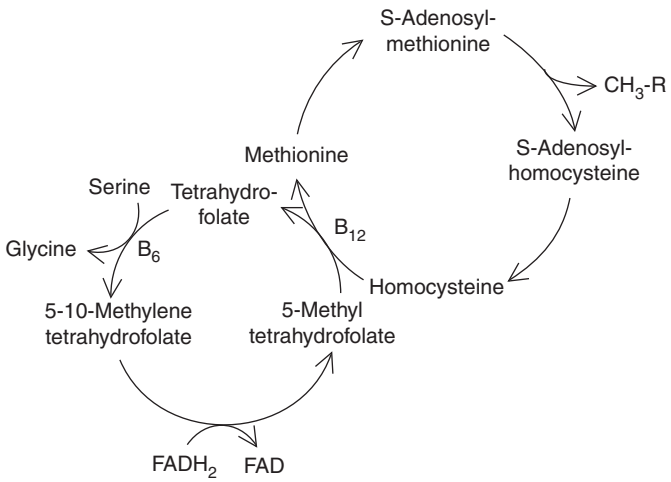


FIGURE 142-1 Tryptophan metabolism.

It is generally held that the DST is of little clinical value as a screening test, and it is debatable whether it offers more information than urinary free cortisol.

Because thyroid hormone assays cannot detect all cases of thyroid hypofunction, they are not an effective screening procedure. The TRH test is significantly more sensitive in diagnosing "subclinical hypothyroidism."[15] A grading system for hypothyroidism as determined by the TRH test has been proposed as follows:

- *Grade 3 (subclinical hypothyroidism—4%).* Patients are usually without classic signs of thyroid failure and have normal T_3RU, T_4, and thyroid-stimulating hormone (TSH) levels but definitely abnormal TSH response to the TRH test.
- *Grade 2 (mild hypothyroidism—3.6%).* Patients may have mild isolated clinical signs or symptoms of hypothyroidism but demonstrate normal T_3RU and T_4 levels. Baseline TSH levels are elevated, and there is an abnormal TRH test.
- *Grade 1 (overt hypothyroidism—1%).* Patients demonstrate signs and symptoms of classic hypothyroidism along with abnormal laboratory values (i.e., reduced T_3RU and T_4 levels, increased TSH levels, and abnormal TRH response).

The TRH test may have wide clinical use, because dysfunction of the thyroid gland is implicated in many conditions.

Environmental Toxins

Heavy metals (lead, mercury, cadmium, arsenic, nickel, and aluminum), as well as solvents (e.g., cleaning materials, formaldehyde, toluene, benzene), pesticides, and herbicides have an affinity to nervous tissue. As a result, various psychological and neurologic symptoms can occur, including the following[16-18]:

- Depression
- Headaches
- Mental confusion
- Mental illness
- Tingling in the extremities
- Abnormal nerve reflexes
- Other signs of impaired nervous system function

A detailed medical history and hair mineral analysis are possible screening mechanisms for environmental toxicity. Refer to Chapter 23 (Metal Toxicity: Assessment of Exposure and Retention) for further discussion.

Lifestyle Factors

A health-promoting lifestyle and diet are important in the treatment of depression. Particularly important is the cessation of smoking, excessive alcohol consumption, excessive sugar intake, and intake of caffeine. These lifestyle changes, coupled with regular exercise and a healthful diet, are more than likely to produce better clinical results than fluoxetine (Prozac), with no side effects and at no cost.

Smoking

Cigarette smoking is one of the major factors contributing to premature death. Cigarette smoking is also a significant factor in depression. Central to the effect of nicotine is the stimulation of adrenal hormones, including the secretion of cortisol. Elevated cortisol levels are a well-recognized feature of depression.[3] One of the key effects of cortisol (and stress) on mood is the activation of tryptophan oxygenase, resulting in the delivery of less tryptophan to the brain. Because the level of serotonin in the brain depends on the level of tryptophan, cortisol dramatically reduces the level of serotonin and melatonin. In addition, cortisol also down regulates serotonin receptors in the brain, making them less sensitive to the serotonin that is available.

Cigarette smoking also leads to a relative vitamin C deficiency, as the vitamin C is used to detoxify the cigarette smoke. Low levels of vitamin C in the brain can result in depression and hysteria.[19]

Alcohol

Alcohol, a brain depressant, increases adrenal hormone output, interferes with many brain cell processes, and disrupts normal sleep cycles. Chronic alcohol ingestion will also deplete a number of nutrients and mood-enhancing prostaglandin E1, all which will disrupt mood. Alcohol ingestion also leads to hypoglycemia. The resultant drop in blood sugar produces a craving for sugar because it can quickly elevate blood sugar. Unfortunately, increased sugar consumption ultimately aggravates the hypoglycemia. Hypoglycemia aggravates the mental and emotional problems of the alcoholic. Treatment options that can address both the depression and addiction of the individual simultaneously are best.[20] Supplementation with selenium can improve mood stability and help change drinking habits as well (see the section on selenium later).

Caffeine

Although caffeine is a well-known stimulant, the intensity of response to caffeine varies greatly, with people prone to feeling depressed or anxious tending to be especially sensitive to caffeine. The term *caffeinism* is used to describe a clinical syndrome similar to generalized anxiety and panic disorders; its symptoms include depression, nervousness, palpitations, irritability, and recurrent headache.[21]

Several studies have looked at caffeine intake and depression. For example, one study found that among healthy college students, those who drank moderate to large amounts of coffee scored higher on a depression scale than those who drank less. Interestingly, the heavier coffee drinkers also tended to perform significantly less well academically.[22] Several other studies have shown that depressed patients tend to consume fairly large amounts of caffeine (e.g., more than 700 mg/day).[23,24] In addition, caffeine intake has been positively correlated with the degree of mental illness in psychiatric patients.[25,26]

The combination of caffeine and refined sugar seems to be even worse than either substance consumed alone. Several studies have found an association between this combination and depression. In one of the most interesting studies, 21 women and 2 men responded to an advertisement requesting volunteers "who feel depressed and don't know why, often feel tired even though they sleep a lot, are very moody, and generally seem to feel bad most of the time."[27] After baseline psychological testing, the subjects were placed on a caffeine- and sucrose-free diet for 1 week. Those subjects who reported substantial improvement were then challenged in a double-blind fashion. They took either a capsule containing caffeine and a Kool-Aid drink sweetened with sugar or a capsule containing cellulose and a Kool-Aid drink sweetened with NutraSweet. Each challenge lasted up to 6 days. About 50% of test subjects receiving the caffeine and sucrose became depressed during the test period.

Another study using a similar format found that 7 of 16 depressed patients were depressed with the caffeine and sucrose challenge but symptom-free during the caffeine- and sucrose-free diet and test period with cellulose and NutraSweet.[28]

The average American consumes 150 to 225 mg of caffeine daily, or roughly the amount of caffeine in one to two cups of coffee. Although most people appear to tolerate this amount, some are more sensitive to the effects of caffeine than others. Even small amounts of caffeine, as found in decaffeinated coffee, are enough to affect them adversely. Patients with depression or any psychological disorder should be advised to avoid caffeine completely.

Exercise

Regular exercise may be the most powerful natural antidepressant available. In fact, many of the beneficial effects of exercise noted in the prevention of heart disease may be related just as much to its ability to improve mood as to its improvement of cardiovascular function.[29] Furthermore, obesity is associated with depression.[30] Various community and clinical studies have clearly indicated that exercise has profound antidepressant effects.[31] These studies have shown that increased participation in exercise, sports, and physical activities is strongly associated with decreased symptoms of anxiety, depression, and malaise. Furthermore, people who participate in regular exercise have higher self-esteem, feel better, and are much happier than people who do not exercise.

Much of the mood-elevating effect of exercise may be attributed to the fact that regular exercise has been shown to increase the level of endorphins, which are directly correlated with mood.[32] One of the most interesting studies that examined the role of exercise and endorphins in depression compared the beta-endorphin levels and depression profiles of 10 joggers with those of 10 sedentary men of the same age. The 10 sedentary men tested were more depressed, perceived greater stress in their lives, and had higher levels of cortisol and lower levels of beta-endorphins. As the researchers stated, this "reaffirms that depression is very sensitive to exercise and helps firm up a biochemical link between physical activity and depression."[33]

At least 100 clinical studies have now evaluated the efficacy of an exercise program in the treatment of depression. In an analysis of the 64 studies before 1980, physical fitness training

TABLE 142-1 **Behavioral Effects of Some Vitamin Deficiencies**

DEFICIENT VITAMINS	BEHAVIORAL EFFECTS
Thiamine	Korsakoff's psychosis, mental depression, apathy, anxiety, irritability
Riboflavin	Depression, irritability
Niacin	Apathy, anxiety, depression, hyperirritability, mania, memory deficits, delirium, organic dementia, emotional lability
Biotin	Depression, extreme lassitude, somnolence
Pantothenic acid	Restlessness, irritability, depression, fatigue
Vitamin B_6	Depression, irritability, sensitivity to sound
Folic acid	Forgetfulness, insomnia, apathy, irritability, depression, psychosis, delirium, dementia
Vitamin B_{12}	Psychotic states, depression, irritability, confusion, memory loss, hallucinations, delusions, paranoia
Vitamin C	Lassitude, hypochondriasis, depression, hysteria

was shown to relieve depression and improve self-esteem and work behavior.[34]

Unfortunately, the quality of many of the studies was less than ideal. However, because of the good results noted in the analysis of these studies, a flurry of well-designed studies were conducted in the 1980s to better determine how effective exercise could be as a therapy. These studies used stricter scientific criteria than the earlier ones, yet they produced similar results. It was concluded that exercise can be as effective as other treatments, including drugs and psychotherapy.[35] More recently, even stricter studies have further demonstrated that regular exercise is a powerful antidepressant.[31,36,37]

The best exercises are either strength training (weight lifting) or aerobic activities such as walking briskly, jogging, bicycling, cross-country skiing, swimming, aerobic dance, and racquet sports.

Nutrition

A deficiency of any single nutrient can alter brain function and lead to depression, anxiety, and other mental disorders (Table 142-1). However, the role of nutrient deficiency is just the tip of the iceberg with regard to the role of effects on the brain and mood. Melvin Werbach, MD, has stated the following[38]:

It is clear that nutrition can powerfully influence cognition, emotion, and behavior. It is also clear that the effects of classical nutritional deficiency diseases on mental function constitute only a small part of a rapidly expanding list of interfaces between nutrition and the mind. Even in the absence of laboratory validation of nutritional deficiencies, numerous studies using rigorous scientific designs have demonstrated impressive benefits from nutritional supplementation.

A high-potency multiple vitamin provides a good nutritional foundation on which to build. In selecting a multiple vitamin and mineral formula, it is important to make sure that it provides the full range of vitamins and minerals at high potency levels. Deficiencies of a number of nutrients are quite common in depressed individuals. The most common deficiencies are folic acid, vitamin B_{12}, and vitamin B_6. The significance of these deficiencies is discussed later.

Dietary Guidelines

Because the brain requires a constant supply of blood sugar, hypoglycemia must be avoided. Symptoms of hypoglycemia can range from mild to severe and include the following:

- Depression, anxiety, irritability, and other psychological disturbances
- Fatigue
- Headache
- Blurred vision
- Excessive sweating
- Mental confusion
- Incoherent speech
- Bizarre behavior
- Convulsions

Several studies have shown hypoglycemia to be common in depressed individuals.[39-42] A study of six countries showed a highly significant correlation between sugar consumption and the annual rate of depression.[43] Simply eliminating refined carbohydrate from the diet is occasionally all that is necessary for effective therapy in patients who have depression due to reactive hypoglycemia.

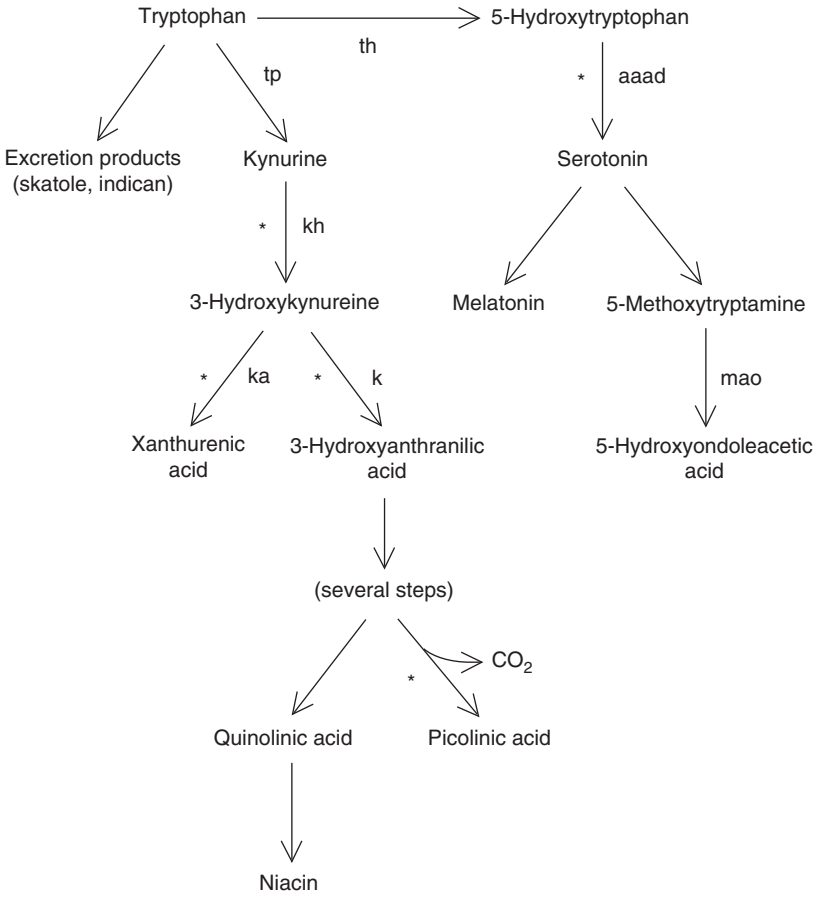
The dietary guidelines for depression are identical to those for optimal health. It is now well established that certain dietary practices cause and others prevent a wide range of diseases. Quite simply, a health-promoting diet provides optimal levels of all known nutrients and low levels of food components that are detrimental to health, such as sugar, saturated fats, cholesterol, salt, and food additives. A health-promoting diet is rich in whole "natural" and unprocessed foods. It is especially high in plant foods such as fruits, vegetables, grains, beans, seeds, and nuts, because these foods contain not only valuable nutrients but also additional compounds that have remarkable health-promoting properties. Although no one diet is a fit for everyone, a 4½ year study of over 10,000 people reported that those who ate a healthy Mediterranean diet, as detailed in Chapter 44, were about one half as likely to develop depression than those who said they did not stick to the diet.[44]

Folic Acid and Vitamin B_{12}

Folic acid and vitamin B_{12} function together in many biochemical processes. Folic acid deficiency is the most common nutrient deficiency in the world. In studies of depressed patients, 31% to 35% have been shown to be deficient in folic acid.[45-48] In elderly patients this percentage may be even higher. Studies have found that among elderly patients admitted to a psychiatric ward, the number with folic acid deficiency ranged from 35% to 92.6%.[49,50] Depression is the most common symptom of a folic acid deficiency. Vitamin B_{12} deficiency is less common than that of folic acid but it can also cause depression, especially in the elderly.[51,52] Correcting folic acid and vitamin B_{12} deficiencies results in a dramatic improvement in mood.

Folic acid, vitamin B_{12}, and S-adenosylmethionine, a form of the amino acid methionine known as SAMe, function as "methyl donors" (Figure 142-2). They carry and donate methyl molecules to important brain compounds including neurotransmitters. SAMe is the major methyl donor in the body. The antidepressant effects of folic acid appear to be a result of raising brain SAMe content.

One of the key brain compounds dependent on methylation is tetrahydrobiopterin (BH_4). This compound functions as an essential coenzyme in the activation of enzymes that manufacture monoamine neurotransmitters like serotonin and dopamine from their corresponding amino acids. Patients with recurrent depression have



* Pyridoxal-5-phosphate (PLP) dependent step
aaad Aromatic amino acid decarboxylase, PLP dependent step; the rate for decarboxylation of 5-hydroxytryptophan is 16% of the rate of DOPA
kh Kynurenine
k Kynureninase, PLP dependent
ka Kynurenine aminotransferase, PLP dependent
mao Monoamine
th Tryptophan hydroxylase, tetrahydrobiopterin dependent
tp Tryptophan pyrolase (oxygenase), inducible

FIGURE 142-2 The relationships among folate cycle, S-adenosylmethionine, and transmethylation.

been shown to have reduced BH_4 synthesis, probably as a result of low SAMe levels. BH_4 supplementation has been shown to produce dramatic results in these patients.[53,54] Unfortunately BH_4 is not currently available commercially. However, because BH_4 synthesis is stimulated by folic acid, vitamin B_{12}, and vitamin C, it is possible that increasing these vitamin levels in the brain may stimulate BH_4 formation and the synthesis of monoamines like serotonin.[55]

Some evidence supports the contention that supplementing the diet with folic acid, vitamin C, and vitamin B_{12} can increase BH_4 levels. In addition, the folic acid supplementation and promotion of methylation reactions have been shown to increase the serotonin content.[51-53] The serotonin-elevating effects are undoubtedly responsible for much of the antidepressant effects of folic acid and vitamin B_{12}.

One review of three folate trials involving 247 depressed patients has been published.[59] Two of the studies involving 151 people assessed the use of folate in addition to other treatments and found that adding folate reduced HDS scores on average by a further 2.65. One of the studies, involving 96 people, assessed the use of folate instead of the antidepressant trazodone. This study did not find a significant benefit from the use of folate. Although the authors of this analysis considered these data "limited," they acknowledged the potential role of folate as a supplement to treat depression. No side effects or toxicities were noted in any of the studies reviewed.

Typically, the dosages of folic acid in the antidepressant clinical studies have been high: 15 to 50 mg. High-dose folic acid therapy is safe except in patients with epilepsy and has been shown to be as effective.[60]

A dosage of 800 mcg of folic acid and 800 mcg of vitamin B_{12} should suffice in most circumstances to prevent deficiencies. Folic acid supplementation should always be accompanied by vitamin B_{12} supplementation to prevent folic acid from masking a vitamin B_{12} deficiency.

Vitamin B_6

Vitamin B_6 levels are typically quite low in depressed patients, especially women taking birth control pills or conjugated estrogen (Premarin).[61-65] Considering the many functions of vitamin B_6 in the brain, including the fact that it is absolutely essential in the

manufacture of all monoamines, it is likely that many of the millions of people taking fluoxetine may be suffering depression simply as a result of low vitamin B_6. Patients with low vitamin B_6 status usually respond well to supplementation. The typical effective dose is 50 to 100 mg.

Zinc

Zinc serves as the mineral cofactor in more than 70 metalloenzymes. Severe zinc deficiency is manifested by bullous-pustular dermatitis, diarrhea, alopecia, and recurrent infections.[66] A growing body of evidence implicates a derangement of zinc homeostasis in mood disorders. Interestingly, it has been shown that depressed patients who have low baseline levels of zinc experience increases in these concentrations in the hippocampus and other brain regions after being given prescription antidepressants.[67] It has been postulated that zinc may act as an antagonist of the *N*-methyl-D-aspartate glutamate receptor.[68]

One small placebo-controlled double-blind pilot study of zinc supplementation in antidepressant therapy was conducted in patients who were diagnosed with major (unipolar) depression; 6 patients received 25 mg of zinc supplementation per day and 8 were given a placebo. These patients were also treated with standard therapy, such as tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs). Using the standard HDS and Beck Depression Inventory to assess the efficacy of these therapies, it was found that zinc supplementation significantly reduced scores in both measures after 6- and 12-week supplementation as compared with placebo treatment.[69] Although this was a small trial, it seems reasonable to use zinc as part of a multinutrient supplementation regimen for depressed patients. Long-term supplementation should be properly balanced with copper.

Selenium

Plasma selenium is clearly lower in alcoholic patients. Serum, erythrocyte, and whole blood levels of selenium are also decreased in patients with alcoholism.[70] Low selenium status encourages depressed mood, whereas high dietary or supplementary selenium has been shown to improve mood.[71] Research has consistently reported that low selenium status was associated with a significantly increased incidence of depression, anxiety, confusion, and hostility.[70] Furthermore, when alcoholism and depression occur together in an individual, there is an increased risk of suicide.[72]

Given the propensity for low selenium status in alcoholic patients and the relationship between selenium levels and mood disorder, selenium supplementation is warranted in an attempt to ameliorate the untoward comorbid psychological and physical profiles of patients with alcohol abuse or dependence.

Chromium

As increased sugar intake is correlated with depression, the essential trace mineral chromium may be a useful means to balance insulin levels. One small study evaluated the effects of chromium supplementation for atypical depression, which is characterized by mood reactivity, increased appetite and weight gain, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity and is associated with earlier onset, greater chronicity, disability, and suicidality than other forms of depression. It is estimated that more than one fifth of all depressive illness falls into this category.

In a placebo-controlled, double-blind pilot study of chromium picolinate conducted in 15 patients with atypical types of major depressive disorder, 10 patients started with a dose of 400 mcg, which was increased to 600 mcg for the remainder of the study. The other 5 patients took a placebo. Seventy percent of the patients on the chromium versus 0% of the placebo patients responded positively to the treatment. Other outcomes were consistent with a greater effect of chromium. Three patients on chromium failed to show any improvement. The chromium picolinate was well tolerated, with no attrition due to side effects.[73] Another successful study of eight patients with depression found some enhanced dreaming and mild psychomotor activation.[74] Chromium's mechanism of action may be by alteration of brain serotonin levels[75] as well as by increasing insulin insensitivity.[76]

Vitamin D

Vitamin D can help treat a critical underlying deficiency. Low levels of vitamin D may be involved in the pathogenesis of depression in several ways. In human beings, the distribution of the vitamin D receptor seems to occur in high concentration in the hypothalamus,[77] suggesting a role in neuroendocrine function. Moreover, the distribution of target neurons of vitamin D suggests an influence on levels of nerve growth factor,[78] acetylcholine, serotonin, testosterone, thyroid hormone, and tyrosine hydroxylase messenger RNA.[79,80] All these have been implicated in the pathogenesis of depression.

A Norwegian study of 441 overweight people measured serum 25-hydroxyvitamin D levels. Those below 16 mg/dL were shown to be more depressed. These subjects were then given either 20,000 or 40,000 international units of vitamin D or placebo once a week. Those given the larger dose had a 33% reduction in depression scores and those given the smaller dose had a 20% reduction. The placebo group had a 5% decrease.[81] Animal studies suggest that prevention of depression in the adult may even occur by treating pregnant women, because gestational deficiency seemed to cause depression-like behavior in offspring.[82]

Because vitamin D is fat-soluble, it is advisable to run laboratory tests before recommending this vitamin. The test indicative of functional vitamin D status measures 25-hydroxy (-OH) vitamin D, which is an intermediate metabolite. Research demonstrates that dosages of 4000 IU once a day in depressed patients tend to improve well-being.[83] This may be a good place to start for depressed patients, although higher levels may be needed for some. The exact amount of vitamin D required to induce hypervitaminosis over a given period of time is unknown, although some research recommends caution at 20,000 international units daily[84] or blood levels of 100 ng/mL.[85]

The main dietary source of vitamin D is fish. Patients should also get adequate exposure to sunlight to increase their levels of vitamin D. One report specifies about 12 minutes per day in the sun is equivalent to an oral intake of 3000 international units of vitamin D3.[86]

Omega-3 Fatty Acids

An insufficiency of omega-3 oils has been linked to depression.[87] Studies have also reported that countries with high rates of fish oil consumption have low rates of depressive disorder.[59] This may be related to the impact of dietary fatty acids on the phospholipid composition of neurologic cell membranes. Although it is thought that the cell is programmed to selectively incorporate the different fatty acids it needs to maintain optimal function, the lack of essential fatty acids (particularly the omega-3 oils) and excess of saturated fats and animal fatty acids can lead to the formation of cell membranes that have much less fluidity than normal.

A relative deficiency of essential fatty acids in cellular membranes substantially impairs cell membrane function. Because the basic function of the cell membrane is to serve as a selective barrier that regulates the passage of molecules into and out of the cell,

a disturbance of its structure or function disrupts homeostasis. The medical literature has demonstrated that there are changes in fatty acid levels in the red blood cells and in the serum fatty acid composition of depressed patients.[88]

Because the brain is the richest source of phospholipids in the human body and proper nerve cell function is critically dependent on proper membrane fluidity, alterations in membrane fluidity affect behavior, mood, and mental function. Studies have shown that the biophysical properties, including fluidity, of brain cell membranes directly influence neurotransmitter synthesis, signal transmission, uptake of serotonin and other neurotransmitters, neurotransmitter binding, and the activity of monoamine oxidase (MAO). All of these factors have been implicated in depression and other psychological disturbances.

In one small study, 20 patients diagnosed with major depressive disorder participated in a 4-week double-blind evaluation of either placebo or an eicosapentaenoic acid addition to their ongoing antidepressant therapy. The effect of eicosapentaenoic acid was significant from week two of treatment, similar to the time course for effectiveness of antidepressant medications. The effect of the placebo was minimal. Item analysis showed that eicosapentaenoic acid also affected core depressive symptoms such as depressed mood, guilt, and feelings of worthlessness as well as insomnia.[89]

Because omega-3 fatty acids may play a key role in the pathophysiology of depression,[90] it is possible that they may reduce the development of depression just as they reduce the development of coronary artery disease.[87] This conclusion was based on several factors:

- Studies have suggested that lowering plasma cholesterol by diet and medications increases the risks of suicide, homicide, and depression.
- The quantity and type of dietary fats consumed influence serum lipids and alter the biophysical and biochemical properties of cell membranes.
- Dietary advice to lower cholesterol levels tends to increase the ratio of omega-6 to omega-3 fatty acids and decreases the level of the essential omega-3 fatty acid, docosahexanoic acid.
- Epidemiologic studies in various countries and the United States have indicated that decreased consumption of omega-3 fatty acids correlates with increasing rates of depression.
- A consistent association between depression and coronary artery disease also exists.

Food Allergies

Depression and fatigue have been linked to food allergies for more than 65 years. In 1930, Rowe coined the term "allergic toxemia" to describe a syndrome that included the symptoms of depression, fatigue, muscle and joint aches, drowsiness, difficulty in concentration, and nervousness.[91] Although the term *allergic toxemia* is no longer used, food allergies still play a major role in many cases of depression.[92]

Monoamine Metabolism and Precursor Therapy

The use of monoamine precursors—particularly tryptophan, 5-hydroxytryptophan (5-HTP), and tyrosine—has offered a more "natural way" of influencing monoamine metabolism than MAO inhibitors or tricyclic antidepressants.

The Tryptophan Catastrophe

For more than 30 years, L-tryptophan was used by millions of people in the United States and around the world safely and effectively to treat insomnia and depression. But in October 1989, some people taking tryptophan started reporting strange symptoms to physicians—severe muscle and joint pain, high fever, weakness, swelling of the arms and legs, and shortness of breath.[93] The syndrome was dubbed eosinophilia-myalgia syndrome (EMS).

Laboratory studies showed that the blood of subjects with EMS contained high levels of eosinophils. In patients with EMS, eosinophil levels rose to greater than 1000/mm^3, roughly double the normal level, and the percentage of eosinophils often increased to levels above 30%.

The problem with such severe elevations in eosinophils is that these white blood cells contain packets that contain high levels of histamine and other allergic and inflammatory compounds. When these compounds are released by eosinophils, it leads to intense symptoms of an allergic and inflammatory nature (e.g., severe muscle and joint pain, high fever, weakness, swelling of the arms and legs, skin rashes, and shortness of breath)—the same symptoms as those experienced by people with EMS. It was suspected that one or more newly introduced contaminants that activated eosinophils and other white blood cells had to be behind the phenomenon of EMS because L-tryptophan had been used safely for so long.

Detailed analysis of all evidence by the Centers for Disease Control and Prevention (CDC) led to the conclusion that the cause of the EMS epidemic could be traced to one Japanese manufacturer, Showa Denko.[94,95] Of the six Japanese companies supplying L-tryptophan to the United States, Showa Denko was the largest, supplying 50% to 60%. The L-tryptophan was used not only as a nutritional supplement but also in infant formulas and nutrient mixtures used for intravenous feeding.

The L-tryptophan produced from October 1988 to June 1989 by Showa Denko became contaminated with substances now linked to EMS owing to changes in the bacteria being used to produce the L-tryptophan and in the filtration process. Because of this change in the filtration process, the L-tryptophan became contaminated. Examination of the prefiltered material indicated that it had no detectable levels of the impurities linked to EMS. Somehow the filtration process produced the contaminants.

Although the epidemic of EMS during the last half of 1989 was clearly related to the contaminated L-tryptophan produced by Showa Denko, there have been a handful of other reported cases of EMS in people who never took L-tryptophan and in others who took L-tryptophan before the contaminated batch manufactured by Showa Denko hit the shelves. It is likely that in these earlier reports the subjects were also using contaminated L-tryptophan and that they may also have had a predisposition to EMS (discussed later).[96,97] This conclusion is based on the fact that uncontaminated tryptophan has never produced EMS. Clearly, it is absolutely essential that only uncontaminated L-tryptophan be used in the course of treatment.

The total number of reported cases of EMS in the United States eventually reached 1511. Included in this number were 36 deaths attributed to L-tryptophan. In Europe the total number of cases was 171 and there were no deaths.[94-97] The difference between the U.S. and European experiences is that the dominant L-tryptophan supplement in Europe was Optimax, a product marketed by Merck, the largest pharmaceutical company in the world. The supplier of the tryptophan used in the Merck product was Ajimomato.

It is surprising that the L-tryptophan catastrophe did not affect more people. Based on very detailed studies, it was concluded that EMS affected 144 out of every 100,000 men and 268 out of every 100,000 women taking L-tryptophan.[98] If 50% of these

individuals were taking Showa Denko–supplied L-tryptophan, we can assume that EMS affected 144 of every 50,000 men and 268 of every 50,000 women taking *contaminated* L-tryptophan. In other words, roughly 1 of every 250 people who took the contaminated L-tryptophan developed EMS.

The obvious question is: Why didn't everyone taking the contaminated L-tryptophan experience EMS? The answer appears to be that only those with an abnormal activation of the kynurenine pathway reacted to the contaminant.[99] Kynurenine and its metabolites (especially quinolic acid) are also linked to other EMS-related illnesses, including the toxic oil syndrome, one of the largest food-related epidemics to date. This syndrome occurred in Spain during May 1991. It affected more than 20,000 people and caused more than 12,000 hospitalizations. It was caused by the ingestion of canola oil contaminated with a compound similar to one found in the contaminated Showa Denko L-tryptophan.[100]

Another finding from studies conducted by researchers from the Centers for Disease Control was that people who took a multivitamin preparation enjoyed some protection against EMS.[101] When regular vitamin users did develop EMS, it was less severe than the illness experienced in non–vitamin users. A likely explanation for this is that either the vitamins (particularly vitamin B_6 and niacin) shunted tryptophan metabolism away from the kynurenine pathway or that the contaminants were somehow metabolized by vitamin-dependent enzymes.

L-Tryptophan

The basic theory of tryptophan supplementation in depression and insomnia is that it will increase the levels of serotonin and melatonin in the brain. This theory is supported by the considerable evidence that many depressed individuals have low tryptophan and serotonin levels. Unfortunately, supplementation with L-tryptophan in depressed patients has produced mixed results in the published clinical trials. L-tryptophan was shown to be more effective than placebo in only 2 out of 8 comparison studies, but 9 of 11 studies comparing L-tryptophan with conventional antidepressant drugs showed no difference.[102-107]

Among the many factors to consider in looking at these studies are study size, severity of depression, duration, and dosage. In addition, a number of factors including hormones like estrogen and cortisol as well as tryptophan itself stimulate the activity of tryptophan oxygenase, which leads tryptophan to be converted to kynurenine; as a result, less tryptophan is delivered to the brain (Figure 142-1 shows the metabolism of tryptophan).

Evidence linking digestive dysfunction and abnormal serotonin levels is also emerging. Twenty percent of patients with functional bowel disorders also have psychiatric comorbidities.[108] Effectively treating digestive dysfunction may also rebalance tryptophan and serotonin levels, thus working to alleviate depressive illness. The naturopathic notion of "treating the gut" may be of use in treating primary mechanisms of depression.

Because dehydration may limit the amount of tryptophan available to the brain, water intake is also important.[109]

In summary, L-tryptophan is only modestly effective in the treatment of depression when used alone. In order to gain any real benefit from L-tryptophan, it must be used along with vitamin B_6 and the niacinamide form of vitamin B_3 to help block the kynurenine pathway, thus providing better results. Better yet is the use of 5-HTP.

5-Hydroxytryptophan

Because the pharmacology of 5-hydroxytryptophan is fully described in Chapter 101, only a brief summary is presented here. Unlike tryptophan, 5-HTP cannot be converted to kynurenine and easily crosses the blood-brain barrier. As a result, although only 3% of an oral dose of L-tryptophan is converted to serotonin, more than 70% of an oral dose of 5-HTP is converted to serotonin. In addition to increasing serotonin levels, 5-HTP causes an increase in endorphin and catecholamine levels. Numerous double-blind studies have shown that 5-HTP has "equipotency" with SSRIs and tricyclic antidepressants in terms of effectiveness and is less expensive, better tolerated, and associated with fewer and much milder side effects.[110-114]

Phenylalanine and Tyrosine

Although the number of clinical studies using phenylalanine or tyrosine for depression does not approach the number using tryptophan and 5-HTP, there is evidence that these monoamine precursors may be effective in some individuals.[115,116] General catecholamine metabolism is briefly illustrated in Figure 142-3.

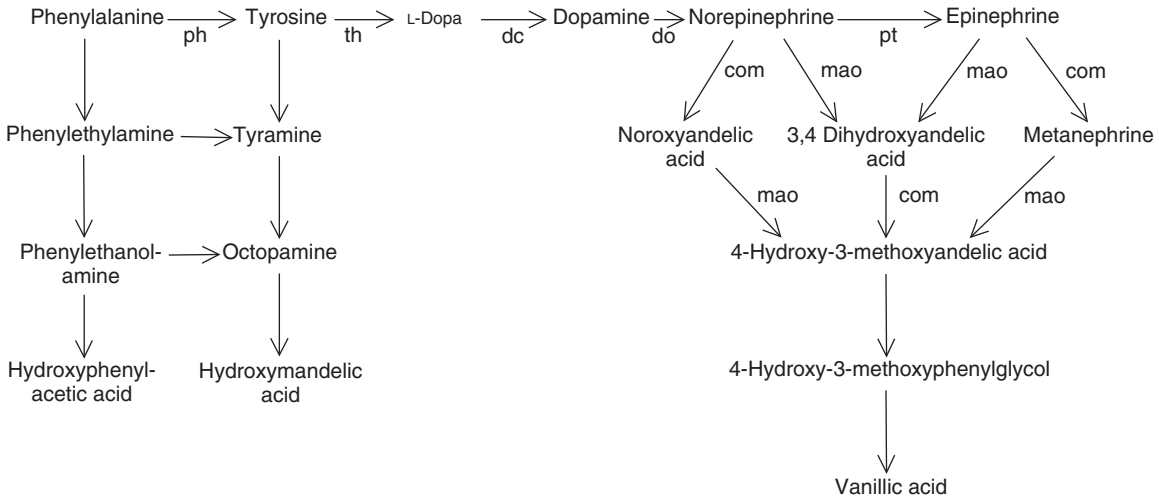
Phenylalanine, beside being hydroxylated to tyrosine and degraded to phenylketonic acids, can be decarboxylated to phenylethylamine (PEA).[115] This compound has amphetamine-like stimulant properties and is suggested to be an endogenous stimulatory or antidepressive substance in humans. (Note that this biogenic amine is found in high concentrations in chocolate, which might explain the latter's addictiveness.) Low urinary PEA levels are found in depressed patients, whereas high levels are found in schizophrenia.[115,116] Phenylalanine, both the D- and L- forms, has been demonstrated to increase urinary PEA output and CNS PEA concentrations. Because phenylalanine is a tyrosine hydroxylase inhibitor, it is expected that more shunting of phenylalanine to PEA synthesis will occur with supplementation.

The pharmacologic activity of supplemental tyrosine in depressives may be related to its increasing of "trace amine" levels (octopamine, tyramine, and PEA) rather than just its enhancement of catecholamine synthesis or possibly its stimulation of thyroid hormone synthesis. The largely negative results using L-dopa alone in affective disorders tend to substantiate this assumption.[114] Central norepinephrine turnover, however, is decreased in depressed patients. This may be a result of the low serum tyrosine levels seen in some depressed individuals.[116]

The brain's tyrosine content, like that of tryptophan, is best determined by the ratio of serum tyrosine concentration to the sum of its brain-uptake competitors (i.e., leucine, isoleucine, valine, tryptophan, phenylalanine). Tyrosine ratios are increased by high-protein meals. Tyrosine supplementation results in increased levels of 3-methoxy-4-hydroxyphenethylene glycol in the urine. This compound is believed to be the principal breakdown product of norepinephrine in the CNS and may provide a biochemical marker for determining which amino acid to supplement.

Table 142-2 summarizes clinical studies using phenylalanine, tyrosine, or both for depression. These results indicate that phenylalanine and tyrosine supplementation offer encouraging alternatives to tricyclics and MAO inhibitors.

In the early 1970s, van Praag and colleagues discovered that about one in five patients who responded well to 5-HTP tended to relapse after 1 month of treatment. The antidepressant effects of 5-HTP in these subjects began to wear off gradually after the first month despite the fact that the level of 5-HTP in the blood, and presumably the level of serotonin in the brain, remained the same as when the patients were experiencing benefit.[114] The researchers discovered that although serotonin levels appeared to stay at the same levels after 1 month of treatment, the levels of the other important monoamine neurotransmitters, dopamine and norepinephrine, declined.[117] These patients responded to supplemental tyrosine.



com	Catechol-O-methyl-transferase; SAMe dependent
dc	Dopa decarboxylase (aaad); pyridoxal-5-phosphate dependent
do	Dopamine oxidase; O_2, ascorbate, copper, and iron dependent; tryptamine and histamine inhibit
mao	Monoamine oxidase; many drugs and plant compounds are inhibitory
ph	Phenylalanine hydroxylase; O_2, dihydrobiopterin dependent
pt	Phenylethanol-amine *N*-methyltransferase; low activity in CNS; S-adenosylmethionine (SAMe) dependent; inhibited by tyramine, dopamine
th	Tryptophan hydroxylase; inhibited by tryptophan, phenylalanine, dopa, and dopamine; tetrahydrobiopterin, O_2, Fe dependent; rate limiting enzyme for dopamine synthesis

FIGURE 142-3 Catecholamine metabolism.

TABLE 142-2 **Phenylalanine and Tyrosine in Depression**

REFERENCES[a]	NUMBER OF PATIENTS	DOSAGES (mg/day)	DURATION (days)	CLINICAL EFFECTS AND COMMENTS
Yaryura et al. (1974)	15	200-400	14	(D,L-P) 10 severely depressed patients responded
Fischer et al. (1975)	23	100	1-13	(D- or D,L-P) A complete response was observed in 17 patients previously unresponsive to tricyclics and MAO inhibitors
Beckman et al. (1977)	20	75-200	20	(D,L-P) Eight complete remissions, four showed marked improvement; used Hamilton Depression Scale and von Zerssen self-rating questionnaire
Heller (1978)	55	100-400	60-180	(D-P) 73% recovered completely after 15 days, 23% had marked improvement, 4% failed to respond
Heller (1978)	60	100	30	(D-P) Complete remission and improvement in 83% for the phenylalanine group compared with 73% for the imipramine group; double-blind controlled study—no diagnostic criteria or rating scales were reported
Beckman (1979)	27	200	30	(D,L-P) No significant difference between phenylalanine and imipramine groups
Gibson et al. (1983)	9	300l	Ongoing	(T) Double-blind, placebo-controlled study; tyrosine demonstrated a rate of response (60%-70%) typical of most major antidepressants without side effects

MAO, monoamine oxidase; P, phenylalanine; T, tyrosine.
[a]References from Beckman H. Adv Biol Psychiat 1983;10:137-147 and Gelenberg AJ, Gibson CJ. Nutr Health 1984;3:163-173.

S-Adenosylmethionine

SAMe was discussed briefly earlier with vitamin B_{12} and folic acid in its methylation role. SAMe is involved in the methylation of monoamines, neurotransmitters, and phospholipids like phosphatidylcholine and phosphatidylserine. Normally the brain manufactures all the SAMe it needs from the amino acid methionine. However, SAMe synthesis is impaired in depressed patients. Supplementation of the diet of depressed patients with SAMe results in increased levels of serotonin, dopamine, and phosphatides and improved binding of neurotransmitters to receptor sites, leading to increased serotonin and dopamine activity and improved fluidity of brain cell membranes, which can lead to significant clinical improvement.[118-120]

The results of a number of clinical studies suggest that SAMe is one of the most effective natural antidepressants.[121-125] Unfortunately its use is still limited owing to its high price. Tables 142-3 and 142-4 summarize double-blind studies comparing SAMe with either a placebo or a tricyclic drug such as imipramine.

The studies cited in these tables used injectable SAMe. However, more recent studies using a new oral preparation at a dosage of 400 mg four times daily (1600 mg total) have demonstrated that SAMe is just as effective orally as it is given intravenously.[126-129]

TABLE 142-3 **Double-blind Clinical Studies with S-adenosylmethionine (SAMe) Compared with Placebo in Depression**

REFERENCES[a]	SAMe RESPONDERS	PLACEBO RESPONDERS	CONCLUSION
Fazio et al (1973)	Not quantified		SAMe superior to placebo based on Hamilton Depression Scale (HDS)
Agnoli et al (1976)	20 of 20	1 of 10	SAMe superior to placebo
Muscettola et al (1982)	4 of 10	0 of 10	SAMe superior to placebo
Janicak (1982)	5 of 7	0 of 5	SAMe superior to placebo
Caruso et al (1984)	Not quantified		SAMe superior to placebo based on HDS
Carney et al (1986)	Not quantified		SAMe superior to placebo based on HDS and Beck Scale
De Leo (1987)	Not quantified		SAMe superior to placebo based on Clinical Global Impression Scale
Total	29 of 37 (78%)	1 of 25 (4%)	SAMe dramatically more effective than placebo

[a]References from Janicak PG, Lipinski J, Davis JM, et al. Parenteral S-adenosyl-methionine (SAMe) in depression: literature review and preliminary data. Psychopharmacol Bull 1989;25:238-242.

TABLE 142-4 **Double-blind Clinical Studies with S-adenosylmethionine (SAMe) Compared with Antidepressant Drugs in Depression**

REFERENCES[a]	SAMe RESPONDERS	DRUG RESPONDERS	CONCLUSION
Mantero et al (1975)	11 of 16	9 of 15	SAMe comparable to imipramine (75 mg/day)
Barberi et al (1978)	10 of 10	8 of 10	SAMe more effective than amitriptyline (100 mg/day)
Del Vecchio et al (1978)	5 of 14	4 of 10	SAMe comparable to clomipramine (100 mg/day)
Miccoli et al (1978)	35 of 45	30 of 41	SAMe comparable to clomipramine (100 mg/day)
Scarzella et al (1978)	9 of 10	9 of 10	SAMe comparable to clomipramine (100 mg/day)
Scaggion et al (1982)	18 of 22	10 of 18	SAMe more effective than nomifensine (200 mg/day)
Kufferle et al (1982)	7 of 9	6 of 9	SAMe comparable to clomipramine (50 mg/day)
Plotkin (1988)	9 of 9	2 of 9	SAMe more effective than imipramine (150 mg/day)
Janicak (1988)	5 of 7	2 of 3	SAMe comparable to imipramine (150 mg/day)
Total	109 of 142 (76%)	80 of 124 (61%)	SAMe significantly more effective than antidepressant drugs

[a]References from Janicak PG, Lipinski J, Davis JM, et al. Parenteral S-adenosyl-methionine (SAMe) in depression: literature review and preliminary data. Psychopharmacol Bull 1989;25:238-242.

SAMe is better tolerated and has a quicker onset of antidepressant action than tricyclic antidepressants.

One study compared SAMe with the tricyclic desipramine. In addition to clinical response, the blood level of SAMe was determined in both groups. At the end of the 4-week trial, 62% of the patients treated with SAMe and 50% of those treated with desipramine had significantly improved. Regardless of the type of treatment, patients with a 50% decrease in their HDS score showed a significant increase in plasma SAMe concentration. These results suggest that one way in which tricyclic drugs exert their antidepressant effects is by raising SAMe levels.[130]

No significant side effects have been reported with oral SAMe. However, because SAMe can cause nausea and vomiting in some people, it is recommended that it be started at a dosage of 200 mg twice daily for the first day, increased to 400 mg twice daily on day 3, then raised to 400 mg three times daily on day 10, and finally, after 20 days, increased to the full dosage of 400 mg four times daily.

Individuals with bipolar (manic) depression should not take SAMe. Because of SAMe's antidepressant activity, these individuals are susceptible to experiencing hypomania or mania. This effect is exclusive only to some individuals with bipolar depression.

Botanical Medicines

Hypericum perforatum

St. John's wort is now becoming a standard treatment in antidepressant therapy.[131] Extracts of St. John's wort standardized for hypericin are the most thoroughly researched natural antidepressants. Mechanisms of action may include serotonin reuptake modulation, increases in interleukin-6 activity, and agonist action of sigma receptors. Past information implicating the inhibition of MAO activity as a suggested mechanism is largely disproved. See Chapter 99 for more information.

More than 27 double-blind randomized trials involving more than 2200 patients with mild to moderately severe depression have shown St. John's wort extracts standardized for hypericin to yield excellent results in the treatment in depression, and with far fewer side effects than standard antidepressant medications.[132]

A total of 1592 patients have been studied in 25 double-blind controlled studies (15 compared with placebo and 10 compared with antidepressant drugs, including 5 studies comparing St. John's wort extract with tricyclics—2 versus imipramine, 2 versus amitriptyline, and 1 versus desipramine).[133-135]

In these studies, St. John's wort extract was shown to produce improvements in many psychological symptoms including the following:

- Depression
- Anxiety
- Apathy
- Sleep disturbances
- Insomnia
- Anorexia
- Feelings of worthlessness

The main advantage of St. John's wort extract over antidepressant drugs was not so much a difference in therapeutic outcome as a significant advantage in terms of side effects, cost, and patient satisfaction. For example, in a study of 102 patients, slightly better

results were obtained with maprotiline (a tetracyclic) in the HDS, Discomfort Scale, and Clinical Global Impression scale; but when side effects and patient tolerance were added to the equation, St. John's wort was considered superior.[136] Maprotiline treatment resulted in the typical side effects of tricyclics (e.g., tiredness, dry mouth, cardiac complaints). It should be noted that St. John's wort has been known to decrease the efficacy of certain drugs including oral contraceptives and may cause photosensitivity when dosed in high amounts. For more information on St. John's wort, consult Chapter 99.

Piper mythisticum

Kava extracts, like St. John's wort, are gaining in popularity in Europe in the treatment of anxiety and depression. Several European countries (e.g., Germany, the United Kingdom, Switzerland, Austria) have approved kava preparations in the treatment of nervous anxiety, insomnia, depression, and restlessness on the basis of detailed pharmacologic data and favorable clinical studies. In fact, kava extract compares quite favorably with benzodiazepines in effectiveness but does not possess the major drawbacks of these drugs (e.g., impaired mental acuity, risk of addiction).[137-139] These approved kava preparations are extracts standardized for kavalactone content (usually 30% to 70%). Because a German study reported a high incidence of improper dosing of kava extract, it is important that practitioners be aware of how to use this botanical properly for best efficacy.[140] A report in 2008 discussed rare but serious side effects that may have occurred due to poor-quality kava as well as other risk factors such as overdose, prolonged therapy, and comedication.[141] Since that time, a review of 435 clinical trial participants taking kava supplements (some at high doses) showed no liver toxicity, indicating that hepatotoxicity is rare side effect.[142] (See Chapter 114 for a more complete discussion of the kava toxicity issue.) Kava appears to be most useful in cases of depression with severe anxiety (for more information on kava, see Chapter 114).

Ginkgo biloba

The extract of *Ginkgo biloba* leaves standardized to contain 24% ginkgo flavonoglycosides and 6% terpenoids exerts good antidepressant effects, especially in patients above 50 years of age. Researchers became interested in the antidepressant effects of *G. biloba* extract as a result of the improvement in mood reported by patients suffering from cerebrovascular insufficiency who were treated with ginkgo in double-blind studies.[125-128] These observations led to several double-blind studies of the efficacy of ginkgo in depression. In one of the more recent double-blind studies, 40 older patients (ranging from 51 to 78 years of age) with depression who had not benefited fully from standard antidepressant drugs were given either 80 mg of *G. biloba* extract three times daily or a placebo.[147]

By the end of the fourth week of the study, the total score on the HDS was reduced on average from 14 to 7. At the end of the 8-week study, the total score in the *G. biloba* extract group had dropped to 4.5. In comparison, the placebo group only dropped from 14 to 13. This study indicates that *G. biloba* extract can be used with standard antidepressants and may enhance their effectiveness, particularly in patients above 50 years of age.

In addition to its effects as seen in human studies, *G. biloba* extract has also demonstrated antidepressant effects in a number of animal models, including the learned helplessness model. The most interesting of these studies demonstrated that *G. biloba* extract was able to counteract one of the major changes in brain chemistry associated with aging—the typical reduction in the number of serotonin receptor sites in brain cells.[148] As a result, the elderly are more susceptible to depression, impaired mental function, insomnia, and sleep disturbances. The study was designed to determine whether *G. biloba* extract could alter the number of serotonin receptors in old (24-month-old) and young (4-month-old) rats. At the beginning of the study, the older rats had a 22% lower number of serotonin binding sites than the younger rats. The results of chronic treatment with *G. biloba* extract for 21 consecutive days demonstrated that there was no change in receptor binding sites in the young rats, but there was a statistically significant increase (by 33%) in the number of binding sites in the older rats. These results indicate that *G. biloba* extract may counteract at least some of the age-dependent reductions of serotonin binding sites in the aging human brain as well.

The exact mechanism of *G. biloba* extract's effect on increasing serotonin receptors has not yet been determined; however, *G. biloba* extract may address two major reasons why serotonin receptors decline with age: impaired receptor synthesis or changes in cerebral neuronal membranes or receptors as a result of free radical damage. *G. biloba* extract has demonstrated an ability to increase protein synthesis. The flavone amentoflavone, also found in *H. perforatum*, binds to benzodiazepine receptors and is a modulator of γ-aminobutyric acid, which may be a major anxiolytic mechanism.[149] In addition, *G. biloba* extract is known to be a potent antioxidant. The most likely explanation probably involves a combination of these two effects (and others) rather than one single mechanism (see Chapter 93 for further discussion).

THERAPEUTIC APPROACH

Treatment depends largely on accurate determination of which factors are contributing to the patient's depression; balancing of errant neurotransmitter levels; and optimizing the patient's nutrition, lifestyle, and psychological health.

Diet

Patients should increase their consumption of fiber-rich plant foods (fruits, vegetables, grains, legumes, and raw nuts and seeds), possibly in the Mediterranean diet style; they should also avoid caffeine, nicotine, other stimulants, and alcohol. Their food allergies must be identified and controlled. Patients should increase their consumption of cold-water fish to at least twice per week.

Lifestyle

- Patients should be referred to a counselor or helped to develop a positive, optimistic mental attitude. This can be accomplished by helping them set goals, use positive self-talk and affirmations, identify self-empowering questions, and find ways to inject humor and laughter into their lives.
- Patients should exercise at least 30 minutes at least three times a week.
- Patients should spend 10 to 15 minutes a day on relaxation/stress reduction techniques.

Supplements

- High-potency multivitamins and minerals
- Vitamin C: 500 to 1000 mg three times a day
- Vitamin D: 2000 to 4000 IU per day or higher, depending on laboratory values until normal levels reached.
- Vitamin E: 200 to 400 IU per day

- Selenium: 200 mcg/day
- Chromium: 400 to 600 mcg/day
- Zinc: 25 mg/day
- Essential fatty acids: 2000 mg/day
- 5-HTP: 100 to 200 mg three times a day
- Folic acid and vitamin B_{12}: 800 mcg of each a day
- SAMe: 200 mg twice a day up to 400 mg three times a day

Botanical Medicines

If a patient is less than 50 years of age, St. John's wort extract (0.3% hypericin) should be used at a dosage of 900 to 1800 mg daily. In severe cases, St John's wort extract can be used in combination with 5-HTP or at a dosage of 50 to 100 mg three times daily.

If a patient is above 50 years of age, *G. biloba* extract (24% ginkgo flavonoglycosides) should be used at a dosage of 240 to 320 mg daily. In severe cases, this can be used in combination with St. John's wort or 5-HTP or both.

If anxiety is a significant factor, kava extract standardized for kavalactone content should be used at a dosage of 45 to 70 mg kavalactones three times daily.

BIPOLAR DISORDER

Bipolar depression is a disorder characterized by periods of major depression alternating with periods of elevated mood. If the elevated mood is relatively mild and lasts for 4 days or less, it is referred to as hypomania. Mania lasts longer and is more intense. To be diagnosed as a bipolar depressive, an individual would be expected to have at least three of the following symptoms:

- Excessive self-esteem or grandiosity
- Reduced need for sleep
- Extreme talkativeness, excessive telephoning
- Extremely rapid flight of ideas along with the feeling that the mind is racing
- Inability to concentrate, easily distracted
- Increase in social or work-oriented activities, often with a 60- to 80-hour working week
- Poor judgment, as indicated by sprees of uncontrolled spending, increased sexual indiscretions, and misguided financial decisions

A full-blown manic attack requires hospitalization. Manic people have lost control, and they may hurt themselves or others. The standard treatment for bipolar depression is lithium, which stabilizes mood. It is especially useful in preventing the manic phase. Lithium is used either alone or in combination with an antidepressant like fluoxetine. However, because fluoxetine and other antidepressant drugs can occasionally induce mania and hypomania, it is often difficult to effectively control the lows in bipolar depressives with drug therapy.

THERAPEUTIC CONSIDERATIONS

Patients experiencing a manic syndrome usually require hospitalization to prevent impulsive and aggressive behavior from ruining their careers or injuring themselves or others. Lithium has become the drug of choice for these patients. Typically, manic patients are initially hospitalized for 2 weeks and kept under sedation with antipsychotic drugs until lithium blood levels have risen sufficiently. Referral seems warranted for most cases until mood can be stabilized.

Many of the principles outlined in the discussion of depression are applicable to mania as well. However, owing to the seriousness of this condition, it is more appropriate to use nutritional therapy as an adjunct rather than as the primary therapy. Also, because SSRIs such as fluoxetine (Prozac), sertraline (Zoloft), and paroxetine (Paxil) are often helpful when used in combination with lithium, 5-HTP and botanical medicines such as St. John's wort extract may prove useful as adjuncts to lithium as well, and without the side effects.

Tryptophan

Although patients have responded to tryptophan supplementation, the effective doses were generally quite large (i.e., 12 g/day of L-tryptophan).[150,151] A better choice appears to be 5-HTP, which has been shown to be helpful in the treatment of bipolar depression when used in combination with lithium at a much lower dosage (e.g., 100 mg three times daily) than L-tryptophan.[152,153]

N-Acetyl-Cysteine (NAC)

NAC is a precursor to the amino acid cysteine, which contributes to glutathione production and to general antioxidant activities of the body. Through its role as a modulator of the glutamatergic system, cysteine influences the reward-reinforcement pathway. Because of these functions, NAC may exert a therapeutic effect on psychiatric disorders allegedly related to oxidative stress, such as schizophrenia and bipolar disorder. It is also gaining notoriety for use in psychiatric syndromes characterized by impulsive and compulsive symptoms such as trichotillomania, pathologic nail biting, gambling, and substance misuse. Although the dosages, pharmacologic strategies (monotherapy versus augmentation), and long-term risks need more research NAC appears to be a promising intervention posing very little risk.[154]

A double-blind randomized placebo-controlled 6-month trial of NAC in 75 participants with bipolar disorder compared 2000 mg/day of NAC or placebo with conventional treatment. Over the 6-month period, there was no difference between groups in dropout rates, with 64% of the total sample completing the trial. Rating scales showed large decreases in depressive symptoms between NAC and placebo groups at the endpoint. Akin to a past schizophrenia trial,[155] improvements were seen on global improvement, severity, and function scales.[156] After discontinuation of NAC treatment, there was loss of benefit, which suggests NAC treatment should be ongoing.

Phosphatidylcholine

Supplementation with large amounts of phosphatidylcholine (15 to 30 g/day in both the pure form and as lecithin) has shown better results than monoamine precursors in the treatment of mania.[157-159] Lithium is believed to promote increased CNS cholinergic activity via inhibition of choline flux across the blood-brain barrier.[160,161] Evidence indicates that mania is associated with reduced CNS cholinergic activity.[160,161] The use of phosphatidylcholine to increase CNS choline may result in significant improvement or amelioration of symptoms in some patients.[160-161] Details of the basic defect in the one-carbon cycle and the cholinergic system need to be worked out, but the defect appears to be a valuable clue to the etiology of mania.

Omega-3 Fatty Acids

One 4-month double-blind placebo-controlled study found marked therapeutic efficacy and no side effects of omega-3 fatty acids in the prevention of bipolar manic-depressive illness. Using 9.6 g/day of omega-3 fatty acids or an olive oil control, the patient

group had a significantly longer period of remission than the placebo group. Furthermore, for nearly every other outcome measure, the omega-3 fatty acid group performed better than the placebo group.[162] The authors of this study also postulated that omega-3 fatty acids may inhibit neuronal signal transduction pathways in a manner similar to that of lithium carbonate and valproate. Other studies in bipolar patients have characterized higher concentrations of arachidonic acid that may be lowered with adequate fatty acid intake.[163]

Vanadium

Vanadium's role in mania has been researched primarily by Naylor and colleagues.[164-166] Increased levels of vanadium are found in hair samples from manic patients, and these values fall toward normal levels with recovery.[164] In contrast, depressed patients typically have normal hair concentrations and elevated vanadium levels in whole blood and serum.[164] These levels also return to normal on recovery. Vanadium, as the vanadate ion, is a strong inhibitor of Na^+,K^+-ATPase. Lithium has been reported to reduce this inhibition.[164-165]

Therapies designed to reduce vanadate to the less inhibitory vanadyl form have used ascorbic acid, methylene blue, and EDTA separately and in combination.[165,166] Ascorbic acid (3 g/day) was shown in a double-blind crossover study to result in significant clinical improvement.[165]

The use of a "low-vanadium diet" has also been advocated by Naylor. However, his dietary suggestions for low vanadium intake are not consistent with the vanadium content of foods, as determined by flameless atomic absorption spectroscopy.[167] Using this method, low-vanadium foods (1 to 5 ng/g) include fats, oils, fresh fruits, and vegetables. Whole grains, seafood, meat, and dairy products are in the range of 5 to 30 ng/g, whereas prepared foods such as peanut butter, white bread, and breakfast cereals range from 11 to 93 ng/g.[167] The benefit of the low-vanadium diet used in Naylor's study was probably due to his simultaneous administration of EDTA.

If Naylor's hypothesis is correct, perhaps other factors known to affect Na^+,K^+-ATPase activity are involved in some cases. Those factors associated with decreased activity would include uremia, hypothyroidism, and catecholamine insensitivity. From a therapeutic viewpoint, correction of these underlying factors may be of some aid. Vitamins E and B_6 have been demonstrated to increase Na^+,K^+-ATPase activity in vitro, and vitamin E stabilizes membranes as well.[168]

Circadian Rhythms

Manic depressive patients have disturbed circadian rhythms, seasonal patterns of exacerbation, and supersensitivity to light, suggesting that alteration of circadian light-dark cycles through light therapy may be of clinical usefulness (see the section on seasonal affective disorder below).[169]

THERAPEUTIC APPROACH

In general, the same dietary and lifestyle guidelines given in the section on depression are appropriate here.

Diet

A low-vanadium diet is recommended. This entails eliminating all refined and processed foods and promoting the consumption of fresh fruits and vegetables.

Supplements

- Phosphatidylcholine: 10 to 25 g/day (Phosphatidylcholine may induce depression in some patients[170]; if this occurs, it should be discontinued immediately.)
- NAC: 1 g twice a day
- Vitamin C: 3 to 5 g/day in divided doses
- Vitamin E: 400 to 800 IU/day
- Pyridoxine: 100 mg/day

SEASONAL AFFECTIVE DISORDER

Seasonal affective disorder (SAD) is associated with winter depression and summer hypomania. Typically, these individuals feel depressed, slow down, and generally oversleep, overeat, and crave carbohydrates in the winter. In the summer, these same patients feel elated, active, and energetic.

THERAPEUTIC CONSIDERATIONS

Melatonin

Although many variables may be responsible for SAD, insufficient light exposure is the most logical explanation. Many mammals exhibit seasonal variations in activity level, sleep patterns, and appetite and are extremely sensitive to changes in day length. The key hormonal change may be a reduced secretion of melatonin from the pineal gland and an increased secretion of cortisol by the adrenal glands. Melatonin supplementation is thought to improve SAD because it increases brain melatonin levels, but it may also suppress cortisol secretion.[171]

Light Therapy

The antidepressant effects of full-spectrum light therapy have been demonstrated in well-monitored, controlled studies not only in SAD but also in clinical depression.[172-175] The antidepressant effect of light therapy is probably due to the restoration of proper melatonin synthesis and secretion by the pineal gland, leading to reestablishment of the proper circadian rhythm. Light therapy has also been shown to decrease TSH levels in SAD patients.[176]

Commercially made lights at a concentration of 10,000 lux yield exposure to full-sprectrum white light (10,000 lux) for at least 30 minutes every day in the morning.

L-Tryptophan and 5-Hydroxytryptophan

An open-label trial of 16 patients with SAD who responded only somewhat or not at all to bright light therapy were given 1 g of L-tryptophan three times a day in addition to 10,000 lux cool-white fluorescent light therapy for 30 minutes every morning. Two patients discontinued medications within 3 days because of side effects. In the 14 patients who completed their treatment, the addition of L-tryptophan significantly reduced mean depression scores. Overall, 9 of 14 patients (64%) showed good clinical responses to combined treatment and minimal side effects.[177] Corroborating work also found that tryptophan depletion in drug-free depressed patients induced a significant decrease in plasma-free and total tryptophan levels, with peak effects occurring 5 hours after ingestion of a tryptophan-free amino acid drink. A transient depressive relapse was observed within a day after the tryptophan depletion, although the same group also found no change in behavior in a subsequent trial despite similar plasma tryptophan decreases.[178]

By modulating serotonergic mechanisms, L-tryptophan may be a reasonable addition to a protocol for those patients who have minimal responses to light therapy. Another more effective therapeutic alternative may be to try 5-HTP (see earlier).

Hypericum perforatum

St. John's wort extract, standardized to contain 0.3% hypericin (see Chapter 101), at a dosage of 300 mg three times daily, has been shown to improve SAD.[179] However, although effective on its own, St. John's wort extract is more effective when used in combination with light therapy. This was demonstrated in a double-blind study in which patients with SAD were randomized in a 4-week treatment study with 900 mg/day of St. John's wort extract (0.3% hypericin content) combined with either bright (3000 lux) or dim (less than 300 lux) light. There was a significant reduction in the HDS in both groups (72% and 60%, respectively), demonstrating that the efficacy of St. John's wort extract in SAD is enhanced with light therapy.

THERAPEUTIC APPROACH

Because the cause of SAD is related to light, the treatment goal is to extend light exposure on winter days. This can be accomplished by using full-spectrum lighting, as described earlier. However, it may be unrealistic to expect most patients to comply fully. Therefore patients may be introduced to full-spectrum lighting throughout their indoors environment and given conjunctive therapy with nighttime melatonin (3 mg 45 minutes before retiring) and daytime St. John's wort or 5-HTP.

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CHAPTER 143

Alcohol Dependence

Michael T. Murray, ND

DIAGNOSTIC SUMMARY

- Alcohol dependence manifested when alcohol is withdrawn: tremulousness, convulsions, hallucinations, delirium
- Alcoholic binges, benders (48 or more hours of drinking associated with failure to meet usual obligations), or blackouts
- Evidence of alcohol-induced illnesses: cirrhosis, gastritis, pancreatitis, myopathy, polyneuropathy, cerebellar degeneration
- Physical signs of excess alcohol consumption: alcohol odor on breath, flushed face, tremor, ecchymoses
- Psychological/social signs of excess alcohol consumption: depression, loss of friends, arrest for driving while intoxicated, surreptitious drinking, drinking before breakfast, frequent accidents, unexplained work absences

GENERAL CONSIDERATIONS

Alcohol dependence, alcohol-use disorder, or, as it was formerly known, alcoholism, is a disabling addictive disorder characterized by alcohol consumption that exceeds acceptable cultural limits or injures health or social relationships. Estimates are that the prevalence of lifetime and 12-month alcohol dependence in the United States is 12.5% and 3.8%, respectively.[1] Alcohol dependence is significantly more prevalent among men, whites, Native Americans, younger and unmarried adults, and those with lower incomes. Alcohol dependence affects over 18 million Americans, making it one of the most serious health problems facing physicians today.[1] The total number of Americans affected, either directly or indirectly, is much greater when one considers disruption of family life, automobile accidents, crime, decreased productivity, and mental and physical diseases. With more than 100,000 deaths annually attributed to alcohol misuse, alcohol-related problems are a cause of considerable mortality.[2] As indicated in Box 143-1, the health, social, and economic consequences of alcohol dependence are alarming.

Physicians should consider alcohol dependence when the information provided by the patient and the doctor's own analysis seems to indicate a missing factor. Often, alcohol dependence is a "hidden" disease. The natural consequences of the alcoholic's behavior may be disguised by sympathetic family and friends. This allows the alcoholic to target other factors as the "real problem" without identifying his or her drinking behavior. Table 143-1 provides an alcohol dependence screening questionnaire.

The etiology of alcohol dependence remains obscure. It represents a multifactorial condition involving genetic, physiologic, psychological, and social factors, each of which seems to be important. Serious drinking often starts in younger people; approximately 35% of alcoholics develop their first symptoms between 15 and 19 years of age, and more than 80% develop their first symptoms before age 30.[3]

Although alcohol dependence is most common in men, the incidence has been increasing in women. Although the figures were once more disparate, the female-to-male ratio for alcohol dependence has tapered to 1:2.[1,2] Women generally seem to develop disease at a lower level of intake than men do. This may be partially because of women's lower volume of distribution for alcohol and may also be related to increased gut permeability to endotoxins.[4]

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BOX 143-1 Consequences of Alcohol Dependence

Increased Mortality
- 10- to 12-year decrease in life expectancy
- Double the usual death rate in men, triple in women
- Six times greater suicide rate
- Major factor in the four leading causes of death in men between the ages of 25 and 44: Accidents, homicides, suicides, cirrhosis

Economic Toll (Yearly)
- Lost production: $14.9 billion
- Health care costs: $8.3 billion
- Accident and fire losses: $5 billion
- Cost of violent crime: $1.5 billion
- Total costs (health care, accidents, violence, lost productivity): $136 billion

Health Effects
- Metabolic damage to every cell
- Intoxication
- Abstinence and withdrawal syndromes
- Nutritional diseases
- Cerebellar degeneration
- Cerebral atrophy
- Psychiatric disorders
- Esophagitis, gastritis, ulcer
- Increased cancers of the mouth, pharynx, larynx, and esophagus
- Pancreatitis
- Fatty degeneration and cirrhosis of the liver
- Arrhythmias
- Myocardial degeneration
- Hypertension
- Angina
- Hypoglycemia
- Decreased protein synthesis
- Increased serum and liver triglycerides
- Decreased serum testosterone
- Myopathy
- Neuropathy
- Osteoporosis
- Rosacea, spider veins
- Coagulation disorders

Effects on Fetus
- Growth retardation
- Mental retardation
- Fetal alcohol syndrome
- Teratogenicity

Modified from Hyman SE, Cassem NH. Alcoholism. In Dale DC, Federman DD, eds. Scientific American medicine. New York: Scientific American 1997;III:1-12, 13.

Research indicates that genetic factors may be particularly important.[5] The finding of a genetic marker for alcohol dependence could result in the diagnosis of the disease in its initial and most reversible stage. Some case-control studies suggest that non–gender-based gene polymorphisms encoding cytokines and other immune modulators may play a role in the predisposition to alcoholism. The gene patterns associated with risk reveal that antibody-mediated mechanisms may play a role in disease pathogenesis.[4] The genetic basis of alcohol dependence has also been supported by the following:

- Genealogic studies showing that alcohol dependence is a family condition

TABLE 143-1 **The Brief Michigan Alcohol Dependence Screening Test**

1. Do you feel you are a normal drinker?	Yes (0)	No (2)
2. Do friends or relatives think you are a normal drinker?	Yes (0)	No (2)
3. Have you ever attended a meeting of Alcoholics Anonymous (AA)?	Yes (5)	No (0)
4. Have you ever lost friends or girlfriends or boyfriends because of drinking?	Yes (2)	No (0)
5. Have you ever gotten into trouble at work because of drinking?	Yes (2)	No (0)
6. Have you ever neglected your obligations, your family, or your work for 2 or more days in a row because you were drinking?	Yes (2)	No (0)
7. Have you ever had delirium tremens (DTs), severe shaking, heard voices, or seen things that were not there after heavy drinking?	Yes (2)	No (0)
8. Have you ever gone to anyone for help about your drinking?	Yes (5)	No (0)
9. Have you ever been in a hospital because of drinking?	Yes (5)	No (0)
10. Have you ever been arrested for drunk driving or driving after drinking?	Yes (2)	No (0)

Alcohol dependence is indicated by a score above 5.
Modified from Hyman SE, Cassem NH. Alcoholism. In Dale DC, Federman DD, eds. Scientific American medicine. New York: Scientific American, 1997:III, 1-12, 13

- Studies of adopted children of alcoholic parents raised by foster parents demonstrating a continued higher risk of alcohol dependence
- Twin studies showing differences between identical and nonidentical twins
- Association with genetic markers: color vision, nonsecretor ABH, HLA-B_{13}, and low platelet monoamine oxidase (MAO)
- Biochemical studies showing the importance of alcohol dehydrogenase polymorphism in racial susceptibility to alcohol dependence[5]

A number of studies have shown that the incidence of alcohol dependence is four to five times more common in the biological children of alcoholic parents than those of nonalcoholic parents.[5] Although it would be ultimately useful, knowledge of family history suggests that clear evidence of a biological marker may not be necessary for the implementation of a relatively innocuous primary prevention program.

INTOXICATION AND WITHDRAWAL

The signs of alcoholic intoxication are typical of a central nervous system depressant: drowsiness, errors of commission, disinhibition, dysarthria, ataxia, and nystagmus. Fifteen milliliters of pure alcohol (the equivalent of 1 oz of whiskey, 4 oz of wine, or 10 oz of beer) raise the blood level of alcohol by 25 mg/dL in a 70-kg person. Table 143-2 shows the effects of varying blood levels of alcohol.

Withdrawal symptoms usually occur 1 to 3 days after the last drink. They typically range from anxiety and tremulousness to mental confusion, tremor, sensory hyperactivity, visual hallucinations, autonomic hyperactivity, diaphoresis, dehydration, electrolyte disturbances, seizures, and cardiovascular abnormalities.

TABLE 143-2 **Effects of Varying Levels of Blood Alcohol**

BLOOD LEVEL (MG/DL)	EFFECT
<50	No significant motor dysfunction
100	Mild intoxication—decreased inhibitions, slight visual impairment, slight muscular incoordination, slowing of reaction time
	Legally intoxicated in most jurisdictions
150	Ataxia, dysarthria, slurring of speech, nausea and vomiting
350	Marked muscular incoordination, blurred vision, approaching stupor
500	Coma and death

METABOLIC EFFECTS OF ALCOHOL AND ALCOHOL DEPENDENCE

Ethanol Metabolism

The primary metabolic processes that regulate the rate of alcohol catabolism in normal individuals are[6]:

- The rate of ethanol absorption
- The concentration and activity of liver alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH)
- The reduced nicotinamide adenine dinucleotide (NADH)/nicotinamide adenine dinucleotide (NAD)+ ratio in the liver mitochondria

It is generally accepted that the availability and regeneration of NAD+ are the dominant rate-limiting factors for ethanol oxidation.[7] Ethanol is converted to acetaldehyde by ADH, with NAD+ as a necessary cofactor.

The aldehyde product of ethanol metabolism is believed to be responsible both for many of the harmful effects of alcohol consumption and for the addictive process itself. Higher than normal blood aldehyde levels have been found in alcoholics and their relatives after alcohol consumption.[7] This suggests either increased ADH activity or depressed ALDH activity in people susceptible to alcohol dependence. Acetaldehyde is converted by ALDH to acetate, with little entering the Krebs cycle; most is converted to long-chain fatty acids.[6]

Fatty Liver

All active alcoholics display fatty infiltration of the liver, with the severity roughly proportional to the duration and degree of alcohol excess. Even moderate doses of ethanol may produce both acute and chronic fatty liver infiltrates. The pathogenesis is due to the following[6,8]:

- Increased endogenous fatty acid synthesis
- Diminished triglyceride utilization
- Impaired lipoprotein excretion
- Direct damage to endoplasmic reticulum by free radicals produced by ethanol metabolism
- The high-fat diet of the alcoholic (as is typical of the average American diet)

Leptin is a peptide hormone involved in the regulation of appetite and energy metabolism. It is most likely directly related to liver pathology in alcoholics. High levels of leptin are known to contribute to liver pathology, including increased rates of fibrosis, a known factor in liver steatosis.[9] Research has demonstrated increased circulating leptin levels in a dose-dependent manner in chronic alcohol dependence regardless of nutritional status.[10]

Hypoglycemia

Alcohol induces reactive hypoglycemia. The resultant drop in blood sugar produces a craving for food, particularly foods that quickly elevate blood sugar (i.e., sugar and alcohol). Increased sugar consumption aggravates the reactive hypoglycemia, particularly in the presence of alcohol, owing to alcohol-induced impairment of gluconeogenesis.[6] Hypoglycemia aggravates the mental and emotional problems of the alcoholic and the withdrawing alcoholic with such symptoms as the following:

- Sweating
- Tremor
- Tachycardia
- Anxiety
- Hunger
- Dizziness
- Headache
- Visual disturbance
- Decreased mental acuity
- Confusion
- Depression

THERAPEUTIC CONSIDERATIONS

Nutrition

Although many of the nutritional problems of alcoholics relate directly to the effects of alcohol, a major contributing factor is that alcoholics tend not to eat, substituting alcohol for food. As a result, the alcoholic has to deal not only with nutritional deficiencies caused by excessive alcohol consumption but also true nutritional deficiencies due to inadequate intake.

Zinc

One of the key nutrients involved in the metabolic handling of alcohol is zinc, as both ADH and ALDH are zinc-dependent enzymes, with the latter being more sensitive to deficiency.[11] Both acute and chronic alcohol consumption result in zinc deficiency.[11,12] Several factors contribute to the development of zinc deficiency in alcoholics:

- Decreased dietary intake
- Decreased ileal absorption (probably due to interference with the zinc-binding ligand, picolinic acid, and nonspecific mucosal damage)
- Hyperzincuria

On hair analysis, both higher zinc and copper values have been observed in a study of 43 male alcoholics versus no higher levels in 39 nonalcoholics.[13] Hair copper was significantly related to the amount of ethanol consumed, whereas hair zinc was higher in consumers of distilled beverages. These data may indicate abnormal metabolism and loss of these minerals in the alcoholic. Low serum zinc levels are associated with impaired alcohol metabolism, a predisposition to cirrhosis, impaired testicular function, and other complications of alcohol abuse.[11,14] Zinc supplementation, particularly when combined with ascorbic acid, greatly increases alcohol detoxification and survival in rats.[15]

Vitamin A

Vitamin A deficiency is also common in alcoholics and appears to work synergistically with zinc deficiency to produce the major

complications of alcohol dependence.[8,14] The mechanism has been hypothesized as follows: reduced intestinal absorption of zinc and vitamin A in conjunction with impaired liver function (reduced extraction of zinc, mobilization of retinol binding protein [RBP], and storage of vitamin A) results in reduced blood levels of zinc, vitamin A, RBP, and transport proteins as well as a shift to nonprotein ligands. These cause the tissues to have reduced concentrations of zinc and vitamin A, abnormal enzyme activities and glycoprotein synthesis, and impaired DNA/RNA metabolism and cause the kidneys to increasingly lose zinc. These metabolic abnormalities then lead to the common disorders of alcohol dependence[14]:

- Night blindness
- Skin disorders
- Cirrhosis of the liver
- Reduced skin healing
- Decreased testicular function
- Impaired immune function

Vitamin A supplementation inhibits alcohol consumption in female rats, an effect inhibited by testosterone administration.[16] Other research on rats further supports the significance of the endocrine system in alcohol preference. Ovariectomized and adrenalectomized rats show a decreased preference for alcohol, whereas corticosterone injections increase alcohol preference.[17]

Vitamin A supplementation in the alcoholic has corrected vitamin A deficiency, as noted by improvements in night blindness and sexual function.[8] Despite the importance and benefits of vitamin A to the alcoholic, great care must be employed in recommending vitamin A supplementation. Excessive amounts of vitamin A are contraindicated owing to the fact that a liver damaged by excessive alcohol consumption significantly loses its ability to store vitamin A. As a result, the alcoholic is at great risk for developing vitamin A toxicity when it is supplemented at dosages above 5000 IU a day.

Antioxidants

Ethanol consumption increases lipid peroxidation in humans, resulting in increased lipoperoxide levels in both the liver and serum. Matters are made even worse by the fact that alcoholics are typically deficient in key antioxidant nutrients, particularly vitamin E, selenium, and vitamin C.[18,19] There is a significant correlation between serum lipid peroxide levels, serum glutamic oxaloacetic transaminase (SGOT) activity, and liver cell necrosis.[20] Antioxidant administration, either before or together with ethanol intake, inhibits lipoperoxide formation and prevents fatty infiltration of the liver.[21] Effective antioxidants include vitamins C and E, zinc, selenium, and cysteine.

Carnitine

Although the use of lipotropic agents appears warranted in treating alcoholic fatty liver disease, many commonly used lipotropic agents (e.g., choline, niacin, cysteine) appear to have little value.[22,23] One lipotropic agent, carnitine, significantly inhibits alcohol-induced fatty liver disease. It has been suggested that chronic ethanol consumption results in a functional deficiency in carnitine.[24-26] Because carnitine normally facilitates fatty acid transportation and oxidation in the mitochondria, a high liver carnitine level may be necessary to handle the increased fatty acid load produced by alcohol consumption. Supplemental carnitine reduces serum triglycerides and levels of SGOT while also elevating high-density-lipoprotein cholesterol.[24]

Amino Acids

Amino acid chromatography patterns are aberrant in alcoholics; restoration to normal levels greatly aids the alcoholic patient.[27-30] Because the liver is the primary site of amino acid metabolism, it is not surprising that alcoholics develop abnormal amino acid patterns. Normalization of plasma amino acids is particularly indicated in those patients showing signs or symptoms of hepatic cirrhosis or depression. The branched-chain amino acids—valine, isoleucine, and leucine—inhibit the hepatic encephalopathy and increased protein catabolism that are common sequelae of cirrhosis.[30] Methionine, a known lipotropic, must be activated to S-adenosylmethionine. However, in severe liver disease, the activity of the corresponding enzyme is depressed. In this case, supplementation with methionine is not as useful. S-adenosylmethionine would be indicated to ameliorate associated deficiencies and resulting pathology.[31] Derangement of neurotransmitter profiles, particularly due to the low plasma levels of tryptophan typically seen in withdrawing alcoholics, will result if these profiles are not normalized, leading to depression, encephalopathy, and coma.[27,29]

Anomalous amino acid profiles are aggravated by the low-protein diet used as standard therapy for cirrhosis but this can can be avoided through the use of free-form amino acids without the risk of hepatic encephalopathy.[27,29] (See "Depression," later for a further discussion of amino acid imbalances.)

Although there are some characteristic amino acid abnormalities in alcoholics, an individual approach is indicated owing to differences in nutritional status, biochemistry, and the amount of liver damage. Correction of the imbalances probably requires amino acid chromatography for best results.

Vitamin C

In one study, a deficiency of ascorbic acid was found in 91% of patients with alcohol-related diseases.[32] Supplemental ascorbic acid helped ameliorate the effects of acute and chronic ethanol toxicity in experimental studies involving humans and guinea pigs, two species unable to synthesize their own ascorbic acid.[15,33] There is a direct correlation between leukocyte ascorbic acid levels (a good index of actual body ascorbic acid status), the rate of ethanol clearance from the blood, and the activity of hepatic ADH.[14] The evidence suggests that ascorbic acid, a strong reducing agent, can function as an electron donor similar to NAD in ethanol metabolism, thereby increasing the conversion of ethanol to acetaldehyde and the further catabolism of acetaldehyde.[15,33]

Selenium

Plasma selenium is clearly lower in alcoholic patients. Serum, erythrocyte, and whole-blood levels of selenium are also decreased in patients with alcohol dependence.[19] Low selenium status encourages depressed mood, whereas high dietary or supplementary selenium has been shown to improve mood.[34] Research has consistently reported that low selenium status was associated with a significantly increased incidence of depression, anxiety, confusion, and hostility.[19] Furthermore, when alcohol dependence and depression occur together, there is an increased risk for suicide.[35]

Given the propensity for low selenium status in alcoholic patients and the relation between selenium levels and mood disorders, selenium supplementation is warranted in an attempt to ameliorate the untoward comorbid psychological and physical profile, of patients with alcohol abuse or dependence.

B Vitamins

Alcoholics are classically deficient in most of the B vitamins.[1,8,32] These deficiencies result from various mechanisms:

- Low dietary intake
- Deactivation of the active form

- Impaired conversion to the active form by ethanol or acetaldehyde
- Impaired absorption
- Decreased storage capacity

Alcohol diminishes thiamine absorption in the intestine and reduces hepatic thiamine storage. It also decreases the phosphorylation of thiamine, leading to a reduction of the active form of thiamine, which also may contribute to development of thiamine deficiency.[36] A thiamine deficiency is both the most common (55% in one study[32]) and the most serious of the B vitamin deficiencies, because a deficiency causes beriberi and the Wernicke-Korsakoff syndrome. In addition, evidence indicates that a thiamine deficiency results in greater intake of alcohol, suggesting that thiamine deficiency is a predisposing factor for alcohol dependence.[37] It should be noted that once present, Wernicke-Korsakoff syndrome is refractory to oral doses of thiamine; therefore, rapid replacement of depleted brain thiamine levels by repeated parenteral therapy is required.[38]

A functional pyridoxine deficiency is also common in alcoholics, due not so much to inadequate intake as to impaired conversion to its active form, pyridoxal-5-phosphate, and enhanced degradation.[39] In addition to inhibiting conversion to more active forms, alcohol also decreases the absorption and utilization by the liver and increases the urinary excretion of many B vitamins, especially folic acid.[8,40]

Magnesium

Magnesium deficiency is common in alcoholics. In fact, hypomagnesemia is present in as many as 60% of alcoholics and is strongly linked to delirium tremens.[41] It is thought to be the major reason for the increased cardiovascular disease noted in alcoholics.[42] This deficiency is due primarily to a reduced magnesium intake coupled with alcohol-induced renal hyperexcretion of magnesium,[1,41] which continues during withdrawal despite low serum magnesium levels. Alcoholic cardiomyopathy, often associated with thiamine deficiency, may instead be due to a magnesium deficiency.

Essential Fatty Acids

Ethanol has been shown to interfere with essential fatty acid (EFA) metabolism and may produce symptoms of EFA deficiency if consumed in excess.[43] A 5-year study of alcohol-consuming rhesus monkeys linked a marginal EFA diet to alcoholic amblyopia, a rare neuropathy characterized by blurred vision, diminished retinal function, and a reduction in visual acuity.[44] Brain biopsies showed that the fatty acyl docosahexaenoic acid (DHA) composition of brain specimens had decreased significantly compared with controls. In the retinas of the alcohol-consuming animals at 5 years, there was a similar decrease in DHA. It may be useful to support neurologic function by giving EFAs in order to prevent these ophthalmologic sequelae.

Glutamine

Glutamine supplementation (1 g/day) has been shown to reduce voluntary alcohol consumption in uncontrolled human studies and experimental animal studies.[45-47] Although this research occurred more than 50 years ago, there has never been any follow-up to these preliminary studies. The failure to follow up this line of research is unfortunate, because the results were promising and showed the supplement to be safe and relatively inexpensive.

Psychosocial Aspects

Psychological and social measures are critical in the treatment of the alcoholic patient. It is important for the physician to maintain a nonjudgmental but not passive attitude toward the patient. Alcohol dependence should be viewed as a chronic, progressive, addictive, and potentially fatal disease, although many aspects of the alcoholic's behavior may make it difficult to maintain this objectivity.[1]

Social support for both patient and family is important, and success often appears proportional to the involvement of Alcoholics Anonymous (AA), counselors, and other social agencies. Because most physicians have not had adequate training or experience in handling the psychosocial aspects of this problem, it is important to establish a close working relationship with an experienced counselor and AA. Al-Anon and Ala-Teen are useful resources for family members.

Successful initiation of treatment requires the following:

- The patient's agreement that he or she has an alcohol problem
- Education of the patient and family about the physical and psychosocial effects of alcohol dependence
- Immediate involvement of the patient in a treatment program

Successful programs (such as AA) usually include strict control of drinking and replacement of the alcohol addiction with another addiction that is nonchemical, time consuming, and heavily supported by family, friends, and peers. Although strict abstinence may not be absolutely necessary, at this time it appears the safest and most effective choice.[1]

Depression

Depression is common among alcoholics and is known to lead to their high suicide rate. Many alcoholics are depressed first and later become alcoholic (primary depressives), whereas others become alcoholic first and later develop a depressive condition in the context of their alcohol dependence (secondary depressives). Alterations in the metabolism of serotonin and the availability of its precursor, tryptophan, have been implicated in some forms of depression, whereas other forms have been linked to alterations in catecholamine metabolism and tyrosine availability.

Alcoholics have severely depleted levels of tryptophan, which may explain both the depression and sleep disturbances common in alcohol dependence, because brain serotonin levels depend on circulating tryptophan levels.[48] Ethanol impairs tryptophan transport into the brain. The enzyme tryptophan pyrrolase, considered to be rate-limiting in tryptophan catabolism, is more active in rats during alcohol withdrawal.[28] In one study, 5 of 6 chronic alcoholics had no detectable plasma tryptophan on withdrawal.[27] The tryptophan levels returned to normal after 6 days of treatment and abstinence.

Another factor influencing tryptophan uptake into the brain is competition from amino acids—tyrosine, phenylalanine, valine, leucine, isoleucine, and methionine—that share the same transport; many of these are elevated in malnourished alcoholics.[27,28] Alcoholics have significantly depressed ratios of tryptophan to these amino acids when compared with normal controls, with depressed alcoholics having the lowest ratios.[28]

The major amino acids, whose elevated levels help to lower this ratio, are the catecholamine precursors, tyrosine and phenylalanine. Elevated plasma catecholamine levels are common in alcoholics and may contribute to depression.[49] An interesting finding is that taurine is also low in depressed alcoholics, with the lowest levels being reported in psychotic alcoholics.[27]

Miscellaneous Factors

Intestinal Flora

The intestinal microflora is severely deranged in alcoholics.[50] Colonization of the small intestine by endotoxin-producing bacteria

may lead to malabsorption of fats, carbohydrates, protein, folic acid, and vitamin B_{12}. This is probably the cause of the abnormalities of the small intestine commonly found in alcoholics. Alcohol ingestion also increases intestinal permeability to endotoxins and macromolecules, allowing increased toxic and antigenic effects.[51] The ensuing allergic reactions and deposition of immune complexes probably contribute to the many complications of alcohol dependence and, considering the addictive tendency of food allergies, may also contribute to alcoholic cravings.

Exercise

Involvement of the alcoholic patient in a graded, individually tailored fitness program has been shown to improve the likelihood of maintaining abstinence.[52] Research has shown that regular exercise is effective in alleviating anxiety and depression and enables individuals to respond better to stress. Improved fitness may allow for more effective responses to emotional upset, thereby reducing the patient's likelihood of resorting to alcohol when he or she is involved in conflict.

Kudzu (Pueraria Lobata)

Kudzu is one of the earliest medicinal plants used in traditional Chinese medicine. It has many profound pharmacologic actions, including antidipsotropic (anti–alcohol abuse) activity.[53,54] Two of its isoflavones, daidzin and daidzein, account for this effect. It appears to act by inhibiting aldehyde dehydrogenase 2 (ALDH-2).[54] A deficiency of this enzyme reduces the risk of alcohol dependence. Decreased drinking due to ALDH-2 inhibition is attributed to the aversive properties of acetaldehyde accumulated during alcohol consumption. However, daidzin can reduce drinking in some rodents without necessarily increasing acetaldehyde.

In human studies, the results have been mixed. In one study, kudzu treatment resulted in a significant reduction in the number of beers consumed, which was paralleled by an increase in the number of sips and the time to consume each beer and a decrease in the volume of each sip.[55] However, in a double-blind trial, kudzu root extract (1.2 g twice a day) produced no statistically significance difference in craving and sobriety scores compared with the placebo group.[56] It may be that kudzu reduces alcohol intake without significantly affecting cravings.

Milk Thistle (Silybum Marianum)

The flavonoid complex of milk thistle (silymarin) appears to be useful for the alcoholic, especially in the presence of considerable liver involvement or cirrhosis. Silymarin has been shown to be effective in the treatment of the full spectrum of alcohol-related liver disease, from relatively mild to serious cirrhosis. Perhaps the most significant benefit is extending the life span of these patients. In one study, 87 cirrhotics (46 with alcoholic cirrhosis) received silymarin while 83 cirrhotics (45 with alcoholic cirrhosis) received a placebo.[57] The mean observation period was 41 months. In the treatment group, there were 24 deaths, among which 18 were related to liver disease; among the controls, there were 37 deaths with 31 related to liver disease. The 4-year survival rate was 58% in the treatment group compared with 39% in the controls.

Silymarin can also improve immune function in patients with cirrhosis.[58] Whether this effect is involved in the hepatoprotective action or a result of improved liver function has yet to be determined.

THERAPEUTIC APPROACH

Alcohol dependence is difficult to treat. Although many therapeutic regimens have been attempted, there has been little documented long-term success except for that of AA (and even the overall success of this program is highly controversial). The approach presented here is unique in that we have attempted to develop an integrated, whole-person, stage-oriented program.

The treatment of the alcoholic patient must be optimized for the four stages of alcohol dependence: active alcohol consumption, withdrawal, recovery, and recovered. The recovery stage is defined here as the period between withdrawal and full reestablishment of normal metabolic function. All alcoholics, at whatever stage, benefit the most by employing simultaneous counseling, lifestyle, and metabolism-balancing therapies. Following are the recommended therapies in the usual context, with additional recommendations for each stage. Also, a complete diagnostic workup is necessary owing to the high risk that the alcoholic patient will develop a wide variety of clinical and subclinical diseases.

Recommendations for All Four Stages

Diet

Stabilization of blood sugar levels is critical to successful treatment. Although a strict hypoglycemic diet may not be warranted, most of the dietary guidelines must be followed. These include elimination of all simple sugars (foods containing added sucrose, fructose, or glucose; fruit juice; dried fruit; and low-fiber fruits such as grapes and citrus fruits); limitation of processed carbohydrates (e.g., white flour, instant potatoes, white rice); and an increase in complex carbohydrates (e.g., whole grains, vegetables, beans).

Supplements

- Vitamin A: 5000 IU a day
- Vitamin B complex: 20 times the recommended daily allowance
- Vitamin C: 1 g two times a day
- Vitamin E: 400 IU a day (d–α-tocopherol)
- Magnesium: 250 mg two times a day
- Selenium: 200 mg a day
- Zinc: 30 mg a day (picolinate)
- Carnitine: 500 mg two times a day (L-carnitine)
- Glutamine: 1 g a day
- *Lactobacillus acidophilus*: 1 tsp a day

Exercise

A graded program should be established, using heart-rate response to determine intensity. The patient should exercise five to seven times a week for 20 to 30 minutes at an intensity sufficient to raise the heart rate to 60% to 80% of maximum for the age group.

Counseling

The physician dealing with alcoholism should have a good working relationship with AA and an experienced counselor who has particular expertise in working with alcoholics.

Additional recommendations for the four stages follow.

Specific Recommendations for Each Stage

Stage I: Active Alcohol Consumption

The physician should work with family, peers, social contacts, and whomever else is involved with the patient to elicit his or her recognition of an alcohol problem and willingness to enter a treatment program.

Additional supplements include the following:

- Pyridoxal-5-phosphate: 20 mg a day
- Riboflavin: 100 mg a day
- Vitamin A: 5000 IU a day
- Zinc: 30 mg a day

Stage II: Withdrawal

The severity of symptomatology varies widely, although it is usually proportional to the degree of physiologic dependence and duration of the disease. Milder cases usually start within a few hours after cessation of drinking and typically resolve within 48 hours. More severe cases usually occur only in patients older than 30 years of age and usually develop after about 48 hours of abstinence. These patients should be admitted to an inpatient facility. Some institutions may not allow the use of supplements; this should be checked before a patient is admitted.

Additional supplements include the following:

- Tryptophan: 3 g a day
- Riboflavin: 100 mg a day
- Electrolyte replacement as necessary
- Flaxseed oil: 1 tbsp three times a day

Stage III: Recovering

A strong network of caring family, friends, and peers should be established, if possible, to regularly support the patient, who would do well to become involved and busy with intense, people-oriented activities. It is also vital for the patient to recognize that alcohol is no answer to the stresses of life; he or she should be helped to develop more effective ways of handling adversity.

Stage IV: Recovering to Advanced Recovery

The patient's support group must always be maintained. Continued total abstinence is the best policy, although carefully controlled drinking may be possible. After a 6-month abstinence, supplement dosages may be slowly reduced to 25% of the initial dosages.

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CHAPTER 144

Alzheimer's Disease

Michael T. Murray, ND

DIAGNOSTIC SUMMARY

- Progressive mental deterioration, loss of memory and cognitive functions, inability to carry out activities of daily life
- Characteristic symmetrical, usually diffuse electroencephalographic (EEG) pattern
- Diagnosis usually made by exclusion
- Definitive diagnosis can be made only by postmortem biopsy of the brain, demonstrating atrophy, senile plaques, and neurofibrillary tangles

GENERAL CONSIDERATIONS

Alzheimer's disease (AD) is a neurodegenerative disorder that clinically manifests itself as a progressive deterioration of memory and cognition or dementia. In the United States, the prevalence of AD is now estimated to be 1.6% before the age of 74, with the rate increasing to 19% in the 75- to 84-age group and to 42% in those above 84 years of age. These numbers are striking compared with data from the 1960s, indicating an incidence of only 2% in people over the age of 85 years. The tremendous increase in AD in people over 85 years of age is often referred to as the "Alzheimer's epidemic."

Neuropathology

AD has distinctive neuropathologic features, including the following[1]:

- Plaque formation
- Amyloid deposition
- Neurofibrillary tangles
- Granulovacuolar degeneration
- The massive loss of telencephalic neurons

These findings are particularly evident in the cerebral cortex and hippocampal formation.

The clinical features of AD are believed to be related to cholinergic dysfunction due to appreciable reductions in the activity of the enzyme choline acetyltransferase, the enzyme that synthesizes acetylcholine, and the neuronal transfer of choline.

Etiology

The two core pathologic hallmarks of AD are an accumulation of β-amyloid and the formation of neurofibrillary tangles. *Amyloid* is a general term for protein fragments that the body produces normally. Beta-amyloid is a fragment snipped from an amyloid precursor protein (APP). In a healthy brain, these fragments are broken down and eliminated. In AD, Beta-amyloid protein fragments accumulate to form hard plaques between neurons, blocking the transmission of messages and leading to the death of brain cells, neurofibrillary tangles, and ultimately, dementia. Tau, a microtubule-associated protein, is the major constituent of neurofibrillary tangles and is produced in soluble hyperphosphorylated form when β-amyloid levels become toxic.

Genetic factors play a major role and are estimated to account for up to 70% of cases of AD. Several genes have been linked to AD: the APP on chromosome 21 (explaining the close association between Down syndrome and AD); the presenilin genes on chromosomes 14 and 1; and the apolipoprotein E *(ApoE)* gene on

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chromosome 19. The first two mutations are rare and associated with symptoms developing before the age of 50. The most significant genetic finding is the link with the ApoE gene. One form of ApoE, the e4-type, is linked to a significantly greater risk for AD; another, the e2-type, is associated with significant protection.

Literature is also accumulating regarding the role of genetically linked aberrant immune system regulation of inflammation as a possible contributor to AD. Although innate immune function in the brain is normally modulated to remove plaque in an attempt to maintain health, research is beginning to characterize a chronic and excessive reaction to immune protofibrils of amyloid proteins in the brain that can promote disease.[2] As a result, immunotherapeutic approaches have recently been developed for the treatment of AD. Chief among these strategies is to immunize AD patients with Abeta peptides so that they will generate antibodies that bind to Abeta protein and enhance its clearance.[3] Although preclinical studies were successful, the initial human clinical trial of an active Abeta vaccine was halted owing to the development of meningoencephalitis in approximately 6% of the vaccinated AD patients.

Although genes play a significant role in determining susceptibility to AD, lifestyle and environmental factors also play significant roles, as in most chronic degenerative diseases. Emerging research reveals that dietary factors are important. Poor-quality diets with excess saturated or trans fatty acids may predispose neurons to environmental toxicities.[4,5] Some data suggest that abnormal sleep-wake cycles and decreased morning light exposure may play a role in the expression of AD (see "Melatonin, later"). Traumatic injury to the head; chronic exposure to aluminum, silicon, or both; exposure to neurotoxins from environmental sources; and free radical damage have all been implicated as causative factors as well. As in the pathophysiology of other chronic degenerative diseases, there is considerable evidence that increased oxidative damage plays a central role. Therapies designed to support antioxidant mechanisms (discussed later) may be quite helpful in the prevention of AD.[6]

The tremendous increase in AD parallels the rise in type 2 diabetes and insulin resistance, suggesting a possible connection. It is well established that individuals with type 2 diabetes have a 1.5- to 4-fold higher than normal risk for AD as well as vascular dementia. Impaired insulin signaling and insulin resistance in the brain or the decrease in cerebral insulin receptors associated with aging may be another important factor in the pathogenesis of AD. Furthermore, hyperglycemia induces increased peripheral utilization of insulin, resulting in reduced insulin transport into the brain. Insufficient insulin signaling make neurons energy-deficient and vulnerable to oxidizing or other metabolic insults, leading to the destruction of mitochondria and ultimately the neuron. Cerebral hypoinsulinemia (as well as hyperinsulinemia) leads to β-amyloid accumulation and increased tau phosphorylation. Measures to improve glycemic control and improve both peripheral and brain insulin sensitivity appear to be important steps in the prevention of AD.[7,8]

Aluminum

Considerable attention has focused on the association of aluminum concentration in the neurofibrillary tangle (NFT). Whether the aluminum concentration develops in response to AD or whether it initiates the lesions has not yet been determined, but significant evidence shows that it contributes, possibly significantly, to the disease.

Aluminum has a strong affinity for the paired helical filament tau (PHF-t), which is involved in the formation of the NFTs. In fact, studies have demonstrated that aluminum is the cofactor along with this tau filament in the formation of the NFTs.[9] The aluminum selectively binds to PHF-t, induces PHF-t to aggregate, and retards the brain's ability to break down PHF-t. Aluminum's role in AD is further supported by a recent animal study that evaluated long-term exposure to ecologic doses of aluminum. In this study, researchers found ghost-like neurons with cytoplasmic and nuclear vacuolations together with aluminum deposits. The hippocampus contained neuritic plaques while the cerebrovasculature exhibited amyloid deposits. The authors also found behavioral changes in these rats reminiscent of those observed in AD.[10]

A great deal of circumstantial evidence links chronic aluminum exposure to AD. Increasing aluminum concentrations in the brain could explain why AD increases with increasing age. A study of 356 healthy people has shown that serum aluminum concentration increases as people age.[11] Those with AD have significantly higher aluminum levels than both normal people and patients with other types of dementias, such as those due to alcohol, atherosclerosis, and stroke. Efforts to remove the aluminum appear to help somewhat, but such measures are probably too late once the disease is well established. For example, intramuscular injections of deferoxamine (a chelating agent for the removal of iron and aluminum) over a 2-year period showed a significant slowing of the rate of decline in 48 AD patients.[12]

Even in those without mental disease, elevated aluminum levels are associated with poorer mental function. For example, in a study of dialysis patients, the 13 patients who had a positive aluminum deferoxamine test (a measure of the amount of aluminum in the body) were compared with 13 who had a negative test. Subjecting the entire group to four attention tests and two memory tests revealed that those with higher levels of aluminum had a moderate to considerable disturbance of mental function.[12]

The aluminum appears to come from the water supply, food, antacids, and deodorants. The most significant source is probably drinking water, because the aluminum in water is in a more bioavailable and thus potentially toxic form. Researchers measured the aluminum absorption of tap water by adding a small amount of soluble aluminum in a radioactive form to the stomachs of animals. They discovered that the trace amounts of aluminum from this single exposure immediately entered the animals' brain tissue. The frightening news is that aluminum in water occurs not only naturally but is also added (in the form of alum) to treat some water supplies.[13]

DIAGNOSTIC CONSIDERATIONS

A comprehensive diagnostic workup is paramount in the approach to the demented patient. It is very important to rule out conditions that can mimic dementia. For example, depression, which can mimic dementia in the elderly, is common. Table 144-1 lists other possible causes of dementia. The most common reversible cause of dementia is drug toxicity. Other important causes are metabolic and nutritional disorders, such as hypoglycemia; thyroid disturbances; and vitamin B_{12}, folate, and thiamine deficiencies.

A comprehensive evaluation should include the following[14]:

- A detailed history
- Neurologic and physical examinations
- Psychological evaluation with particular attention to depression
- A general medical evaluation with emphasis on the detection of subtle metabolic, toxic, or cardiopulmonary disorders that can precipitate confusion, especially in the elderly
- A series of standardized neurophysiology tests such as the Mini–Mental State Examination or Folstein test to document the type and severity of cognitive impairment

TABLE 144-1 **Causes of and Mechanisms in the Development of Senile Dementia**

ETIOLOGY	PATHOGENESIS
Degenerative etiology	Disturbances of gene expression and thus of protein metabolism
Altered genetic code	Disturbance of the synthesis of specific proteins
Alzheimer's disease	Reduction in acetylcholine synthesis resulting from decreased choline acetyltransferase activity
Huntington's chorea	Disturbance of the GABA-nergic system
Idiopathic dementia	
Localized form	Decline in cognitive function
Parkinson's disease	Reduction in dopamine turnover
Pick's disease	Reduction in cholinergic activity
Loss of neuronal redundancy	Disturbance of cerebral metabolism following infection or trauma
	Reduction in cholinergic activity caused by loss of neurons and synapses
Cerebrovascular disease	
Chronic meningitis	
Tuberculous, mycotic	
Encephalomyelitis	
Encephalopathy following head injury (boxers)	
Epileptic dementia	
Virus encephalopathy	
Nutritive etiology	
Chronic alcoholism	
Diabetes mellitus	
Disturbances of electrolyte metabolism	
Hypoglycemia	Insulin, starvation
Hyponatremia	Diuretics
Hypothyroidism	
Korsakoff's syndrome	Thiamine transketolase deficiency
Nicotinamide deficiency	
Vitamin B deficiency	Disturbances of energy formation
Toxic etiology	
Addiction to barbiturates, psychotropic drugs, etc.	
Chronic carbon monoxide intoxication	
Chronic cesium intoxication	
Mycotoxins	
Renal/hepatic encephalopathy	
Vincristine intoxication	

TABLE 144-2 **Recommended Laboratory Tests Used in the Diagnosis Dementia**

TEST	RATIONALE
CBC	Anemia, infection
VDRL	Syphilis
Electrolytes	Metabolic dysfunction
Liver function tests	Hepatic dysfunction
BUN	Renal dysfunction
TSH, T_4, T_3, T_3U	Thyroid dysfunction
Serum B_{12} and RBC folate	Deficiency
Urinalysis	Renal/hepatic dysfunction
Hair mineral analysis	Heavy metal intoxication
ECG	Heart function
EEG	Focal vs. diffuse
CT scan	Atrophy, intracranial mass

BUN, Blood urea nitrogen; CBC, complete blood cell count; CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalogram; RBC, red blood count; TSH, thyroid-stimulating hormone; VDRL, Venereal Disease Research Laboratory.

Table 144-2 lists recommended tests for appropriate laboratory assessment.

The EEG is an important diagnostic tool serving to differentiate types of dementia. Although a normal EEG does not rule out the diagnosis of dementia, particularly in its early stages, it does provide valuable information. AD is associated with a characteristic symmetrical, usually diffuse slowing of the EEG. More importantly, the EEG differentiates focal (e.g., intracranial mass or vascular disease) from diffuse (e.g., metabolic disorders or normal-pressure hydrocephalus) brain dysfunction.

Computed tomography or magnetic resonance imaging with single photon emission computed tomography (SPECT) or positron emission tomography (PET) can help to exclude other cerebral pathology or subtypes of dementia.

A new technique known as PiB PET has been developed for directly and clearly imaging β-amyloid deposits in vivo using a chemical tracer that binds selectively to the A-beta deposits. This modality is showing tremendous promise.

Fingerprint Patterns

Abnormal fingerprint patterns are associated with both AD and Down syndrome.[15] Compared with the normal population, AD and Down syndrome patients show an increased number of ulnar loops on the fingertips, with a concomitant decrease in whorls, radial loops, and arches. Ulnar loops (pointing toward the ulnar bone, away from the thumb) are frequently found on all 10 fingertips. Radial loops (pointing toward the thumb), when they do appear, tend to be shifted away from the index and middle fingers—where they most commonly occur—to the ring and little fingers. In patients with this fingerprint pattern, which is characteristic of AD, it is recommended that an aggressive preventive approach be instituted immediately.

THERAPEUTIC CONSIDERATIONS

The primary areas of intervention from a natural medicine perspective involve prevention by addressing suspected pathophysiology and using natural measures to improve mental function in the early stages of the disease. In the advanced stages of AD, natural measures will provide only limited benefit.

Diet

Dietary factors are clearly important in the etiology of AD. Food choices consistent with the standard American diet are associated with a significant risk for the development of AD. A diet high in

saturated fat and *trans* fatty acids and low in dietary antioxidants may lead to increased serum and brain concentrations of aluminum and transition metal ions, which are implicated in oxidative stress, potentially leading to the neurologic damage characteristic of AD. In addition, poor-quality diets may also increase the prevalence of AD by eliciting cerebral inflammation, which may cause the neurologic damage that results in AD.[4,5,12]

Many dietary risk factors for AD are shared with those implicated in atherosclerosis. Likewise, adherence to a Mediterranean-type diet is associated with decreased cognitive decline just as it is with a reduced risk for cardiovascular disease. Recent prospective studies have provided clear evidence that following a Mediterranean-type diet is associated with slower cognitive decline, reduced risk of progression from mild cognitive impairment (MCI) to AD, reduced risk of AD, and a decreased all-cause mortality in AD patients. These findings suggested not only a lower risk for AD, but also of predementia syndromes and their progression to overt dementia.[16,17]

The key dietary factors from epidemiologic data that reduce AD risk are higher fish consumption (and omega-3 fatty acids), monounsaturated fatty acids (primarily from olive oil), light to moderate alcohol use (primarily red wine), and increased nonstarchy vegetable and fruit consumption. It is likely that it is the combination of all of these factors rather than any single one that provides the highest degree of protection.[16,17]

One study in particular produced some very interesting findings. Given the ability of the Mediterranean diet to reduce inflammation and improve insulin sensitivity, it is assumed that this action may be of extreme importance in its ability to reduce AD. However, in a 4-year prospective study, the lower risk of AD with the Mediterranean diet did not seem to be mediated by C-reactive protein, fasting insulin, or adiponectin levels.[18] Other aspects of the diet or specific foods are likely responsible, including dietary components that work directly on reducing β-amyloid formation or deposition. For example, polyphenols found in grapes, grape seed extract, and red wine have been shown to prevent β-amyloid formation and promote tau disassembly.[19,20] Pharmacokinetic studies in animals with radiolabeled grape polyphenols show absorption into the brain after oral administration.[21]

Even something as simple as celery (*Apium graveolens*) consumption may offer significant protection against AD. Celery and celery seed extracts contain a unique compound, 3-n-butylphthalide (3nB), that is both responsible for the characteristic odor of celery and its health benefits. In an animal model of AD, 3nB treatment significantly improved learning deficits as well as long-term spatial memory. 3nB treatment also significantly reduced total cerebral β-amyloid plaque deposition and lowered brain β-amyloid levels. It was also shown that 3nB markedly directed amyloid precursor protein processing toward a pathway that precludes β-amyloid formation. The researchers concluded, "3nB shows promising preclinical potential as a multitarget drug for the prevention and/or treatment of AD."[22]

The research on grape polyphenols and 3nB stimulates a powerful question. How many other foods contain unique compounds that address the pathophysiology of AD? From preliminary investigations it looks like a great many, especially promising are sources of phenols and polyphenols.[23-27]

Estrogen

Estrogen has been promoted to offer protective and possibly therapeutic benefits in AD. However, the epidemiologic and clinical evidence to support the potential benefits of estrogen is contradictory. Sixteen population-based studies have indicated that women on hormone replacement therapy (HRT) had a lower rate of AD.[28] But the problem with these studies is that the women taking HRT were much healthier before taking the hormones compared with the control group (i.e., women who are prescribed HRT are less likely to have hypertension, diabetes, and history of stroke than nonusers).[28] Data from the only large randomized controlled trial published to date, the Women's Health Initiative Memory Study, did not confirm these observations and even suggest an increase in dementia risk for women using HRT compared with controls, especially in the cases of women given HRT after menopause.[29] Clinical trials in women with AD have concluded that estrogen therapy does not improve dementia symptoms in women with AD and should definitely be avoided postmenopause.[30-32] Given the cloud of uncertainty about the benefits of HRT, it seems most reasonable to consider that at this point the risks of conventional estrogen therapy to prevent AD outweigh the benefits. See Chapter 188, on menopause, for a discussion of the critical differences.

Aluminum

Encouraging the avoidance of all known sources of aluminum—aluminum-containing antacids, aluminum-containing antiperspirants, cooking in aluminum pots and pans, the wrapping of food in aluminum foil, and the use of nondairy creamers—certainly seems appropriate. Aluminum is also found in baking powder and table salt, because it is added to keep them from becoming lumpy. In addition, citric acid, as well as calcium citrate supplements, appear to increase the efficiency of absorption of aluminum (but not lead) from water and food.[33] Aluminum absorption can be decreased by magnesium, because magnesium competes with aluminum for absorption, not only in the intestines but also at the blood–brain barrier.[34] A diet rich in magnesium is recommended. Have the patient focus on unprocessed foods; avoid milk and dairy products; and increase the consumption of vegetables, whole grains, nuts, and seeds—all good sources of magnesium.

NUTRITIONAL CONSIDERATIONS

Nutritional status is directly related to cognitive function in the elderly.[35] Given the frequency of nutrient deficiency in the elderly population, it is likely that many cases of impaired mental function may have a nutritional etiology. As pointed out above, diet is critically important in the prevention and arrest of AD, with various components working together in a synergistic fashion to address many of the key underlying pathophysiologic features of AD.

Antioxidants

As mentioned above, considerable evidence indicates that oxidative damage plays a major role in the development and progression of AD.[6,36,37] Epidemiologic evidence suggests that antioxidant nutrients offer significant protection against AD.[4,38] Prospective and clinical studies have primarily focused on vitamins C and E and β-carotene with somewhat favorable results (see Table 144-3).[36,39-42] As with other chronic degenerative diseases, better results may be achieved with a broader range of supplemental nutrients. For example, in a French cohort of middle-aged adults, 13 years of daily supplementation of 120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of β-carotene, 100 mcg of selenium, and 20 mg of zinc compared with placebo was significantly associated with better verbal memory, a cognitive domain that is particularly vulnerable to pathologic aging and AD. These results appear to be significantly better

TABLE 144-3 **Prospective Studies of Antioxidants and the Risk of Alzheimer's Disease**

STUDY	FOLLOW-UP	FINDINGS
Rotterdam Study	6 years	Dietary vitamin E effective (more among current smokers)
Canadian Study of Health and Aging	5 years	Combination of vitamins E and C supplementation and/or multivitamin consumption effective
Chicago Health Aging Study	3.9 years	Dietary vitamin E effective only among non-apoE4 carriers
Washington Heights-Inwood Columbia Aging Project	4 years	No effect of vitamin E (diet or supplement)
Cache County Study	3 years	Vitamin E alone not effective but effective when combined with vitamin C
Honolulu-Asia Aging Study	30 years	Dietary vitamin E not effective
Duke Established Populations for Epidemiologic Studies of the Elderly	10 years	No effect of vitamins C and/or E
Group Health Cooperative	5.5 years	No effect of supplemental vitamins E and C alone or in combination

Data from Practico D. Oxidative stress hypothesis in Alzheimer's disease: a reappraisal? Trends Pharmacol Sci 29(12):609-615, 2008.

than those achieved with vitamins C, E, and β-carotene either alone or in combination.

It is entirely possible (and likely probable) that vitamins E and C, and β-carotene may simply be markers of increased "phytochemical antioxidant" intake rather than playing a significant role on their own. Fruits and vegetables contain an array of antioxidant compounds beyond nutritional antioxidants. Some of these may exert specific effects of considerable benefit against the pathophysiology of AD. Often researchers make the mistake of thinking that the antioxidant activity of a particular fruit or vegetable is due solely to its vitamin C, E, or β-carotene content. However, these nutrient antioxidants often account for only a small fraction of a food's antioxidant effect. For example, these nutrients account for only about 0.5% of the total antioxidant activity of an apple. The overwhelming antioxidant activity of fruits and vegetables comes from phytochemicals such as flavonoids, phenols, and other carotenoids.[43] Several phytochemicals are showing tremendous promise in protecting against AD by interfering with the formation and deposition of β-amyloid.[23-25]

Thiamine

Although severe thiamine deficiency is relatively uncommon except in alcoholics, many Americans do not consume even the recommended daily allowance (RDA) of 1.5 mg, especially the elderly. In an attempt to gauge the prevalence of thiamine deficiency in the geriatric population, 30 unselected consecutive outpatients visiting a university outpatient clinic in Tampa, Florida, were tested for thiamine levels. Depending on the thiamine measurement (plasma vs. red blood cell thiamine), low levels (defined as a level below the lowest reference range for younger age groups) were found in 57% and 33%, respectively.[44]

In addition to its role as a nutrient, thiamine also demonstrates some pharmacologic effects on the brain. Specifically, it mimics the important neurotransmitter involved in memory—acetylcholine. Thiamine has been shown to potentiate and mimic the effects of acetylcholine in the brain.[45] This effect explains the positive clinical results that have been noted for thiamine, (3-8 g/day) in improving mental function in AD and age-related impaired mental function (senility).[46,47] High-dose thiamine supplementation exerts its benefits without side effects.

These results highlight the growing body of evidence that a significant percentage of the geriatric population is deficient in one or more of the B vitamins. Given the essential role of thiamine and other B vitamins in normal human physiology, especially cardiovascular and brain function, routine B vitamin supplementation appears to be worthwhile in this age group. AD may simply be the result of chronic low intake of essential nutrients—key among which are the B vitamins.

Vitamin B_{12}

Another key B vitamin linked to AD is vitamin B_{12}. Vitamin B_{12} deficiency results in impaired nerve function, which can cause numbness, paresthesias, or a burning feeling in the feet as well as impaired mental function, which in the elderly can mimic AD. Vitamin B_{12} deficiency is thought to be quite common in the elderly and is a major cause of depression in this age group. Determination of vitamin B_{12} deficiency is best achieved by measuring the level in the blood (serum cobalamin) or the level of methylmalonic acid in the urine. In addition, measurement of the level of plasma homocysteine is emerging as a method to determine the status of both vitamin B_{12} and folate.

Several investigators have found that the level of vitamin B_{12} declines with age and that vitamin B_{12} deficiency is found in 3% to 42% of persons aged 65 and older. Diagnosing cobalamin deficiency early in the elderly is important because it is easily treatable and, if left untreated, can lead to impaired neurologic and cognitive function.[48,49]

In one study among 100 consecutive geriatric outpatients who were seen in office-based settings for various acute and chronic medical illnesses but not for vitamin B_{12} deficiency–related diseases like pernicious anemia, 11 patients had serum cobalamin levels at 148 pmol/L or below; 30 patients had levels between 148 and 295 pmol/L; and 59 patients had levels above 296 pmol/L.[50] After the initial cobalamin determination, the subjects were followed for up to 3 years. The patients with cobalamin levels below 148 pmol/L were treated and not included in the analysis of declining cobalamin levels. The average annual decline in serum cobalamin level was 18 pmol/L for patients who had higher initial serum cobalamin levels (actual range, 224-292 pmol/L). For patients with lower initial cobalamin levels, the average annual serum cobalamin decline was much higher, at 28 pmol/L.

These results indicate that measurement of the level of vitamin B_{12} in the blood (serum cobalamin), the urinary excretion of methylmalonic acid, or the level of homocysteine[51] as a screening test for vitamin B_{12} deficiency appears to be indicated in the elderly, given the positive cost-benefit ratio.[52,53] To test for vitamin

B_{12} deficiency, the urinary methylmalonic acid assay is perhaps the best in that it is sensitive as well as being noninvasive and relatively convenient for the patient. Correction of an underlying vitamin B_{12} deficiency can significantly improve mental function and quality of life in these patients. Serum homocysteine is also being studied, for a growing body of literature demonstrates clear correlations between high levels of this marker and cardiovascular disease and, more recently, dementia and AD. High homocysteine levels (>14 mmol/L) nearly double the risk of AD.[54]

The importance of a detailed examination in elderly patients with mental symptoms is highlighted by results from a study that analyzed the plasma homocysteine, serum cobalamin, and blood folate in 296 consecutive patients referred to a geriatric psychiatric ward in Sweden for the diagnosis of mental disease.[55] Patients who were deficient in vitamin B_{12} or folic acid or who had elevated levels of homocysteine were given vitamin B_{12} (dosage not specified) or folic acid (10 mg/day), or both. When individuals with low cobalamin levels were supplemented with vitamin B_{12}, significant clinical improvements were noted.

In other studies, supplementation with vitamin B_{12} has shown tremendous benefit in reversing impaired mental function due to low levels of vitamin B_{12}.[48] In one large study, a complete recovery was observed in 61% of similar cases of mental impairment.[56] The fact that 39% did not respond is probably a result of long-term low levels of vitamin B_{12}. Several studies have shown that the best clinical responders are those who have been showing signs of impaired mental function for less than 6 months.[29] In one study, 18 subjects with low levels of serum cobalamin and evidence of mental impairment were given vitamin B_{12}. Only those patients who had symptoms for less than 1 year showed improvement.[57] The importance of diagnosing and correcting low vitamin B_{12} levels in the elderly cannot be overstated.

Serum vitamin B_{12} levels are significantly low, and vitamin B_{12} deficiency is significantly common in AD patients.[48,58,59] It has recently been demonstrated that an oral daily dose as low as 50 mcg can significantly increase serum vitamin B_{12} levels in vitamin B_{12}–deficient elderly persons.[60] Supplementation of vitamin B_{12}, folic acid, or both may result in complete reversal in some patients, but generally there is little improvement in patients who have had AD symptoms for more than 6 months. It has been hypothesized that prolonged low levels of vitamin B_{12} may lead to irreversible changes that will not respond to supplementation. Vitamin B_{12} supplementation to elderly subjects with AD will improve hematologic parameters but will not usually improve mental function.[61]

Vitamin B_{12} is available in several forms. The most common form is cyanocobalamin; however, vitamin B_{12} is active in the human body in only two forms: methylcobalamin and adenosylcobalamin. Although methylcobalamin and adenosylcobalamin are active immediately on absorption, cyanocobalamin must be converted to either methylcobalamin or adenosylcobalamin by removal of the cyanide molecule and addition of either a methyl or adenosyl group. This conversion may be reduced with aging and may be another factor responsible for the vitamin B_{12} disturbances noted in the elderly population.

Zinc

Zinc deficiency is one of the most common nutrient deficiencies in the elderly and has been suggested to be a major factor in the development of AD.[62] Included in the list of zinc-containing enzymes are most enzymes involved in DNA replication, repair, and transcription. It has been suggested that dementia, possibly because of a long-term zinc deficiency, may represent the long-term cascading effects of error-prone or ineffective DNA-handling enzymes in nerve cells.[63] In addition, zinc is required by many antioxidant enzymes, including superoxide dismutase. The end result could be the destruction of nerve cells and the formation of NFTs and plaques. The levels of zinc in the brain and cerebrospinal fluid in patients with AD are markedly decreased, and there is a strong inverse correlation between serum zinc levels and the senile plaque count.[64]

Zinc supplementation has demonstrated good benefits in AD. In one study, 10 patients with AD were given 27 mg/day of zinc (as zinc aspartate). Only two patients failed to show improvement in memory, understanding, communication, and social contact. In one 79-year-old patient, the response was labeled "unbelievable" by both medical staff and family.[65] Unfortunately there does not seem to be much interest in the scientific community in following up these impressive results with zinc therapy.

The most recent medical literature acknowledges zinc's apparent duality as "The Zinc Paradox."[66] Fueling this ambivalence is conflicting information that zinc may be problematic for AD patients because, in vitro, it accelerates the formation of insoluble β-amyloid peptide.[67] Although zinc is neurotoxic at high concentrations and accumulates at sites of degeneration, total tissue zinc is markedly reduced in the brains of AD patients. Other research has shown a much higher concentration of copper-zinc superoxide dismutase in and around the damaged brain tissue of AD patients.[68] This suggests that the increased concentration of zinc in the damaged areas is due to the body's efforts to neutralize free radicals through the increased local production of dismutases. A possible corollary is that the higher focal levels of zinc result in increased amyloid formation when the free radical scavenging mechanisms have been inadequate.

Phosphatidylcholine

Because dietary phosphatidylcholine can increase acetylcholine levels in the brain in normal patients and AD is characterized by a decrease in cholinergic transmission, it seems reasonable to assume that phosphatidylcholine supplementation would benefit AD patients. However, the basic defect in cholinergic transmission in AD relates to impaired activity of the enzyme acetylcholine transferase. This enzyme combines choline (as provided by phosphatidylcholine) with an acetyl molecule to form acetylcholine, the neurotransmitter. Providing more choline does not necessarily increase the activity of this key enzyme, so phosphatidylcholine supplementation is not beneficial in the majority of patients with AD. Not surprisingly, clinical trials using phosphatidylcholine have largely been disappointing. Studies have shown inconsistent improvements in memory from choline supplementation in both normal and AD patients.[69-72] The studies have been criticized for small sample size, low dose of phosphatidylcholine, and poor design. Furthermore, some researchers are questioning the form of choline used.[73] Other forms, such as phosphatidylserine (see later) or choline alphoscerate,[74] may prove more useful in supporting cholinergic transmission.

In a patient with mild to moderate dementia, the use of a high-quality phosphatidylcholine preparation may be worth a try. A dosage of 15 to 25 g/day of phosphatidylcholine is required. If there is no noticeable improvement within 2 weeks, supplementation should be discontinued.

Phosphatidylserine

Phosphatidylserine is the major phospholipid in the brain, where it plays a major role in determining the integrity and fluidity of cell

membranes. Normally, the brain can manufacture sufficient levels of phosphatidylserine, but a deficiency of methyl donors like S-adenosylmethionine (SAMe), folic acid, and vitamin B_{12} or essential fatty acids may inhibit the production of sufficient phosphatidylserine. Low levels of phosphatidylserine in the brain are associated with impaired mental function and depression in the elderly.

The primary use of phosphatidylserine is in the treatment of depression, impaired mental function, or both in the elderly, and also in the treatment of AD. To date, the 11 double-blind published studies have all reported the successful use of phosphatidylserine in the treatment of age-related cognitive decline, AD, or depression.[75-84] In the largest study, a total of 494 elderly patients (between 65 and 93 years of age) with moderate to severe senility were given either phosphatidylserine (100 mg three times a day) or a placebo for 6 months.[85] The patients were assessed for mental performance, behavior, and mood at the beginning and end of the study. Statistically significant (P <0.01) improvements were noted in mental function, mood, and behavior for the phosphatidylserine group.

L-Acetylcarnitine

A great deal of research has been conducted over the past decade with L-acetylcarnitine (LAC) in the treatment of AD, senile depression, and age-related memory defects. LAC is composed of acetic acid and L-carnitine bound together. This reaction occurs naturally in the human brain. Therefore, it is not exactly known how much more of an effect is achieved with LAC versus L-carnitine. However, LAC is thought to be substantially more active than other forms of carnitine in conditions involving the brain.[85,86]

The close structural similarity between LAC and acetylcholine led to an interest in using LAC in AD. Research has shown that LAC does mimic acetylcholine and is of benefit not only in patients with early-stage AD but also in elderly patients who are depressed or have impaired memory.[86] It has also been shown to act as a powerful antioxidant within the brain cell, stabilize cell membranes, and improve energy production within the brain cell as well as enhance or mimic the function of acetylcholine.[87]

The latest meta-analysis involving studies of LAC in mild cognitive impairment and mild (early) AD is promising in terms of showing both clinical and psychometric improvements. Double-blind placebo-controlled prospective parallel-group comparison studies of at least 3 months' duration were reviewed. Using a dose range of 1.5 to 3 g/day, treatment time points were assessed at 3, 6, 9, and 12 months. This analysis showed a significant advantage for acetyl-L-carnitine compared with placebo. The advantage for acetyl-L-carnitine was seen by the time of the first assessment at 3 months and increased over time. Additionally, acetyl-L-carnitine was well tolerated in all studies.[88]

Further studies also show efficacy regarding the use of LAC in situations where AD patients were unresponsive to acetylcholinesterase inhibitors. One study evaluated the effect of LAC using 2 g/day orally for 3 months in association with donepezil or rivastigmine in 23 patients with mild AD who had not responded to treatment with acetylcholinesterase inhibitors (AChE-Is). Clinical effects were evaluated by assessing cognitive functions, functional status, and behavioral symptoms. The response rate, which was 38% after AChE-I treatment, increased to 50% after the addition of LAC, indicating that the combination of both the pharmaceutical and LAC works better than the pharmacologic treatment alone.[89]

The memory impairment need not be as severe as in AD in order for LAC to demonstrate benefit.[90-92] In one double-blind study of 236 elderly subjects with mild mental deterioration, as evidenced by detailed clinical assessment, the group receiving 1500 mg/day of LAC demonstrated significant improvement in mental function, particularly in memory and constructional thinking.[92]

OTHER THERAPIES

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is the most abundant hormone in the bloodstream and is found in extremely high concentrations in the brain. As DHEA levels decline dramatically with aging, low levels of DHEA in the blood and brain are thought to contribute to many symptoms associated with aging, including impaired mental function.

Although DHEA itself has no known function, it does serve as the source of all other steroid hormones in the body, including sex hormones and corticosteroids. Therefore, the function of DHEA seems to lie in supplying the body with what it needs to maintain optimal levels and balance of all the steroid hormones that regulate the body's activities.

Over the past 15 years it has been demonstrated that declining levels of DHEA are linked to such conditions as diabetes, obesity, elevated cholesterol levels, heart disease, arthritis, and other age-related diseases. In addition, DHEA shows promise in enhancing memory and improving cognitive function.[93-95] As of this writing, the only double-blind placebo-controlled study was a small pilot study (58 subjects) in which 50 mg of DHEA was given twice a day. Although some benefit was reported at 3 months, DHEA did not significantly improve cognitive performance or overall ratings of change in severity in this small-scale pilot study.[96]

The levels of DHEA necessary to improve brain power in men older than 50 years of age appear to be 25 to 50 mg/day. For women, a dose of 15 to 25 mg appears to be sufficient in most cases. As men and women reach their 70s, they may require higher levels (e.g., 50-100 mg). Excessive dosages of DHEA can cause acne and, in women, menstrual irregularities. Although most elderly people probably need DHEA, laboratory assessment before prescription may help to determine whether DHEA would be beneficial in an individual case and to assess the needed doses.

Melatonin

Formed by the body from serotonin and released by the pineal gland, melatonin is considered by many to be "the master hormone" of the body. It is well known for its use in normalizing circadian rhythms and sleep cycles and, more recently, as a powerful antioxidant for cancer therapies. Virtually ignored in conventional textbooks until only relatively recently, medical research is beginning to value its ostensibly commanding role in many physiologic processes.

In vitro studies have shown that melatonin protects neuronal cells from heavy metal cobalt damage. Cobalt is a transition metal found in high levels in AD patients. It was found that the induction of oxidative damage and β-amyloid release were both avoided with melatonin treatment. Because cobalt is an essential nutrient, often bound to vitamin B_{12}, melatonin may prove to be an important preventive treatment in AD-susceptible individuals.[97]

One double-blind, placebo-controlled study has studied melatonin in AD patients. Researchers from Nippon Medical School, who previously reported on bright light therapy as a means to improve cognitive function in AD, evaluated the effectiveness of melatonin. Three milligrams of melatonin were given to 11 subjects at 8:30 PM every day for a month, while 9 other subjects were given placebo (mean age of 79.2 years). Based on standard dementia and AD assessment scales, the melatonin group had a

significantly increased sleeping time and decreased nighttime activity, with improved levels of cognitive and noncognitive functions. Even though the authors noted that these results were significant and clearly supported the use of melatonin in AD, they acknowledged that morning bright light therapy still showed greater improvements in AD patients.[98]

Botanical Medicines

Ginkgo Biloba Extract

Ginkgo biloba extract (GBE) standardized to contain 24% ginkgo flavonglycosides exerts many effects beneficial in the prevention and early treatment of AD, as detailed in Chapter 93. It must be pointed out that GBE should be taken consistently for at least 12 weeks in order to determine its effectiveness. Although some people experience benefits within a 2- to 3-week period, most will need to take GBE for a longer time in order to see any significant changes.

Huperzine A

Huperzine A is an alkaloid isolated from the moss *Huperzia serrata,* long used in China to treat primarily fever and inflammation. Although it has been shown to have no antipyretic or antiinflammatory properties in experimental models, Huperzine A is a potent inhibitor of acetyl-cholinesterase. In fact, it is significantly more selective and substantially less toxic than the acetylcholinesterase (AChE) inhibitors currently used in conventional medicine (physostigmine, tacrine, and donepezil). Toxicity with synthetic AChE inhibitors has been a major drawback in their clinical use. In contrast, Huperzine A, purified from *H. serrata,* has been used as a prescription drug in China since the early 1990s and has reportedly been used by more than 100,000 people with no serious adverse effects.[99]

Initial clinical studies with Huperzine A conducted in China, which first focused on its use in myasthenia gravis, showed considerable benefit in the treatment of dementia. One double-blind clinical study found that Huperzine A at a dose of 200 mcg twice a day produced measurable improvements in memory, cognitive function, and behavioral factors in 58% of AD patients.[100] In contrast, 36% in the placebo group showed improvement.

In the most recent double-blind study, 210 individuals with AD were randomized to receive placebo or Huperzine A (200 mcg or 400 mcg twice a day), for at least 16 weeks. Huperzine A 200 mcg twice a day did not influence any change in the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-Cog), but this agent at 400 mcg twice a day showed a 2.27-point improvement in ADAS-Cog at 11 weeks versus a 0.29-point decline in the placebo group and a 1.92-point improvement versus a 0.34-point improvement in the placebo arm at week 16. Changes in clinical global impression of change and activities of daily living were not significant at either dose.[101]

Bacopa Monniera

Bacopa monniera (BM) is an Ayurvedic botanical medicine used for memory enhancement, epilepsy, insomnia, and as a mild sedative. Additionally, it has been able to reduce memory dysfunction in rat models of AD. One recent study evaluated an extract of BM on a culture of purified rat astrocytes exposed to toxins mimicking the effect of excess nitric oxide exposure, a condition shown to be a factor in AD. Results showed that the extract of BM inhibited the formation of reactive species and DNA damage in a dose-dependent manner. These data support the traditional use of BM and indicate that this medicinal plant has therapeutic potential in the treatment or prevention of AD.[102-104]

Curcuma Longa (Turmeric)

There is considerable experimental evidence that curcumin protects against age-related brain damage and AD in particular. Researchers began exploring this effect after noting that elderly (aged 70-79) residents of rural India who eat large amounts of turmeric have been shown to have the lowest incidence of AD in the world: 4.4 times lower than that of Americans. In in vitro studies, curcumin has been reported to inhibit amyloid-β-protein (Aβ) aggregation, and Aβ-induced inflammation as well as the activities of β-secretase and acetylcholinesterase. In in vivo studies, oral administration of curcumin has resulted in the inhibition of Aβ deposition, Aβ oligomerization, and tau phosphorylation in the brains of AD animal models and improvements in behavioral impairment in animal models. Unfortunately, the two clinical trials conducted to date have failed to show any benefit.[105] However, the failure to produce positive results may have been due to the poor pharmokinetic profile of the curcumin used in the trials. For more information on curcumin, see Chapter 84.

There remains the possibility that curcumin might be one of the most promising compounds for the development of AD therapies.

Studies in stroke models have also suggested a neuroprotective role of curcumin[8] as well as the ability to reduce plaque burden in models of AD. Curcumin has also been shown to decrease naphthalene and 4-hydroxy-2-nonenal–induced cataract formation on the lens by decreasing the rate of apoptosis and subsequent opacification resistance of the lens.[56,57] The authors postulate that induction of the glutathione S-transferase, which acts to decrease lipid peroxidation, was probably responsible for the cataractogenesis-inhibiting effects.

THERAPEUTIC APPROACH

The primary therapeutic goal is prevention or initiation of therapy as soon as any dementia is noted.

Dietary and Lifestyle Recommendations

- Avoid aluminum (found in many antiperspirants, antacids, and cookware).
- Follow a generally healthful dietary and lifestyle plan.
- Achieve ideal body weight and take measures to improve insulin sensitivity.
- Increase intake of whole-food products including fish, cereals, vegetables, and monosaturated fats.
- Employ the principles of the Mediterranean diet.
- Decrease total calories, high-glycemic-load foods, and unhealthy fats.
- Use morning light therapy.

Supplements

- High-potency multivitamin/multimineral supplement
- Vitamin C: 500 to 1000 mg three times a day
- Vitamin E: 100 to 200 IU daily
- Thiamin: 3 to 8 g daily
- Fish oils: 1000 to 3000 mg EPA+DHA daily
- Phosphatidylserine: 100 mg three times a day
- L-Acetylcarnitine: 500 mg three times a day
- Methylcobalamin: 1000 mg twice a day
- Melatonin: 3 mg in the evening at least a half hour before bed

Botanical Medicine

- GBE (24% *Ginkgo* flavonglycosides): 240 to 320 mg daily
- Huperzine A: 400 mcg twice a day

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CHAPTER 145

Angina

Michael T. Murray, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- Squeezing or pressure-like pain in the chest appearing immediately after exertion. Other precipitating factors include emotional tension, cold weather, or a large meal. Pain may radiate to the left shoulder blade, left arm, or jaw. The pain typically lasts for only 1 to 20 minutes.
- Stress, anxiety, and high blood pressure are typically present.
- The majority of people demonstrate an abnormal electrocardiographic reading (transient ST-segment depression) in response to light exercise (stress test).

GENERAL CONSIDERATIONS

Angina pectoris results when the supply of oxygen, and occasionally other nutrients, is inadequate to meet the metabolic needs of the heart muscle. The primary cause is atherosclerosis, although platelet aggregation, coronary artery spasm, nonvascular mechanisms such as hypoglycemia, and increased metabolic need (such as in hyperthyroidism) can also be important.

The primary lesion of atherosclerosis is the atheromatous plaque, which progressively narrows and ultimately blocks the coronary artery, resulting in a decreased supply of blood and oxygen to the heart tissue. Symptoms typically begin to appear after a major coronary artery is blocked by more than 50%.

Blood flow to the heart may also be compromised by transient platelet aggregation (discussed in more detail in Chapter 148) and coronary artery spasm. Prinzmetal's variant angina, the most commonly recognized form of coronary artery spasm, is not due to plaque in the coronary arteries and is more apt to occur at rest or at odd times during the day or night. It is more common in women younger than age 50. Magnesium insufficiency–induced coronary artery spasm, more common in men than women, is now recognized as an important cause of myocardial infarction (MI) and may be of significance in angina pectoris.

DIAGNOSTIC CONSIDERATIONS

The diagnosis of angina is frequently made by history alone. Clinical evaluation of all patients with angina should include an electrocardiogram (ECG) at rest and a chest radiograph. Because more than one half of patients with typical angina and confirmed coronary atherosclerosis have normal 12-lead ECG readings at rest, diagnosis must often be confirmed using ECG stress testing or 24-hour Holter monitoring (ambulatory ECG).

The most common diagnostic ECG changes associated with angina are evidence of previous MI and ST-segment and T-wave changes that occur *during* attacks of pain. The most characteristic change is displacement of the ST segment with or without T-wave inversion. Complicating diagnosis, however, is the observation that hypoglycemia-induced angina does not manifest with rate or ST-segment abnormalities.[1]

THERAPEUTIC CONSIDERATIONS

Angina is a serious condition that requires careful treatment and monitoring. In the severe case as well as in the initial stages of mild to moderate angina, prescription medications may be necessary. Eventually the condition should be controlled with the help of natural measures. If there is significant blockage of the coronary

artery, intravenous ethylenediaminetetraacetic acid (EDTA) chelation therapy, angioplasty, or coronary artery bypass may be appropriate.

From the perspective of natural medicine, there are two primary therapeutic goals in the treatment of angina: improving energy metabolism within the heart and improving blood supply to the heart. These goals are interrelated, as an increased blood flow means improved energy metabolism and vice versa.

The heart uses fats as its major metabolic fuel. It converts free fatty acids to energy in much the same way as an automobile uses gasoline. Defects in the utilization of fats by the heart greatly increase the risk of atherosclerosis, heart attacks, and anginal pains. Specifically, impaired utilization of fatty acids by the heart results in the accumulation of high concentrations of fatty acids within the heart muscle. This makes the heart extremely susceptible to cellular damage, which ultimately leads to a heart attack.

Carnitine, pantethine, and coenzyme Q_{10} (CoQ_{10}) are essential compounds in normal fat and energy metabolism and are of extreme benefit to sufferers of angina. These nutrients prevent the accumulation of fatty acids within the heart muscle by improving the conversion of fatty acids and other compounds into energy.

Nutritional Supplements for Angina

The use of antioxidant supplementation in patients with angina is important. In an analysis of normal controls and patients with either stable or unstable angina, the plasma level of antioxidants has been shown to be a more sensitive predictor of unstable angina than the severity of atherosclerosis.[2,3] One group of researchers concluded: "These data are consistent with the hypothesis that the beneficial effects of antioxidants in coronary artery disease (CAD) may result, in part, by an influence on lesion activity rather than a reduction in the overall extent of fixed disease."[2]

Antioxidant nutrients are also important in preventing nitrate tolerance. Oral nitrates are widely used in the conventional treatment of angina, but their continuous administration can result in the rapid development of tolerance. Experimental findings indicate that nitrate tolerance is associated with increased vascular production of superoxide. The superoxide anions generated quickly degrade the nitric oxide formed from the administration of nitroglycerin and result in lower levels of cyclic guanosine monophosphate (an important intracellular regulator that promotes vasorelaxation). Because vitamin C is the main aqueous-phase antioxidant and free radical scavenger of superoxide and vitamin E is the main lipid-phase antioxidant, their importance in preventing nitrate tolerance is obvious. Clinical trials have upheld this connection, showing that high-dose vitamins C and E supplementation can prevent nitrate tolerance.[4,5]

Carnitine

Carnitine, a vitamin-like compound, stimulates the breakdown of long-chain fatty acids by the energy-producing units in cells—the mitochondria. Carnitine is essential in the transport of fatty acids into the mitochondria. A deficiency in carnitine results in a decrease in fatty acid concentrations in the mitochondria and reduced energy production.

Normal heart function is critically dependent on adequate concentrations of carnitine. Although the normal heart stores more carnitine than it needs, if the heart does not have a good supply of oxygen, carnitine levels quickly decrease. This leads to decreased energy production in the heart and increased risk for angina and heart disease. Because angina patients have a decreased supply of oxygen, carnitine supplementation makes good sense.

Several clinical trials have demonstrated that carnitine improves angina and heart disease.[6-10] Supplementation with carnitine normalizes heart carnitine levels and allows the heart muscle to use its limited oxygen supply more efficiently. This translates to an improvement in cases of angina. Improvements have been noted in exercise tolerance and heart function. The results indicate that carnitine is an effective alternative to drugs in cases of angina.

In one study of patients with stable angina, oral administration of 900 mg of L-carnitine increased mean exercise time and the time necessary for abnormalities to occur on a stress test (6.4 minutes in the placebo group compared with 8.8 minutes in the carnitine-treated group).[10]

These results indicate that carnitine may be an effective alternative to other antianginal agents such as beta blockers, calcium channel antagonists, and nitrates, especially in patients with chronic stable angina pectoris.

Carnitine, by improving fatty acid utilization and energy production in the heart muscle, may also prevent the production of toxic fatty acid metabolites. These compounds are extremely deleterious as they activate various phospholipases and disrupt cellular membrane structures. The changes in the properties of cardiac cell membranes induced by fatty acid metabolites are thought to contribute to impaired heart muscle contractility and compliance, increased susceptibility to irregular beats, and the eventual death of heart tissue. Supplemental carnitine increases heart carnitine levels and prevents the production of toxic fatty acid metabolites. This has been demonstrated clinically, where the early administration of L-carnitine (40 mg/kg per day) in patients having heart attacks was found to considerably reduce heart damage.[11]

Pantethine

Pantethine is the stable form of pantetheine, the active form of pantothenic acid, which is the fundamental component of coenzyme A (CoA). CoA is involved in the transport of fatty acids to and from cells as well as to the mitochondria. The synthetic pathway from pantethine to CoA is much shorter than that of pantothenic acid, making pantetheine the preferred therapeutic substance. In addition, pantetheine has significant lipid-lowering activity, whereas pantothenic acid has very little if any effect in lowering cholesterol and triglyceride levels.

The standard dose for pantethine is 900 mg/day. Like carnitine, pantethine has been shown in clinical trials to significantly reduce serum triglyceride and cholesterol levels while also increasing high-density-lipoprotein cholesterol levels.[12-14] Its lipid-lowering effects are most impressive when its toxicity (virtually none) is compared with that of conventional lipid-lowering drugs. Its mechanism of action is due to the inhibition of cholesterol synthesis and acceleration of fatty acid breakdown in the mitochondria.

Pantethine is well indicated in angina. Like carnitine, heart pantethine levels decrease during times of reduced oxygen supply. Demonstrated effects in animals indicate that it would greatly benefit individuals with angina.[15]

Coenzyme Q_{10}

CoQ_{10}, also known as ubiquinone, is an essential component of the mitochondria, where it plays a major role in energy production. Like carnitine and pantethine, CoQ_{10} can be synthesized within the body. Nonetheless, deficiency states have been reported. Deficiency can be a result of impaired CoQ_{10} synthesis due to nutritional deficiencies, a genetic or acquired defect in CoQ_{10} synthesis, or increased tissue needs.[16]

Cardiovascular diseases—including angina, hypertension, mitral valve prolapse, and congestive heart failure—are examples of diseases that require increased tissue levels of CoQ_{10}.[16] In addition, many of the elderly may have increased CoQ_{10} requirements: the decline of CoQ_{10} levels that occurs with age may be partly responsible for the age-related deterioration of the immune system.

CoQ_{10} deficiency is common in individuals with heart disease. Heart tissue biopsies in patients with various heart diseases show a CoQ_{10} deficiency in 50% to 75% of cases.[16] One of the most metabolically active tissues in the body, the heart may be unusually susceptible to the effects of CoQ_{10} deficiency. Accordingly, CoQ_{10} has shown great promise in the treatment of heart disease.

In one study, 12 patients with stable angina pectoris were treated with CoQ_{10} (150 mg/day for 4 weeks) in a double-blind crossover trial.[17] Compared with placebo, CoQ_{10} reduced the frequency of anginal attacks by 53%. In addition, there was a significant increase in treadmill exercise tolerance (time to onset of chest pain and time to development of ECG abnormalities) during CoQ_{10} treatment. The results of this study and others suggest that CoQ_{10} is a safe and effective treatment for angina pectoris.

Carnitine, pantethine, and CoQ_{10} should be considered in all heart disorders, not just angina.

Magnesium

Magnesium deficiency may play a major role in angina, including Prinzmetal's variant. A magnesium deficiency has been shown to produce spasms of the coronary arteries and is thought to be a cause of nonocclusive heart attacks.[18] Furthermore, it has been observed that men who die suddenly of heart attacks have significantly lower levels of heart magnesium, as well as potassium, than matched controls.[19]

Making magnesium the treatment of choice for angina due to coronary artery spasm has been suggested.[19-21] Magnesium administration has also been found to be helpful in the management of arrhythmias and in angina due to atherosclerosis. Its benefit in these situations is presumably via the same mechanisms responsible for its effects in an acute MI.

Since the mid-1980s, eight well-designed studies involving more than 4000 patients have demonstrated that intravenous magnesium supplementation during the first hour of admission to a hospital for an acute MI produces a favorable effect in reducing immediate and long-term complications as well as death rates.[22-24]

The beneficial effects of magnesium in acute MI relate to its ability to do the following:

- Improve energy production within the heart
- Dilate the coronary arteries, resulting in improved delivery of oxygen to the heart
- Reduce peripheral vascular resistance, resulting in reduced demand on the heart
- Inhibit platelets from aggregating and forming blood clots
- Reduce the size of the infarct (blockage)
- Improve heart rate and arrhythmias

Arginine

Arginine supplementation has been shown to be beneficial in a number of cardiovascular diseases, including angina pectoris. Its benefit is thought to occur via increasing nitric oxide levels, thereby improving blood flow, reducing thrombosis, and improving rheology. The degree of improvement offered by arginine supplementation in angina and other cardiovascular diseases can be quite significant as a result of improved nitric oxide levels. In double-blind studies, it has been shown to be especially effective in increasing exercise tolerance. Typical dosage is 6 g/day in divided dosages.[25-27] In a short-term study, arginine supplementation of 3g/day for 15 days resulted in increased activity of the free radical scavenging enzyme superoxide dismutase and increased the levels of total thiols and ascorbic acid, with a concomitant decrease in lipid peroxidation, carbonyl content, serum cholesterol and the activity of the prooxidant enzyme xanthine oxidase.[28] These beneficial changes point to additional mechanisms for the use of arginine in angina and cardiac ischemia. Use of arginine is cautioned by a report in one study in survivors of MI where supplementation with arginine (9 g/day for 6 months) was associated with an increase in mortality compared with the placebo group (8.6% vs. 0%).[29] This effect may have been an aberration or due to the use of higher dosages of arginine.

Botanical Medicines

Crataegus Species

Hawthorn berry and extracts of the flowering tops are widely used in Europe for their cardiovascular activity. They exhibit a combination of effects that are of great value to patients with angina and other heart problems. Studies have demonstrated that hawthorn extracts are effective in reducing anginal attacks as well as in lowering blood pressure and serum cholesterol levels.[30-32]

The beneficial effects in the treatment of angina are due to improvement in the blood and oxygen supply of the heart resulting from dilation of the coronary vessels, as well as improvement of the metabolic processes in the heart.[30-33]

The ability of *Crataegus* species to dilate coronary blood vessels has been repeatedly demonstrated in experimental studies.[30-32] In addition, *Crataegus* extracts have been shown to improve cardiac energy metabolism in human and experimental studies. This combined effect is extremely important in the treatment of angina because it results in improved myocardial function with more efficient use of oxygen. This improvement results not only from increased blood and oxygen supply to the heart muscle but also from hawthorn flavonoids interacting with key enzymes to enhance myocardial contractility (see Chapter 82 for a comprehensive discussion of this important botanical).

Ammi visnaga

Khella is an ancient medicinal plant native to the Mediterranean region, where it has been used in the treatment of angina and other heart ailments since the time of the pharaohs. Several of its components have demonstrated the ability to dilate the coronary arteries. Its mechanism of action appears to be similar to that of the calcium channel blocking drugs.

Since the late 1940s, there have been numerous scientific studies on the clinical effect of khella extracts in the treatment of angina. More specifically, khellin, a derivative of the plant, was shown to be extremely effective in relieving anginal symptoms, improving exercise tolerance, and normalizing ECGs. This is evident by the concluding statements in a study by Osher and colleagues[33] in 1951: "The high proportion of favorable results, together with the striking degree of improvement frequently observed, has led us to the conclusion that khellin, properly used, is a safe and effective drug for the treatment of angina pectoris."

At higher doses (120 to 150 mg/day), pure khellin was associated with mild side effects such as anorexia, nausea, and dizziness. Although most clinical studies used high dosages, several studies show that as little as 30 mg/day appears to offer as good results with fewer side effects.[34,35]

Rather than using the isolated compound khellin, khella extracts standardized for khellin content (typically 12%) are the preferred form. A daily dose of such an extract would be 250 to 300 mg. Khella appears to work well with hawthorn extracts.

Other Therapies

Acupuncture

Several studies have shown acupuncture to be of benefit in improving angina, specifically in reducing nitroglycerin use, decreasing the number of anginal attacks, and improving exercise tolerance and ECG readings.[36-39]

Relaxation and Breathing Exercises

Relaxation and breathing exercises may be helpful in improving anginal symptoms, especially when anxiety is a significant contributor.[40,41] In one study in patients with cardiac syndrome X, a form of angina in people with otherwise normal coronary arteries, transcendental meditation (20 minutes twice daily of silently chanting a mantra with eyes closed) was found to reduce angina-like chest pain and to normalize ECGs.[40]

Intravenous Ethylenediaminetetraacetic Acid Chelation Therapy

EDTA chelation therapy is an alternative to coronary artery bypass surgery and angioplasty, which may prove to be more effective and is definitely safer and less expensive. EDTA is an amino acid–like molecule that, when slowly infused into the bloodstream, binds with minerals such as calcium, iron, copper, and lead and carries them to the kidneys, where they are excreted. EDTA chelation has been commonly used for lead poisoning, but in the late 1950s and early 1960s it was found to help patients with atherosclerosis.

The discovery of EDTA chelation therapy in the treatment of angina and other conditions associated with atherosclerosis happened accidentally. In 1956, a battery worker whom Norman Clarke was treating with EDTA for lead poisoning noticed that his symptoms of angina disappeared. Clarke and others began using EDTA chelation therapy in patients with angina, cerebral vascular insufficiency, and occlusive peripheral vascular disease.

In a series of 283 patients treated by Clarke and his colleagues from 1956 to 1960, a total of 87% showed improvements in their symptoms. Heart patients improved, and patients with blocked arteries in the legs, particularly those with diabetes, avoided amputation.[42,43]

It was originally thought that EDTA opened blocked arteries by chelating out the calcium deposits in the cholesterol plaque. However, the benefit now seems more related to chelating out excess iron and copper, minerals that, in the presence of oxygen, stimulate free radicals. Free radicals damage arterial cells, and this is a primary cause of atherosclerosis.

In a review of the progression and regression of atherosclerosis, the authors write that the process of atherosclerosis is "dependent on the presence of some metals (copper and iron) and can be completely inhibited by chelating agents such as EDTA."[44]

Despite obvious benefits to heart patients, EDTA fell out of favor in the mid-1960s. Advocates believe this occurred for two reasons: (1) the lucrative surgical approach to heart and vessel disease was on the rise and (2) the patent on EDTA that was held by Abbott Laboratories expired, so there was no financial interest for drug companies to fund research.

Fortunately in 1972, a small group of practicing physicians using EDTA chelation therapy founded an organization now called the American College for the Advancement of Medicine to continue education and research in this important area.

In the early days of EDTA chelation therapy, several serious problems were discovered. Giving too much EDTA or giving it too fast was soon noted to be dangerous. In fact, several deaths attributed to kidney failure were caused by toxicity to EDTA. Fortunately, additional research resulted in more appropriate protocols, and EDTA chelation therapy as used now is safe. No deaths or significant adverse reactions have occurred in more than 500,000 patients who have undergone EDTA chelation therapy. Because EDTA chelation improves blood flow throughout the body, the "side effects" are usually beneficial and only a few adverse effects are noticed.

A substantial body of scientific evidence exists on the use of EDTA chelation therapy in the treatment of angina, peripheral vascular disease, and cerebral vascular disease.[45-49]

Nonetheless, there is a paucity of well-designed placebo-controlled studies to definitively assess the efficacy of this approach. This shortcoming is unfortunate considering the early successes. The conclusion from a recent Cochrane Review summarizes the situation well: "At present, there is insufficient evidence to decide on the effectiveness or ineffectiveness of chelation therapy in improving clinical outcomes of patients with atherosclerotic cardiovascular disease." For more information refer to the American College of Advancement in Medicine (ACAM), 23121 Verdugo Drive, Suite 204, Laguna Hills, CA, 92653; 1-800-532-3688 (outside California) or 1-800-435-6199 (inside California); www.acam.org.

THERAPEUTIC APPROACH

The primary therapy for angina is prevention, because angina is usually secondary to atherosclerosis. Once angina has developed, restoring proper blood supply to the heart and enhancing energy production within the heart are necessary. Particularly important nutrients for accomplishing these results are vitamins C and E, carnitine, pantethine, CoQ_{10}, magnesium, and arginine. Magnesium is of additional benefit because of its ability to relax spastic coronary arteries and improve heart function.

Hawthorn berries or extracts offer a number of benefits to individuals with angina, including coronary artery dilation and improved heart muscle metabolism.

Patients with unstable angina pectoris (characterized by a progressive increase in the frequency and severity of pain, increased sensitivity to precipitating factors, progression of symptoms over several days, and prolonged coronary pain) should be hospitalized.

Diet

The dietary guidelines given in Chapter 44 are appropriate here. In particular, an increase of dietary fiber is recommended, especially the gel-forming or mucilaginous fibers (e.g., flaxseed, oat bran, pectin). Onions and garlic (both raw and cooked), vegetables, and fish should also be increased, while the consumption of saturated fats, cholesterol, sugar, and animal proteins should be reduced. All fried foods and food allergens should be avoided. Patients with reactive hypoglycemia should eat regular meals and carefully avoid simple carbohydrates in all forms (e.g., sugar, honey, dried fruit, fruit juice).

Lifestyle

The individual with angina should not smoke or drink alcohol or coffee. Stress should be decreased by using stress management

techniques such as progressive relaxation, meditation, or guided imagery. A carefully graded progressive aerobic exercise program (30 minutes three times a week) is a necessity. Walking is a good exercise with which to start.

Nutritional Supplements

- Vitamin C: 500 to 1500 mg a day
- Vitamin E: 200 to 400 IU a day
- CoQ_{10}: 150 to 300 mg a day
- L-Carnitine: 500 mg three times a day
- Pantethine: 300 mg three times a day
- Magnesium, preferably bound to aspartate, citrate, or other Krebs cycle intermediate: 200 to 400 mg three times a day
- Arginine: 1000 to 2000 mg three times a day

Botanical Medicines

- *Crataegus oxyacantha* (three times a day)
 Berries or flowers (dried): 3 to 5 g or as a tea
 Fluid extract (1:1): 2 to 4 mL (0.5-1 tsp)
 Solid extract (10% procyanidins or 1.8% vitexin-4'-rhamnoside): 100 to 250 mg
- *Ammi visnaga* (three times a day)
 Dried powdered extract (12% khellin content): 100 mg three times a day

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CHAPTER 146

Aphthous Stomatitis

Michael L. Traub, ND, DHANP, FABNO, and Michael T. Murray, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- Single or several discrete, shallow, painful ulcers found anywhere on the oral mucosa: labial and buccal mucosa, maxillary and mandibular sulci, gingiva, soft palate, tonsillar fauces, floor of the mouth, ventral surface of the tongue.
- Lesions are from 1 to 15 mm in diameter, have fairly even borders, are surrounded by an erythematous border, and are often covered by a pseudomembrane.
- Lesions usually resolve in 7 to 10 days but are often recurrent; larger ulcers may last several weeks to months and can leave a scar.

GENERAL CONSIDERATIONS

Aphthous stomatitis, recurrent aphthous ulcers (RAUs), or canker sores is a common condition, estimated to affect 20% of the population. RAU is an idiopathic multifactorial disorder that can cause significant morbidity. Although usually self-limited, in some individuals recurrence can be almost continuous. Inflammatory bowel disease, systemic lupus erythematosus, and Behçet's syndrome are systemic disorders associated with RAUs. Many people mistakenly identify RAUs as herpes simplex, although there is an uncommon form, known as herpetiform RAU, consisting of clusters of aphthae less than 1 mm in diameter. No consistent genetic associations have been demonstrated. The etiology, based on studies of initiating factors, appears to be related to food sensitivities (especially gluten sensitivity) and nutrient deficiency. These factors unify the key underlying feature of recurrent aphthous stomatitis (RAU)—dysregulation of the immune system in the oral mucosa. Histologically, RAU consists of mucosal ulcerations with mixed inflammatory cell infiltrates. T-helper cells predominate in the preulcerative and healing phases, whereas T-suppressor cells predominate in the ulcerative phase. Other findings associated with immune dysregulation include the following:

- Lymphomononuclear infiltrate and hemagglutination antibodies against oral mucosa
- Reduced response of lymphocytes to mitogens
- Circulating immune complexes
- Alterations in natural killer (NK) cell activity
- Increased adherence of neutrophils
- Release of tumor necrosis factor-alpha (TNF-α)
- Significant involvement of mast cells in the pathogenesis of RAU
- Reduced levels and function of regulatory T cells in aphthae
- Reduced expression of heat shock protein 27 and interleukin 10 in lesions[1]
- Elevated salivary and serum cortisol[2]
- Elevated Toll-like receptor activity[3]
- Oxidative stress as measured by glutathione and malonidialdehyde[4]

THERAPEUTIC CONSIDERATIONS

Allergies and Environmental Factors

The oral cavity is obviously the first site of contact for ingested and many inhaled allergens. The histologic appearance of the lesions and the association of RAU with increased serum antibodies to food antigens and atopy strongly suggest that an allergic reaction is involved.[5] Furthermore, immunoglobulin E–bearing lymphocytes

are significantly increased in aphthous lesions, and mast cells are increased in tissue sections from prodromal stages of recurrent ulcers.[6] Mast cell degranulation plays an important role in the production of the aphthous lesion.[7] An elimination diet has been shown to have good therapeutic results.[8]

The allergen is not necessarily a food. Frequent allergens inducing RAU are as follows:[9]

- Benzoic acid
- Cinnamaldehyde
- Nickel
- Parabens
- Dichromate
- Sorbic acid

Elimination of allergens usually brings complete resolution or significant improvement.[10]

Local, chemical, or physical trauma often initiates aphthae in susceptible individuals (pathergy). Strong evidence from numerous studies is lacking to support the role of an infectious etiology, including herpes simplex virus, human herpesvirus, varicella zoster virus, cytomegalovirus, and *Helicobacter pylori*.[11,12] Approximately 66% of HIV-positive individuals have herpetiform ulcers and RAUs, which must be differentiated from those caused by antiretroviral medications and bacterial, viral, or fungal infections.[13] RAU can result from a T cell–mediated response to antigens of *Streptococcus sanguis* that cross-react with heat-shock proteins. One controlled study has shown a statistically significant increase in RAU in subjects taking nonsteroidal antiinflammatory drugs (NSAIDs).[14] Oral hygiene products, chewing gum, candy, acidic foods, and walnuts have been associated with RAU. The avoidance of toothpaste containing sodium lauryl sulfate may be helpful in this author's (MT) experience, although it has not been proved.

Gluten Sensitivity

Considerable evidence indicates that sensitivity to gluten is associated with RAU. The incidence of RAU is increased in patients with celiac disease.[15-18] Jejunal biopsy of 33 patients with RAU showed 8 to have the villous atrophy typical of celiac disease, along with histologic signs of immunologic reactions to food antigens.[15] The remaining patients also exhibited these types of signs but to a lesser degree. Although villous atrophy is a prerequisite for the diagnosis of celiac disease, gluten sensitivity may take other forms: gluten may act directly on the oral mucosa or produce functional changes in the small intestine by immunologic or other mechanisms that are distinct from those causing the characteristic abnormalities of celiac disease.[17] An underlying gluten-sensitive enteropathy would also contribute to nutritional deficiencies. Withdrawing gluten from the diet results in complete remission of RAU in patients with celiac disease and some improvement in others.[15-18]

Even in the absence of villous atrophy, gluten sensitivity can definitely produce RAU. For example, in one small study, 3 of 4 gluten-sensitive patients identified by positive antibodies to alpha-gliadin but with normal small intestinal biopsy responded dramatically to a gluten-free diet.[19]

We strongly recommend measuring tissue transglutaminase and reticulin antibodies in any patient presenting with RAU.

Stress

Stress is often a precipitating factor in RAU, suggesting a breakdown in normal host protective factors.[20]

Nutrient Deficiency

The oral cavity is often the first place that nutritional deficiency becomes visible to the physician because of the high turnover rate of the mucosal epithelium. Although a number of nutrient deficiencies can lead to aphthous stomatitis, thiamin appears to be the most significant. In one study seeking to examine whether thiamin deficiency is associated with RAU, the levels of transketolase (a thiamin-dependent enzyme) were determined in 70 patients with RAU and 50 patients from a control group.[21] Low levels of transketolase were found in 49 of 70 patients with RAS, compared with only 2 of 50 among the controls. These results clearly demonstrate an association between low levels of thiamin and RAU.

Several other studies show that nutrient deficiencies are much more common in RAU sufferers than others. For example, a study of 330 patients with RAS found that 47 (14.2%) were deficient in iron, folate, or vitamin B_{12}, or a combination of these nutrients.[22] In another study of 60 patients, 28.2% were deficient in thiamin, riboflavin, or pyridoxine.[23] When these patients' deficiencies were corrected, the majority had complete remission. Lower dietary intake of folate and vitamin B_{12} is common in persons with RAU, and treatment with 1000 mcg/day has shown benefit regardless of serum vitamin B_{12} levels.[24] Other studies have shown similar deficiency rates for the same nutrients and equally good responses to supplementation.[25]

Zinc supplementation has also been shown to be helpful. In one double-blind study, 40 patients with RAU were given either zinc sulfate (220 mg providing 50 mg of elemental zinc) or a placebo once daily for 1 month.[26] Results showed that the levels of serum zinc before treatment were below the normal value in 42.5% of the patients with RAU. After 1 month of zinc therapy, the aphthae reduced and did not reappear for 3 months. A small study of adolescents showed a reduction in the incidence of RAU and associated pain from 2000 mg/day of ascorbate.[27]

Low nutrient status may explain why patients with RAU have an increased oxidant/antioxidant status in comparison with healthy controls. In one study, superoxide dismutase, glutathione peroxidase (GSHPx) and catalase (CAT) activities as well as and malondialdehyde (MDA) and antioxidant potential (AOP) levels were measured in plasma and erythrocytes from 22 patients with RAS and 23 controls.[28] Researchers found decreased CAT and GSHPx activities and AOP levels in the erythrocytes as well as decreased AOP and increased MDA plasma levels in patients with RAU in comparison with control subjects. This study clearly demonstrated that enzymatic and nonenzymatic antioxidant defense systems are impaired in patients with RAU.

Quercetin

Quercetin is known to inhibit mast cell degranulation, basophil histamine release, and the formation of other mediators of inflammation.[29] The antiallergy drug disodium cromoglycate, a compound similar in structure and function to quercetin, has been shown to be effective in the treatment of RAU, resulting in more ulcer-free days and mild symptomatic relief.[30] Other flavonoids (acacetin, apigenin, chrysin, and phloretin but not catechin, flavone, morin, rutin, or taxifolin) have also shown antiallergy effects similar to those of disodium cromoglycate.[29]

Deglycyrrhizinated Licorice

Deglycyrrhizinated licorice (DGL) may be effective in promoting the healing of RAU. In one study, 20 patients were instructed to

use a solution of DGL as a mouthwash (200 mg of powdered DGL dissolved in 200 mL of warm water) four times daily.[31] Of the 20 patients, 15 (75%) experienced 50% to 75% improvement within 1 day, followed by complete healing of the ulcers by the third day. DGL in tablet form may be more convenient and effective.

Topical preparations containing the solid extract of licorice root are also available (e.g., Canker Goo, from Wise Woman Herbals, Creswell, OR; CankerMelts from OraHealth, Bellevue, WA).

A randomized controlled trial also showed significant efficacy of a paste containing *Myrtus communis* (myrtle) for RAU when applied four times daily for 6 days.[32]

THERAPEUTIC APPROACH

These data suggest that no single factor is solely responsible for the initiation of the aphthous lesion in any specific patient. However, an underlying tendency to ulceration may be present, the expression of which is facilitated by these factors. Considerable evidence suggests that gluten sensitivity may be a contributing factor in some patients. In addition, nutrient deficiencies must be corrected and antiinflammatory nutrients prescribed. Also, a randomized controlled trial showed significant benefit from individualized homeopathic treatment, where the medicine was administered in 6c potency as oral liquid for two doses only.[33]

For symptom relief, amlexanox (Aphthasol) is the first FDA-approved topical prescription for RAU. It is an immunomodulator that appears to accelerate the healing of aphthous ulcers. It has demonstrated potent inhibition of inflammatory mediators (histamine and leukotrienes) from mast cells, neutrophils, and mononuclear cells in vitro, and clinical studies have shown 75% faster healing and 90% faster pain resolution.

Diet

The patient's diet should be free of known allergens and all gluten sources if gluten sensitivity is present.

Nutritional Supplements

- High-potency multivitamin and mineral formula
- Calcium ascorbate: 2000 mg/day
- Sublingual vitamin B_{12}: 1000 mcg/day

Botanical Medicines

- DGL: one to two 380-mg chewable tablets 20 minutes before meals
- Topical licorice root preparations (e.g., Canker Goo, CankerMelts) applied as needed

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CHAPTER 147

Asthma

Michael T. Murray, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- Recurrent attacks of dyspnea, cough, and expectoration of tenacious mucoid sputum
- Prolonged expiration phase with generalized wheezing and musical rales
- Eosinophilia, increased serum immunoglobulin (Ig) E, positive food/inhalant allergy tests

GENERAL CONSIDERATIONS

Bronchial asthma is a hypersensitivity disorder characterized by bronchospasm, mucosal edema, and excessive excretion of a viscous mucus that can lead to ventilatory insufficiency. Asthma affects approximately 7% of the population of the United States and causes 4210 deaths per year. Although it occurs at all ages, it is most common in children below age 10. There is a 2:1 male:female ratio in children, which equalizes by the age of 30.[1]

Major factors involved in asthma are the following:

- Hypersensitivity of the airways
- Beta-adrenergic blockade
- Cyclic nucleotide imbalance in airway smooth muscle
- Release of inflammatory mediators from mast cells

The incidence of asthma is rising rapidly in the United States, especially in children. Reasons often given to explain the rise in asthma include the following:

- Increased stress on the immune system due to factors such as greater chemical pollution in the air, water, insect allergens from mites and cockroaches, and food
- Earlier weaning and earlier introduction of solid foods to infants
- Food additives
- Higher incidence of obesity[2]
- Genetic manipulation of plants, resulting in food components with greater allergenic tendencies

In addition, multiple genetic variables may make certain individuals more susceptible to asthma. For example, researchers have demonstrated that a deficiency in the glutathione S-transferase M1, a gene involved in response to oxidative stress, may also make those with this deletion more susceptible to asthmatic attacks, thus supporting the need for antioxidant therapy in these individuals.[3] The ADAM33 gene on chromosome 20p13 has been linked to the pathogenesis involved in airway remodeling (see mediators section later) and is probably a factor in corticosteroid resistance in some asthmatics.[4] Other research teams have identified genes on chromosomes 7 and 12 as probable players in the pathogenesis of asthma.[5,6]

Major Categories

Asthma has typically been divided into two categories: extrinsic and intrinsic. Extrinsic or atopic asthma is generally considered an immunologically mediated condition with a characteristic increase in serum IgE. Intrinsic asthma is associated with a bronchial reaction that is due not to antigen-antibody stimulation but rather such factors as chemicals, cold air, exercise, infection, agents that activate the alternative complement pathway, and emotional upset.

Asthma is often clinically classified according to the frequency of symptoms, forced expiratory volume in 1 second (FEV_1), and peak expiratory flow rate.

TABLE 147-1 **National Asthma Education and Prevention Program (NEAPP) Classification of Asthma Severity Before Treatment in Adults and Youths 12 Years and Older***

		Persistent		
COMPONENT OF SEVERITY	**INTERMITTENT**	**MILD**	**MODERATE**	**SEVERE**
Symptoms	≤2 days/week	>2 days per week but not daily	Daily	Throughout the day
Nighttime awakenings	≤2x/month	3-4x/month	>1x/week but not nightly	Often 7x/week
Short-acting β-agonist use for symptoms	≤days/week	>2 days per week but not >1x/day	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Pulmonary function	Normal FEV_1 between exacerbations; FEV_1 ≥80% predicted; FEV_1/FVC normal	FEV_1 <80% predicted; FEV_1/FVC normal	FEV_1 ≥60% but <80% predicted; FEV_1/FVC reduced ≥5%	FEV_1 <60%; FEV_1/FVC reduced >5%
Exacerbations (consider frequency and severity)	0-1 per year		≥2 per year	

Data from Expert panel report 3: guidelines for the diagnosis and management of asthma. National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute, Bethesda, MD, 2007.
FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
*Severity level is determined in accordance with the worst impairment category.

Diagnostic Considerations

The U.S. National Asthma Education and Prevention Program (NAEPP) guidelines for the diagnosis and management of asthma (Table 147-1) state that a diagnosis of asthma begins by assessing whether any of the following list of indicators is present:

- Wheezing—high-pitched whistling sounds on expiration—especially in children. (Lack of wheezing and a normal chest examination do not exclude asthma.)
- History of any of the following:
 - Cough, worse particularly at night
 - Recurrent wheeze
 - Recurrent difficulty in breathing
 - Recurrent chest tightness
- Symptoms occur or worsen in the presence of:
 - Exercise
 - Viral infection
 - Animals with fur or hair
 - House dust mites (in mattresses, pillows, upholstered furniture, carpets)
 - Mold
 - Smoke (tobacco, wood)
 - Pollen
 - Changes in weather
 - Strong emotional expression (laughing or crying hard)
 - Airborne chemicals or dusts
 - Menstrual cycles
- Symptoms occur or worsen at night, awakening the patient

Spirometry plays a central role in the management of asthma and should be performed at the time of initial diagnosis, after treatment is initiated and symptoms are stabilized, whenever control of symptoms deteriorates, and every 1 or 2 years on a regular basis.

Causes

Asthma is caused by a complex interaction of environmental and genetic factors. The strongest risk factor for developing asthma is a history of atopic disease. The presence of atopic dermatitis increases the risk of asthma by three- to fourfold. Allergies and the response of the immune system are obviously involved in asthma.

Inflammation and Th1/Th2 Balance. Imbalances in T-helper cell immune responses appear to be a fundamental mechanism of immunologically mediated airway inflammation. $CD4^+$ T-helper cells are generally categorized into Th1 and Th2 cells. Via the release of interferons and interleukin 2, the Th1 pathway is increased in the immunologic responses to cancer, multiple sclerosis, viruses, and type IV hypersensitivities. Th2 responses are related to increases in interleukins 4, 6, 9, and 13; IgE, eosinophilia; and activated B-cell humoral immunity. Clinical conditions that reflect increased Th2 responses include asthma and atopic syndromes as well as allergies. Research involving asthmatic subjects demonstrates a normal Th1 gene expression but a constant up-regulation of Th2-specific genes, leading to Th2 predominance.[7] Although it is unclear what the cause of this exaggerated Th2 response is in asthma, it seems that genetics, fungi, heavy metal toxicities, nutrition, viruses, and pollution are factors in this up-regulation.[8] The "hygiene hypothesis" is also gaining ground in the standard medical literature. It asserts that by minimizing exposure to infectious agents owing to lifestyle choices based on hygienic concerns, the dominance of Th2 immune responses to environmental allergens has been favored and thus also the probable encouragement of asthma and atopic diseases.[9,10]

Mediators

Both extrinsic and intrinsic factors involved primarily with Th2 imbalances trigger the cytokine-activated release of mast cell–derived chemical mediators. These mediators are responsible for bronchoconstriction, mucus production, and other signs and symptoms in the majority of cases. These mediators are either preformed within granules or generated from membrane-bound phospholipids. The preformed mediators include histamine, various chemotactic peptides such as eosinophilic chemolactic factor (ECF) and high-molecular-weight neutrophil chemotactic factor (NCF), proteases, glycosidases, and heparin proteoglycan. The membrane-derived agents include lipoxygenase products such as

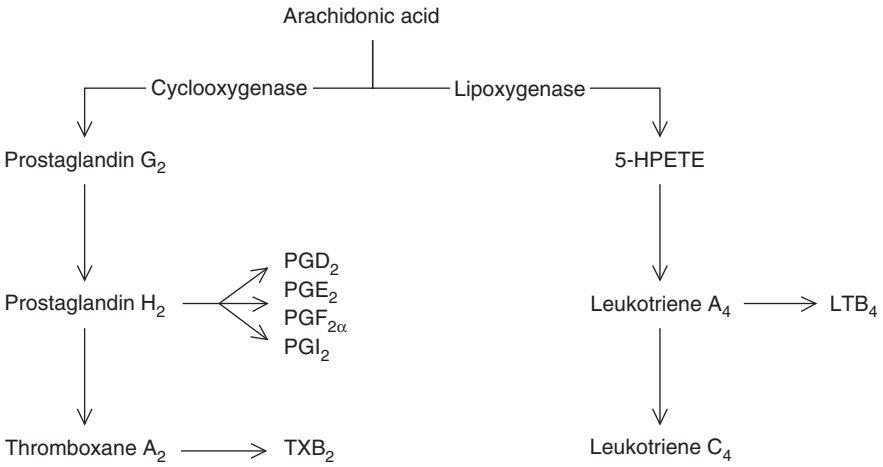


FIGURE 147-1 Arachidonic acid metabolism.

leukotrienes (LTs) and the so-called slow-reacting substance of anaphylaxis (SRS-A), prostaglandins (PGs), thromboxanes (TXs), and platelet-activating factor (PAF).

These mediators are diverse in chemical composition and modes of action and account for many of the signs and symptoms of asthma. Their actions include bronchial smooth muscle constriction (histamine, LTC_4, LTD_4 and LTE_4, PGF_{2a}, PGD_2, and PAF), mucosal edema (increased permeability, histamine, LTC_4, LTD_4, and PAF), vasodilation (PGD_2 and PGE_2), mucous plugging (histamine, hydroxyeicosatetraenoic [HETE] acids, and LTC_4), inflammatory cell infiltrate (NCF, ECF-A, HETEs, LTB_4, and PAF), and desquamation of epithelium (proteases and glycosidases, together with lysosomal enzymes and basic proteins derived from neutrophils and eosinophils). In chronic asthma, eventual airway remodeling is a consequence of these mediator effects. The cellular and mediator elements responsible for airway remodeling involve the anomalous interface between the airway epithelium and the underlying mesenchymal tissues. This process is highlighted by the induction of growth factors that encourage fibroblastic and smooth muscle proliferation and the deposition of matrix proteins, which cause the thickening of the airway wall linked to bronchial hyperresponsiveness and fixed airflow obstruction.[4]

Mild episodic asthma differs from moderate to severe sustained asthma in that the latter is largely dependent on a subacute/chronic inflammation of the bronchi with infiltration of eosinophils, neutrophils, and mononuclear cells, while episodic asthma is due primarily to bronchial smooth muscle contraction.

Lipoxygenase Products

The most potent chemical mediators in asthma are the lipoxygenase products (i.e., leukotrienes) (Figure 147-1). The leukotrienes composing SRS-A (LTC_4, LTD_4, LTE_4) are 1000 times more potent as stimulators of bronchial constriction than histamine. Researchers have observed that asthmatics have an imbalance in arachidonic acid metabolism, leading to a relative increase in lipoxygenase products.[11] Platelets from asthmatic patients show a 40% decrease in cyclooxygenase-derived metabolites and a 70% increase in lipoxygenase products. This pathophysiologic alteration is further aggravated in "aspirin-induced asthma." Aspirin and other nonsteroidal anti-inflammatory drugs (e.g., indomethacin, phenylbutazone) inhibit cyclooxygenase while promoting lipoxygenase.[12,13] The net result is a shunting of arachidonic acid toward the lipoxygenase pathway and the production of excessive levels of leukotrienes.

Tartrazine (yellow dye no. 5) is also a cyclooxygenase inhibitor and known inducer of asthma, particularly in children.[12] Tartrazine is ubiquitous in processed foods and can even be found in vitamin preparations and antiasthmatic prescription drugs (e.g., aminophylline). Tartrazine may also indirectly support the asthmatic process via its role as an antimetabolite of vitamin B_6 (see later discussion of tryptophan).

Autonomic Nervous System

The relationship between the autonomic nervous system and bronchial asthma represents an interaction between parasympathetic and sympathetic innervation and $beta_2$ adrenergic receptors (which are localized in lung tissue and react to circulating catecholamines).[14] Stimulation of the parasympathetic vagus nerve results in airway constriction. This vagal mechanism involves the following: release of acetylcholine at the synapse, subsequent binding to its receptor on smooth muscle tissue, and subsequent formation of cyclic guanosine monophosphate (cGMP). Accumulation of cGMP or a relative deficiency in cyclic adenosine monophosphate (cAMP), or both, result in constriction of the airway smooth muscle, as well as degranulation of mast cells and basophils. Decreased sympathetic activity or diminished $beta_2$ receptor numbers or sensitivity also promote the cyclic nucleotide imbalance. Some of the mediators discussed earlier block $beta_2$ receptors and elevate cGMP levels both directly and indirectly.

Adrenal Gland

The activity of the adrenal gland is important in asthma owing to its hormones cortisol and epinephrine. Cortisol is an effective prime activator of beta receptors and epinephrine is considered to be the prime stimulator of beta receptors. It has been suggested that during asthmatic attacks there is a relative deficiency of cortisol and epinephrine (which stimulates $beta_2$ receptors to catalyze the formation of cAMP from AMP). This leads to a decrease in the cAMP:cGMP ratio, resulting in bronchial constriction.

Pertussis Vaccine

An evaluation of health criteria among 448 children and adolescents in Britain who had received only breast milk for the first 6 months of life and in particular on the first day after birth produced some interesting findings. All of the children were weaned

after 1 year of age and were older than 4 years at the time the parents responded. The mean age was 7.87 years. In response to the question "Has your child ever been diagnosed as asthmatic?" there were 30 positive answers (6.72%). The surprise came when the researchers classified the respondents according to whether or not they had received the pertussis vaccine.[15]

Among the 243 immunized children, 26 were diagnosed as having asthma (10.69%). In contrast, of the 203 children who had not been immunized, only 4 had asthma (1.97%). The relative risk of developing asthma from the pertussis vaccine was 5.43 in this study. The significance of this finding was at the $P = 0.0005$ level.

Even though all of the children who received the pertussis vaccine received other vaccinations, the researchers suspected that the statistical evidence focused on pertussis. Among the children who did not receive the pertussis vaccine, most had received some other vaccination. Of the 91 subjects of the study who received no vaccines, only 1 had asthma, compared with 3 with asthma in the 112 who had other vaccinations. Therefore, the relative risk of developing asthma is about 1% in children receiving no immunizations, 3% in those receiving vaccinations other than pertussis, and 11% in those receiving pertussis vaccine. Another finding to weigh in the group not immunized to pertussis is that 16 developed whooping cough compared with only 1 in the immunized group.

Influenza Vaccine

One evaluation of more than 9600 children was employed to determine the safety of cold-adapted trivalent intranasal influenza virus vaccine in children. Although this relatively new vaccination was deemed safe for children and adolescents, a significantly increased relative risk of 4.06 was observed in children 18 to 35 months of age for asthma and associated reactive airways disease.[16]

THERAPEUTIC CONSIDERATIONS

As with many complex diseases, the initial cause or causes of asthma (e.g., hypochlorhydria) may initiate a sequence of events that becomes self-propagating (e.g., hypochlorhydria-induced food allergies leading to increased intestinal permeability and then to increased susceptibility to food allergy). Effective treatment requires control of both the initiating cause or causes and the induced physiologic abnormalities.

General

Hypochlorhydria

Fractional gastric analyses in 200 asthmatic children by Bray in 1931 showed that 80% of them had gastric acid secretions below normal levels.[17] This high occurrence suggests that decreased gastric acid output may predispose these children to food allergies and has a major impact on the success of rotation or elimination diets or both and, if not corrected, on the development of additional food allergies.

Increased Intestinal Permeability

The presence of food allergies is thought to be responsible for asthmatics having been shown to have "leaky guts."[18] As a result of increased gut permeability, there an is increased antigen load on the immune system. This subsequently overwhelms the immune system, increasing the likelihood of developing additional allergies as well as increasing bronchoconstrictive compounds in the circulation. It is essential to identify offending foods as soon as possible so as to avoid the development of further allergies.

Candida Albicans

An overgrowth of the common yeast *Candida albicans* in the gastrointestinal tract has been implicated as a causative factor in allergic conditions including asthma. Apparently the acid protease produced by *C. albicans* is the responsible allergen.[19] Appropriate anticandidal therapy may result in significant clinical improvement of asthma in many cases.

Food Additives

Vitally important in the control of asthma is the elimination of food additives.[20] Artificial dyes and preservatives are widely used in foods, beverages, and drugs. The most common coloring agents are azo dyes—tartrazine (orange), sunset yellow, amaranth, and coccine (red)—and the nonazo dye pate blue. The most commonly used preservatives in food are sodium benzoate, 4-hydroxybenzoate esters, and sulfur dioxide. Various sulfites are commonly used in prepared foods.

Tartrazine, benzoates, sulfur dioxide, and sulfites in particular have been reported to cause asthma attacks in susceptible individuals.[20,21] It is estimated that 2 to 3 mg of sulfites are consumed each day by the average U.S. citizen, while an additional 5 to 10 mg are ingested by wine and beer drinkers.[21] The largest sources are the salads, vegetables (particularly potatoes), and avocado dip served in restaurants. A customer can ingest 25 to 100 mg of metabisulfite in as little as one restaurant meal. It has been postulated that a molybdenum deficiency may be responsible for sulfite sensitivity.[22] Sulfite oxidase, the enzyme responsible for neutralizing sulfites, is molybdenum dependent.

Salt

Strong evidence indicates that an increased intake of salt increases bronchial reactivity and mortality from asthma.[23,24] The degree of bronchial reactivity to histamine is positively correlated with the 24-hour urinary sodium excretion and rises with increased dietary sodium. Because the severity of asthma correlates with the degree of bronchial reactivity, the severity of asthma can clearly be influenced by alterations in dietary sodium consumption.

Estrogen and Progesterone

For female patients who experience severe asthma symptoms, it may be useful to consider therapeutic regimens that encourage a decrease in hormonal fluctuations. Some studies find estrogen withdrawal to increase lung contractility.[25] However, other studies find little relationship between estrogen use and asthmatic symptoms.[26-28] Estrogen[29] and progesterone are both known to act as smooth muscle relaxants. It may be that the airways of premenopausal and postmenopausal women may respond differently to exogenous hormone replacement and therefore need to be assessed independently with this intervention.

One interesting review of more than 90 papers published from 1966 to 2001 found that during the premenstrual and menstrual phases, when hormone levels are low, asthmatic women have been found to experience increased asthma exacerbations, increased hospitalizations for asthma, and decreased pulmonary function. Additionally, women who experienced decreased fluctuations in hormone levels either by becoming pregnant or by starting oral contraceptive therapy tended to have improvements in pulmonary function and fewer requirements for medication.[25] Natural hormone replacement may offer a safer approach than synthetic hormones, although no studies to verify the safety or efficacy of

these natural forms of female sex hormones have been conducted. In the longer term, natural therapeutics designed to balance estrogen and progesterone, along with specific recommendations from this chapter, may offer the most risk-free relief for those premenopausal and postmenopausal women who suffer from asthmatic exacerbations (see Chapter 188 and 202).

Dehydroepiandrosterone

Decreased levels of dehydroepiandrosterone (DHEA) have been shown to be common in postmenopausal women with asthma compared with matched controls.[30] One study of 55 asthmatic and 20 healthy postmenopausal women aged 48 to 60 before hormone replacement therapy and after 6 months of transdermal 17b-estradiol (E2) and medroxyprogesterone acetate treatment demonstrated a significant increase in serum DHEA levels in the asthmatic group, with no change in the control group.[31] Whether DHEA itself produces any therapeutic benefit in asthma remains to be demonstrated; however, given its important role in proper immune function, an ability to produce positive effects is certainly possible.

Melatonin

There is some concern regarding elevated melatonin levels contributing to increased airway inflammation in patients with nocturnal asthmatic exacerbations[32,33] as well as proinflammatory reactions in rheumatoid arthritis.[34] In the study of people with nocturnal asthma, peak measured serum melatonin level was significantly and inversely correlated with overnight change in FEV_1 in subjects with nocturnal asthma but not in those with nonnocturnal asthma or healthy controls. An interesting note is that this study observed a delayed release of melatonin in the patients with nocturnal asthma. Therefore it is theoretically possible that supplementation combined with an earlier sleep regimen may help regulate this late peaking of melatonin and possibly mitigate symptoms. Nevertheless, the practitioner may want to avoid giving this supplement to patients with asthma, especially the nocturnal type, until more studies are conducted regarding melatonin's immunotherapeutic effect.

Diet

Beneficial Foods

A number of publications corroborate the notion that people who have a diet rich in fruits and vegetables have a lower risk of poor respiratory health.[35-37] This effect is most likely due to the increased levels of antioxidants in such foods. One epidemiologic review[38] found that among children, consumption of fresh fruit, particularly fruit high in vitamin C, has been related to a lower prevalence of asthma symptoms and better lung function. This effect was observed even at low levels of fruit consumption (one or two servings per week vs. fewer than one serving per week), which suggests that a small increase in fruit intake could be beneficial. This same review discussed consumption of fish as also being related to lower airway hyperreactivity among children and better lung function in adults.

A study of Scottish adults also found a dose-response relationship between fruit consumption and pulmonary function, whereby increased fruit consumption led to decreases in phlegm and better pulmonary function.[39] In addition, a "reasonable" intake of fruit (>180 g/day), whole grains (>45 g/day), and moderate alcohol consumption (one to three glasses a day) was associated with a 139-mL higher FEV_1 and a 50% lower prevalence of chronic obstructive pulmonary disease versus diets that did not meet these intake requirements.[35] Finally, one study of 607 asthma patients and 864 controls highlighted apples and moderate red wine consumption as sources of antioxidants that decreased asthma severity.[40]

Dietary intake of soy foods may be helpful, as the soy isoflavone genistein is associated with reduced severity of asthma. Although this effect may be due to some antioxidant action, studies have also shown that genistein is able to block eosinophil leukotriene C(4) synthesis and inhibit the pathway of NF-κB and TNF-α in asthma patients.[41-43]

Food Allergy

Many studies have indicated that food allergies play an important role in asthma (see Chapter 15.)[44-48] Adverse reactions to food may be immediate or delayed. Double-blind food challenges in children have shown that immediate-onset sensitivities are usually due (in decreasing order of frequency) to egg, fish, shellfish, nuts, and peanuts, while foods most commonly associated with delayed onset include (in decreasing order of frequency) milk, chocolate, wheat, citrus, and food colorings.[46] Elimination diets have been successful in identifying allergens and treating asthma and are a particularly valuable diagnostic and therapeutic tool in infants.[49] Elimination of common allergens during infancy (first 2 years) has been shown to reduce allergic tendencies in high-risk children (e.g., strong familial history).[50]

Breastfeeding

Many studies have demonstrated the protective effect of breastfeeding in the prevention of asthma. One study examined the association of breastfeeding and the presence of chronic respiratory symptoms among 5182 Brazilian schoolchildren 7 to 14 years of age. Ninety percent of the mothers in this population had breastfed their infants. After adjusting for potential confounding factors, these researchers revealed that children who had not been breastfed were more likely to have a medical diagnosis of asthma.[51] One Iraqi study additionally showed that the vitamin C content of breast milk was significantly correlated with the maternal intake of vitamin C: low vitamin C intake by mother translates to low intake by the child, thus leaving him or her more susceptible to oxidative stress.[52]

The Canadian Asthma Primary Prevention study collected 2 years of data in which researchers chose 545 infants who were considered at high risk for asthma on the basis of a history of familial atopy. These children were broken down into control and intervention groups. The interventions included (1) measures to control house dust; (2) recommendations for avoidance of pets, environmental tobacco smoke, and day care during the first year; and (3) only breastfeeding or use of partially hydrolyzed whey formula until at least the age of 4 months. At 1 year of age, risk of asthma was significantly reduced by 34%. At 2 years of age, significantly fewer children had asthma in the intervention group than in the control group (16.3% vs. 23%) and 60% fewer of those in the intervention group had persistent asthma. A 90% reduction in recurrent wheeze was seen in the intervention group compared with the control group.[53] Multifactorial studies like these are quite useful in order to elucidate the multitude of changes necessary to affect multifactorial diseases like asthma in an effective manner.

Antibiotics, Probiotics, and Mucosal IgA

In a combined analysis of seven studies involving more than 12,000 youngsters, researchers at the University of British Columbia found that those prescribed antibiotics before their first birthday were

more than twice as likely as untreated kids to develop asthma.[54] And, if they had multiple courses of antibiotics it bumped up the risk even higher—16% for every course of the drugs taken before age 1. There are a couple of explanations for this association between antibiotic use and asthma. One is that antibiotics contribute to a state of "excess hygiene," leading to a reduced exposure to microbes. This, in turn, creates an oversensitive immune system, mounting an over-the-top allergic reaction to pollen and dust mites and ultimately resulting in asthma. The second explanation is that antibiotics have a negative effect on the normal flora of the gastrointestinal tract and respiratory passages. Some studies have shown that giving probiotics (active cultures of *Lactobacillus* and *Bifidobacterium* species) lowers the risk of atopic allergic diseases like asthma and eczema. Some of this protective effect may be mediated by mucosal IgA, which participates in antigen elimination. In a cohort of 237 allergy-prone infants given a combination of four probiotic strains or placebo, it was shown that supplementation with probiotics increased fecal IgA and calprotectin while reducing inflammatory markers (e.g., α_1-antitrypsin and tumor necrosis factor alpha).[55] In infants with high fecal IgA concentration at the age of 6 months, the risk of having any allergic disease or any IgE-associated (atopic) disease before the age of 2 years was cut by nearly 50%. High intestinal IgA in early life is associated with minimal intestinal inflammation and indicates a reduced risk for IgE-associated allergic diseases.

Vegan Diet

A long-term trial of a vegan diet (elimination of all animal products) provided significant improvement in 92% of the 25 treated patients who completed the study (9 dropped out).[56] Improvement was determined by a number of clinical variables including vital capacity, FEV_1, and physical working capacity as well as by biochemical indices such as haptoglobin, IgM, IgE, cholesterol, and triglyceride levels in the blood. The researchers also found a reduction in the vulnerability to infection. Importantly, however, although 71% of the patients responded within 4 months, 1 year of therapy was required before the 92% level was reached.

The diet excluded all meat, fish, eggs, and dairy products. Drinking water was limited to spring water (chlorinated tap water was specifically prohibited), and coffee, ordinary tea, chocolate, sugar, and salt were excluded. Herbal spices were allowed, and water and herbal teas were allowed up to 1.5 L/day. Vegetables eaten freely were lettuce, carrots, beets, onions, celery, cabbage, cauliflower, broccoli, nettles, cucumber, radishes, Jerusalem artichokes, and all beans except soybeans and green peas. Potatoes were allowed in restricted amounts. A number of fruits were also eaten freely: blueberries, cloudberries, raspberries, strawberries, black currants, gooseberries, plums, and pears. Apples and citrus fruits were not allowed, and grains were either restricted or eliminated.

The beneficial effects of this dietary regimen are probably related to three areas:

- Elimination of food allergens
- Altered prostaglandin metabolism
- Increased intake of antioxidant nutrients and magnesium

The importance of avoiding food allergies was discussed earlier. In regard to altered prostaglandin metabolism, the avoidance of dietary sources of arachidonic acid (derived from animal products) appears to be significant. The prostaglandins and leukotrienes derived from arachidonic acid contribute significantly to the allergic reaction in asthma. The decreased availability of arachidonic acid as a substrate of these inflammatory compounds appears to explain some aspects of the efficacy of the vegan diet. The benefits of altering prostaglandin metabolism are further discussed later, as is the role of increased dietary antioxidants in preventing asthma.

Perhaps the most significant effect noted in the trial of the vegan diet, beside the patients' improvement in health, was the great reduction in health care costs (the patients had been receiving corticosteroids and other drugs and therapies for an average of 12 years) and, according to the authors, patients' changed attitudes in taking greater responsibility for their own health.

Nutrition

Omega-3 Fatty Acids

Epidemiologic studies have shown that children who eat fish more than once a week have one-third the risk of asthma of children who do not eat fish regularly.[57] Several clinical studies have shown that increasing the intake of omega-3 fatty acids through supplementation with fish oils containing eicosapentaenoic acid and docosahexanoic acid offers significant benefits in asthma, as noted by improvements in airway responsiveness to allergens as well as improvements in respiratory function.[58,59] These benefits are related to an increased ratio of omega-3 to omega-6 fatty acids in cell membranes, thereby reducing the availability of arachidonic acid. In particular, the ingestion of omega-3 fatty acids leads to a significant shift in leukotriene synthesis from the extremely inflammatory 4-series to the less inflammatory 5-series leukotrienes. This shift is directly related to improvements in asthma symptoms.[60] The benefits may take as long as 1 year to become apparent, as it seems to take time to turn over cellular membranes in favor of the omega-3 fatty acids.

Tryptophan Metabolism and Pyridoxine Supplementation

Children with asthma have been shown to have a metabolic defect in tryptophan metabolism and reduced platelet transport for serotonin.[61,62] Tryptophan is converted to serotonin, a known bronchoconstricting agent in asthmatics. High serotonin levels in the blood and sputum are common findings in asthmatics and are reflected by an elevated urinary level of 5-hydroxyindoleacetic acid (5-HIAA), the breakdown product of serotonin. The levels of 5-HIAA in the urine correlate well with the severity of asthmatic symptoms. Double-blind clinical studies have shown that patients benefit from either a tryptophan-restricted diet[61] or pyridoxine supplementation[62,63] to correct the blocked tryptophan metabolism.

Pyridoxine may also be of direct benefit to asthmatic patients. In one study, plasma and erythrocyte pyridoxal phosphate levels in 15 adult patients with asthma were significantly lower than in 16 controls.[62] Oral supplementation with 50 mg of pyridoxine twice daily to 7 of the patients failed to produce a substantial elevation of these low levels. However, all patients reported a dramatic decrease in the frequency and severity of wheezing as well as asthma attacks while taking the supplements. In a study of 76 asthmatic children, pyridoxine at a dosage of 200 mg daily produced significant reductions in symptoms and dosages of bronchodilators and corticosteroids. However, a double-blind study failed to demonstrate any significant improvement with vitamin B_6 supplementation in patients who depended on steroids to control symptoms.[64]

Although vitamin B_6 supplementation may not help patients on steroids, it is definitely indicated in asthmatics being treated with the drug theophylline. Theophylline significantly depresses pyridoxal-5-phosphate levels.[65] In addition, another study has shown that vitamin B_6 supplementation can significantly reduce the typical side effects of theophylline (e.g., headaches, nausea, irritability, sleep disorders).[66]

Antioxidants

The substantial increase in the prevalence of asthma over the past 20 years can be partially explained by the reduced dietary intake of antioxidant nutrients like beta-carotene and vitamins A, C, and E as well as the mineral cofactors essential for antioxidant defense mechanisms, such as zinc, selenium, and copper.[67] Patients undergoing acute asthmatic distress are known to have lowered serum total antioxidants.[68] Genetic influences may also play a role in the need for antioxidants (see "General Considerations," previously).[3]

One study of 158 children with moderate to severe asthma revealed that supplementation of 50 mg/day of vitamin E and 250 mg/day of vitamin C conferred significant protection against ozone-induced reductions in pulmonary function.[69] Antioxidants are thought to provide important defense mechanisms for maintaining the redox state of the lungs. This protection is significant because oxidizing agents can both stimulate bronchoconstriction and increase hyperactivity to other agents. Asthma appears to be another disease process that is influenced greatly by antioxidant mechanisms. Analgesics like acetaminophen, known to deplete antioxidant levels such as glutathione in animals, should be used with caution in asthmatic patients.[70]

Vitamin C

Especially important to the health of the lung is vitamin C, as it is the major antioxidant substance present in extracellular fluid lining the airway surfaces.[71] Vitamin C intake in the general population appears to correlate with asthma, indicating that low vitamin C (in the diet and the blood) is an independent risk factor for asthma. In a survey of 771 persons with current asthma, 352 with former asthma, and 15,418 without asthma, lower vitamin C concentrations were observed among those with current or former asthma than those who had never had asthma.[72] Additional support is offered by the fact that children of smokers have a higher rate of asthma (cigarette smoke is known to deplete respiratory vitamins C and E levels), and symptoms of ongoing asthma in adults appear to be increased by exposure to environmental prooxidants and decreased[52] by vitamin C supplementation.

Nitrogen oxides are examples of oxidants that can arise from both endogenous and exogenous sources. Vitamin C has been shown to offer significant protection against nitrogen oxide damage in the lungs of animal models.[73]

Both treated and untreated asthmatic patients have been shown to have significantly lower levels of ascorbic acid in serum and leukocytes.[73] From a clinical perspective, it appears that asthmatics have a higher need for vitamin C. Since 1973 there have been 11 clinical studies of vitamin C supplementation in asthma.[74] Seven of these studies showed significant improvements in respiratory measures and asthma symptoms as a result of supplementing the diet with 1 to 2 g of vitamin C daily. This dosage recommendation appears extremely wise based on the increasing exposure to inhaled oxidants, along with the growing appreciation on the antioxidant function of vitamin C in the respiratory system.

High-dose vitamin C therapy may also help asthma by lowering histamine levels.[75] The importance of vitamin C as a natural antihistamine has emerged for several reasons, including concern over the safety of antihistamine medications and the recently recognized immune-suppressing effects of histamine. In the initial stages of an immune response, histamine amplifies the immune response by increasing capillary permeability and smooth muscle contraction, thus enhancing the flow of immune factors to the site of infection. Subsequently, histamine exerts a suppressive effect on the accumulated white blood cells in an attempt to contain the inflammatory response.

Vitamin C exerts a number of effects against histamine. Specifically, it prevents the secretion of histamine by white blood cells and increases the detoxification of histamine. One study examined the antihistaminic effect of acute and chronic vitamin C administration and its effect on white blood cell (neutrophil) function in healthy men and women. In the chronic study, 10 subjects ingested a placebo during weeks 1, 2, 5, and 6 and 2 g/day of vitamin C during weeks 3 and 4. Fasting blood samples were collected after the initial 2-week period (baseline) and at the end of weeks 4 and 6. Blood vitamin C levels rose significantly following vitamin C administration, while blood histamine levels fell by 38% during the weeks vitamin C was given. The ability of white blood cells to move in response to an infection (chemotaxis) increased by 19% during vitamin C administration and fell 30% after vitamin C withdrawal. However, these changes were linked to histamine concentrations. Chemotaxis was greatest when histamine levels were the lowest. In the part of the study looking at the acute effects of vitamin C, blood histamine concentrations and chemotaxis did not change 4 hours after a single dose of vitamin C. This result suggests that vitamin C will lower blood histamine only if it is taken over time. Individuals prone to allergy or inflammation are encouraged to increase their consumption of vitamin C through supplementation.[75]

In a small study of asthma and documented exercise-induced bronchoconstriction, the subjects participated in a randomized placebo-controlled double-blind crossover trial.[76] They entered the study on their usual diets and were placed on either 2 weeks of ascorbic acid supplementation (1500 mg/day) or placebo, followed by a 1-week washout period, before crossing over to the alternative treatment. The ascorbic acid diet significantly reduced (P <0.05) the maximum fall in postexercise FEV_1 (–6.4 %) compared with the usual diet (–14.3%) and a placebo diet (–12.9%). Asthma symptom scores significantly improved on the ascorbic acid diet compared with the placebo and usual diets. Postexercise inflammatory mediators were also significantly lower with ascorbic acid supplementation.

Flavonoids

Flavonoids appear to be key antioxidants in the treatment of asthma. Various flavonoids, chief among them being quercetin, have been shown to inhibit the following[77-80]:

- Histamine release from mast cells and basophils when stimulated by antigens and other ligands
- Phospholipase A_2 in neutrophils
- Lipoxygenase
- Anaphylactic contraction of smooth muscle
- Phosphodiesterase in the lung (resulting in increased cAMP levels)
- Biosynthesis of SRS-A
- Calcium influx

In addition, quercetin has both a vitamin C–sparing effect and a direct stabilizing effect on membranes including mast cells. Flavonoids are also extremely effective antioxidants.

Standard quercetin or more bioavailable forms of quercetin can be used. However, flavonoid-rich extracts such as those from grape seed, pine bark, green tea, or *Ginkgo biloba* may prove even more helpful in the treatment of asthma owing to their better bioavailability. In particular, the proanthocyanidins from grape seed or pine bark extracts appear to have an affinity for the lungs (for more information, see Chapter 117). In a randomized placebo-controlled double-blind study involving 60 subjects 6 to 18 years of age, a proprietary pine bark extract (Pycnogenol) significantly improved pulmonary function and asthma symptoms compared

with placebo. Specifically, the Pycnogenol group was able to reduce or discontinue their use of rescue inhalers more often than the placebo group. There was also a significant reduction of urinary leukotrienes in the Pycnogenol group.[81]

In another study, a flavonoid preparation derived from purple passion fruit peel (PFP) was studied in a 4-week randomized placebo-controlled, double-blind trial in asthma patients. The dosage of the PFP extract was 150 mg daily. The prevalence of wheeze, cough, and shortness of breath was reduced significantly in the group treated with PFP extract, whereas the placebo caused no significant improvement. PFP extract supplementation also resulted in a marked increase in FEV_1, whereas placebo showed no effect.[82]

Carotenes

Carotenes are powerful antioxidants that may increase the integrity of the epithelial lining of the respiratory tract and act as substrates for lipoxygenase, possibly competing with arachidonic acid and thereby decreasing leukotriene formation.[83] Some studies have shown that asthmatics have reduced plasma antioxidant potential due to low whole-blood carotenoids (beta-carotene, lycopene, alpha-carotene, beta-cryptoxanthin, lutein/zeaxanthin),[84] in particular low lycopene levels,[85] thus making them more susceptible to the damaging effects of oxidative stress. This highlights the potential role of carotenoid supplementation in these subjects. Lycopene may emerge as the most useful supplemental carotenoid. In animal models of asthma, lycopene supplementation suppressed Th2 responses and reduced eosinophilic infiltrates in the bronchoalveolar lavage fluid, lung tissue and blood as well as the number of mucus-secreting cells in the airways.[86]

In a proof-of-concept human study, asthmatic adults (n = 32) consumed a low-antioxidant diet for 10 days and then commenced a randomized crossover trial involving three 7-day treatment arms (placebo, tomato extract [45 mg lycopene per day], and tomato juice [45 mg lycopene per day]).[87] With consumption of a low-antioxidant diet, plasma carotenoid concentrations decreased, Asthma Control Score worsened, lung function (FEV_1) and forced vital capacity (FVC) decreased, and sputum neutrophils increased. Treatment with both tomato juice and extract reduced airway neutrophil influx. Treatment with tomato extract also reduced sputum neutrophil elastase activity. This short-term study indicate that antioxidant status, particularly in terms of carotenoids, modifies some parameters in asthma.

There have been two double-blind studies of lycopene supplemenation (30 mg/day) in exercise-induced asthma. One failed to show any benefit[88] while another showed that in some patients it prevented airway constriction and reduced FEV_1.[89]

Vitamin E

Vitamin E's activity as an antioxidant, lipoxygenase inhibitor, and phospholipase inhibitor makes it a useful supportive agent in asthma treatment.[90]

Selenium

Reduced selenium levels have been demonstrated in asthma patients.[91-93] Glutathione peroxidase, a selenium-dependent metalloenzyme, is important for reducing hydroperoxyeicosatetraenoic acid (HPETE) to HETE acid, thereby reducing leukotriene formation. Reduced levels of glutathione peroxidase have also been reported for asthmatics.[91] Supplemental selenium appears warranted to address any deficiency of glutathione peroxidase. In addition, supplemental selenium may reduce the production of leukotrienes by ensuring optimal activity of glutathione peroxidase.

Vitamin B_{12}

Wright believes that "B_{12} therapy is the mainstay in childhood asthma."[94] In one clinical trial, weekly intramuscular injections of 1000 mg produced definite improvements in asthmatic patients.[95] Of 20 patients, 18 showed less shortness of breath on exertion as well as improved appetite, sleep, and general condition. Vitamin B_{12} appears to be especially effective in sulfite-sensitive individuals. It offers the best protection when given orally (1 to 4 mcg) before challenge compared with other pharmacologic agents (e.g., cromolyn sodium, atropine, doxepin).[96] The mode of action is the formation of a sulfite-cobalamin complex that blocks sulfite's effect.

Magnesium

In 1912, Trendelenburg demonstrated that magnesium relaxed bovine bronchial smooth muscle in vitro.[97] Later, uncontrolled clinical studies revealed magnesium's beneficial effect in the treatment of patients with acute attacks of bronchial asthma.[98] Unfortunately this promising line of research was dropped as antihistamines and bronchodilators became available. However, the advent of calcium channel blockers for the treatment of asthma generated renewed interest in the therapeutic use of magnesium for asthma. In fact, intravenous magnesium (2 g of magnesium sulfate infused every hour up to a total of 24.6 g) is now a well-proven and clinically accepted measure to halt an acute asthma attack as well as acute exacerbations of chronic obstructive pulmonary disease.[99-103]

Although these initial studies used injectable magnesium, it has been demonstrated that this is not necessary to restore magnesium status except in the case of an emergency situation such as an acute heart attack or acute asthma attack.[104] Oral magnesium therapy is an effective measure to raise body magnesium stores, but it will usually take 6 weeks to achieve significant elevations in tissue magnesium concentrations. Oral supplementation appears to be warranted because low levels of plasma magnesium have been found in asthmatic patients[70] and dietary magnesium intake is independently related to lung function and the severity of asthma.[105] Several double-blind studies in adults and children with asthma have demonstrated an improvement in respiratory function, antioxidant status (i.e., increased glutathione concentrations), reduced reactivity to chemical challenge to methacholine, and measures of asthma control and quality of life.[106-108] Dosages used ranged from 300 mg a day in children to 340 mg a day in adults, usually in divided dosages.

Isotonic nebulized magnesium has also proved useful as an adjunct treatment to standard bronchodilation therapies in severe asthmatics, with a greater response in those with life-threatening asthma.[109]

Vitamin D

Vitamin D deficiency is linked to increased airway reactivity, poorer lung function, and worse asthma control.[110] One study in over 1000 children with asthma showed that 35% were vitamin D–insufficient as defined by a level of 30 ng/mL or less of 25-hydroxyvitamin D.[111] After adjusting for age, sex, body mass index, income, and treatment group, insufficient vitamin D status was associated with higher odds of hospitalization or emergency department visits (odds ratio 1.5). In addition to correcting a vitamin D insufficiency, vitamin D supplementation may improve asthma control by blocking the cascade of inflammation-causing proteins in the lung as well as increasing the production of interleukin-10, which has anti-inflammatory effects. Preliminary clinical evidence is encouraging, especially in the

prevention of childhood asthma, at a dosage of 1200 IU per day of vitamin D_3.[112]

Botanical Medicines

Asthma patients commonly employ self-treatment with botanicals. A cross-sectional analysis of 601 adults with asthma found that 14% used either herbal products, coffee, or black tea in order to treat their condition. Unfortunately this study illustrated that those who used these methods had a higher incidence of hospitalizations.[113] Because of the possibility of improper use of botanicals and the inability of the users to recognize the need for acute conventional interventions, we recommend that before using natural therapies, patients with asthma consult a naturopathic physician or other qualified practitioner who understands the proper use of botanicals and can assess the asthmatic patient's severity of risk.

The most popular historic herbal treatment of asthma involved the use of *Ephedra sinensis* (Ma huang) in combination with herbal expectorants. This approach appeared to have considerable merit, as *Ephedra* and its alkaloids have proven to be effective as bronchodilators in treating mild to moderate asthma and hay fever.[114,115] However, *Ephedra* preparations are no longer sold in the United States owing to safety concerns.

Hedera Helix (Ivy)

In Europe, herbal preparations containing extracts from the leaves of ivy enjoy great popularity for the relief of cough as well as asthma. In 2007, more than 80% of herbal expectorants prescribed in Germany comprised ivy extract and amounted to nearly 2 million prescriptions nationwide. Ivy leaf contains saponins that show expectorant, mucolytic, spasmolytic, bronchodilatory, and antibacterial effects. The mucolytic and expectorant action of ivy is based on indirect $beta_2$ adrenergic effects and this action is due to the saponins α-hederin and hederacoside C, the latter of which is metabolized to α-hederin when ingested.[116] The indirect effect is that α-hederin inhibits the intracellular uptake of $beta_2$ receptors and leads to an increased $beta_2$ adrenergic response of the cell.

A 2003 meta-analysis of three double-blind studies in children showed that the ivy preparations used were significantly superior to placebo.[117] One study compared ivy leaf extract coughdrops to placebo, one compared suppositories to drops, and one tested syrup against drops. The reviewers concluded that the results showed ivy leaf extract preparations to be effective with respect to the improvement of respiratory function in children with chronic bronchial asthma but noted that the study had a very meager database to assess. In the only placebo-controlled double-blind study reviewed, 24 children with asthma between the ages of 4 and 12 were given a dry ivy leaf extract (35 mg) in cough drops or placebo for 3 days with a washout of 3 to 5 days before crossing over to the other treatment. Superiority of ivy leaf extract over placebo was noted by small improvements for airway resistance, residual volume, vital capacity, FVC, and FEV_1 when the baseline measurements were compared to day 3 at 3 hours postdosing (morning dose).

Glycyrrhiza Glabra

Licorice root has a long history of use as an anti-inflammatory and antiallergic agent, as documented in the scientific literature (see Chapter 96). The primary active component of licorice root in this application is glycyrrhetinic acid, a compound that has shown cortisol-like activity. In particular, glycyrrhetinic acid has been shown to inhibit phospholipase A_2, the enzyme responsible for cleaving arachidonic acid from the phospholipid membrane pool and initiating eicosanoid synthesis.[118] Licorice is also an expectorant, which is useful in the treatment of asthma.

Lobelia Inflata

Indian tobacco contains the alkaloid lobeline, an efficient expectorant. Although it has a long history of use in asthma, it does promote bronchoconstriction and is a respiratory stimulant in vitro.[119] Although this suggests a cholinergic effect in the respiratory system, it also binds to nicotine acetylcholine receptors in ganglions, thus promoting the release of epinephrine and norepinephrine. It is this action on adrenal hormone secretion that is responsible for lobelia's therapeutic effects.[120] Although effective when used alone, it has traditionally been used in combination with other botanical agents such as *Capsicum frutescens* and *Symphlocarpus factida*.

Capsicum Frutescens

Experimental evidence has shown that capsaicin, cayenne pepper's major active component, induces long-lasting desensitization of airway mucosa to various mechanical and chemical irritants.[121] This effect is probably due to capsaicin-induced depletion of substance P (which normally increases vascular permeability and flow) in the respiratory tract nerves. Substance P is an undecapeptide associated with "neurogenic inflammation" via a direct effect and a synergistic action with histamine on the peripheral nervous system.[122] The respiratory and gastrointestinal tracts have large numbers of substance P–containing neurons. Because of its location and physiologic action, it is believed to play an important role in atopic conditions such as asthma and atopic dermatitis. Therefore depletion of substance P may be desirable in these conditions.

Zizyphi Fructus

The jujube plum has been used extensively in Chinese medicine for the treatment of asthma and allergic rhinitis.[123] It contains 100 to 500 nmol/g of dry weight, a concentration 10 times greater than that of any other plant or animal tissue thus far reported in the literature.[124] It also contains a beta-adrenergic receptor stimulator that raises cAMP levels. These experimental findings, in conjunction with zizyphi's long historical use, strongly support its clinical use.

Thea Sinensis

Green tea is useful as an adjunctive in asthma treatment due to its methylxanthine and antioxidant components (see Chapter 72).

Allium Family

Onions and garlic inhibit lipoxygenase and cyclooxygenases, which generate TxA_2, PGD_2, and PGE_2[125] Oral pretreatment of guinea pigs (who were sensitized to ovalbumin) with 1 ml of an alcohol/onion extract markedly reduced the asthmatic response to allergen inhalation challenges. Onion contains quercetin, which may account for some of its pharmacologic effect,[126] but the major protective actions appear to be related to its content of benzyl and other isothiocyanates (mustard oils).[127] Although the mechanism of action is unknown, it has been suggested that it is due to inhibition of the biosynthesis of arachidonic acid metabolites.

Tylophora Asthmatica

The leaves of *Tylophora asthmatica* have been used extensively in Ayurvedic medicine in asthma and other respiratory tract disorders. The mode of action of tylophora is unknown but is thought to be due to the alkaloids, especially tylophorine, which have been reported to possess antihistamine and antispasmodic activity, as well as inhibition of mast cell degranulation.[128,129] However,

a more central mechanism may be responsible for the clinical effects in asthma.

Several double-blind clinical studies have shown tylophora to produce good results.[130-133] In one study of 135 patients, those given 200 mg of tylophora leaves twice daily for 6 days demonstrated improvements in symptoms and respiratory function during the treatment period and for up to 2 weeks after treatment.[130] Symptom score, FEV in 1 second, and peak expiratory flow rate (PEFR) were used as parameters. Side effects such as nausea and vomiting occurred in 9.8% in the tylophora group and 14% in the placebo group.

In another double-blind study of 103 patients, those receiving 40 mg of the dry alcoholic extract of *Tylophora indica* daily for only 6 days demonstrated significant improvement in symptoms of asthma compared with a placebo group.[132] At the end of the first week, 56% had complete to moderate improvement, as compared with 31.6% of the 92 patients receiving the placebo. At the end of 4 weeks, the respective figures were 32% and 23.8%; at 8 weeks, 23.8% and 8.4%; and at 12 weeks, 14.8% and 7.2%. The incidence of side effects such as nausea, partial diminution of taste for salt, and slight mouth soreness was 16.3% in the tylophora group and 6.6% in the placebo group. These results, as well as the results from an additional study, indicate that the benefits of tylophora are short-lived.[133,134]

Ginkgo Biloba

G. biloba contains several unique terpene molecules known collectively as ginkgolides that antagonize platelet-activating factor (PAF), a key chemical mediator in asthma, inflammation, and allergies. Ginkgolides compete with PAF for binding sites and inhibit the various events induced by PAF. The antiasthmatic effects of orally administered or inhaled ginkgolides have been shown to produce improvements in respiratory function and to reduce bronchial reactivity in several double-blind studies.[134,135] Treatment consisted of 120 mg of the pure ginkgolides daily—a dosage that is currently expensive to achieve using the 24% ginkgo flavonglycoside and 6% total terpenoid *G. biloba* extract.

Aloe Vera

Administration of *Aloe vera* preparations may be effective for patients who are not dependent on corticosteroids. In one study, the oral administration of an extract of *A. vera* for 6 months was shown to produce good results in the treatment of asthma in some individuals of various ages.[136] The extract was produced from the supernatant of fresh leaves stored in the dark at 4°C for 7 days. Subjecting the leaves to dark and cold results in an increase in the polysaccharide fraction. One gram of the crude extract obtained from leaves stored in a cold, dark environment produced 400 mg of neutral polysaccharide, compared with only 30 mg produced from leaves not subjected to cold or dark. The dosage was 5 mL of a 20% solution of the *A. vera* extract in saline twice daily for 24 weeks, and 11 of 27 patients (40%) without corticosteroid dependence felt much better at the study's conclusion. The mechanism of action is thought to be via restoration of protective mechanisms, followed by augmentation of the immune system.

Coleus Forskohlii

Coleus forskohlii extracts may be particularly useful in asthma, as increasing intracellular levels of cAMP result in relaxation of bronchial muscles and relief of respiratory symptoms. Forskolin has been shown to have remarkable effects in relaxing constricted bronchial muscles in asthmatics (see Chapter 80).[137,138] However, these studies used inhaled doses of pure forskolin. Whether orally administered forskolin in the form of *C. forskohlii* extract would produce similar bronchodilatory effects has yet to be determined. However, on the basis of the plant's historic use and additional mechanisms of action, it appears likely.

Boswellia

The Indian Ayurvedic botanical *Boswellia* is known for its ability to inhibit leukotriene biosynthesis.[139] In one double-blind placebo-controlled study, bronchial asthma was reduced in 70% of 40 patients treated with gum resin at 300 mg three times daily for 6 weeks, whereas only 27% of the control group improved. Disappearance of physical symptoms and signs such as dyspnea and rhonchi; fewer attacks; increased FEV_1, vital capacity, and peak expiratory flow rate (PEFRs); and decreased eosinophilia counts and sedimentation rates were recorded as measures of improvement.[139]

Acupuncture and Acupressure

In traditional Chinese medicine, chronic asthmatic symptomatology is usually characterized as a lung or spleen deficiency. This model considers that acute symptoms may be caused by environmental invasion from cold wind (environmental factors) or an internal condition stemming from a lung heat condition (increased inflammation and eosinophilia). Chronic asthma is considered more of a weakness in the lung itself or a weakness of the spleen, which is responsible for nourishing the lung *qi* (or vitality). In traditional Chinese medicine, the emotion of grief is also said to weaken lung *qi*.

In one prospective randomized study of chronic asthma patients, 41 patients with chronic obstructive asthma were randomly assigned to receive acupuncture in addition to standard care, acupressure and standard care, or standard care alone. For each subject, 20 acupuncture treatments were given, and self-administered acupressure was performed daily for 8 weeks. On the St. George's Respiratory Questionnaire, the acupuncture subjects showed an average 18.5-fold improvement, whereas the improvement for the acupressure-only subjects was 6.57-fold. Additionally, for patients who received acupressure, the irritability domain score exhibited an 11.8-fold improvement.[140] Another study involved 44 patients receiving bona fide or sham acupressure. They received five treatments per week lasting 16 minutes each for 4 weeks. Using pulmonary function and dyspnea scores, 6-minute walking distance measurements, and State Anxiety Scale scores, the acupressure group had significant improvements in breathing and less anxiety compared with those of the sham group.[141]

THERAPEUTIC APPROACH

The effective treatment of asthma requires the consideration and control of many aspects. In particular, the specific underlying defects and initiating factors must be determined, since many different defects and metabolic abnormalities result in the same clinical picture of asthma. Otherwise only a much less successful "shotgun" approach is possible. The development of an appropriate treatment plan includes the following five steps:

1. Determining and rectifying the underlying defect that allows the development of sensitization
2. Determining and balancing the underlying metabolic defect that causes an excessive inflammatory response
3. Finding the allergens and developing a lifestyle, diet, and environment that allow the allergens to be avoided

4. Modulating the inflammatory process to limit the severity of the response
5. Preparing an effective treatment for the bronchoconstriction of the acute attack

Environment

Airborne allergens such as pollen, dander, and dust mites[142] are often difficult to avoid entirely, but measures can be taken to reduce exposure. Eliminating dogs, cats, carpets, rugs, upholstered furniture, and other surfaces where allergens can collect is a great first step. Also, methods to discourage the presence of dust mite and cockroach antigen should be used, although pesticide exposure should be minimized. If environmental exposures cannot be controlled entirely, make sure that the bedroom is as allergy-proof as possible. Have the patient encase the mattress in an allergen-proof plastic; wash sheets, blankets, pillowcases, and mattress pads every week; consider using bedding material made from Ventflex, a special hypoallergenic synthetic material; and install an air purifier. The best mechanical air purifiers are high-efficiency particulate-arresting filters that can be attached to central heating and air-conditioning systems. These units are available from suppliers of heating and air-conditioning units.

Diet

All food allergens and food additives should be eliminated. The patient who has many food allergies may have to use a 4-day rotation diet. In the early stages of treatment, mild dietary tryptophan reduction should be useful but is not critical unless there is a metabolic defect in tryptophan metabolism. Garlic and onions should be used liberally unless the patient reacts to them. If the patient is willing or his or her asthma is unresponsive to this recommended therapy, a vegan diet should be tried (for a minimum of 4 months) with the possible exception of cold-water fish. Moderate fruit consumption, especially of apples, should also be encouraged.

Supplements

- Vitamin B_6: 25 to 50 mg two times a day
- Vitamin B_{12}: 1000 mcg/day (oral) or weekly injection; evaluate for efficacy after 6 weeks
- Vitamin C: 10 to 30 mg/kg in divided dosages
- Vitamin D: 1000 to 8000 IU daily. Monitor blood levels to determine needed dosage as there is wide variability. Those whose blood levels do not rise in response to supplementation should have their $1,25(OH)2D_3$ checked.
- Vitamin E: 100 to 200 IU daily
- Magnesium: 200 to 400 mg three times a day
- Quercetin: 400 mg 20 minutes before meals or enzymatically modified isoquercitrin (EMIQ) 100 mg daily.
- Grape seed extract (95% PCO content) or pine bark extract (e.g., Pycnogenol): 150 to 300 mg daily
- Lycopene: 30 to 45 mg/day
- Selenium: 200 mcg/day

Botanical Medicines

Choose one or more of the following:

Hedera helix

Ivy leaf is available primarily in tincture and fluid extract; and the dry powdered extract comes in the form of capsules and tablets. Based on clinical studies, the daily dosages should deliver the following equivalent to dried herbal substance: 1 to 5 years: 150 mg; 6 to 12 years: 210 mg; over 12 years: 420 mg. The typical dosage of a 4:1 powdered extract for adults and children over 12 years of age is 100 mg daily.

Lobelia inflata

- Dried herb: 0.2 to 0.6 g three times a day
- Tincture: 15 to 30 drops three times a day
- Fluid extract: 8 to 10 drops three times a day

Glycyrrhiza glabra

- Powdered root: 1 to 2 g
- Fluid extract (1:1): 2 to 4 mL (1/2 to 1 Tsp)
- Solid (dry-powdered) extract (4:1): 250 to 500 mg

Camellia sinensis

Liberal use (green tea only)

Tylophora asthmatica

200 mg of tylophora leaves or 40 mg of the dry alcoholic extract two times daily

Coleus forskolii

Extract standardized to contain 18% forskolin: 50 mg (9 mg of forskolin) two to three times daily

Counseling

For patients who respond to emotional crises with asthmatic attacks, counseling is important. Counseling is also important for children with moderate to severe asthma, who may develop behavioral problems.

Acupuncture and Acupressure

Regular acupuncture and home acupressure treatments should be used.

In Acute Attack

An acute asthma attack can be a medical emergency. If intravenous magnesium cannot be administered, the patient should be referred to an emergency department immediately.

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CHAPTER 148

Atherosclerosis

Michael T. Murray, ND

DIAGNOSTIC SUMMARY

- Characteristically associated with high blood pressure, weak pulse, and wide pulse pressure
- Symptoms and signs depend on the arteries involved and degree of obstruction: angina, leg cramps (intermittent claudication), gradual mental deterioration, weakness or dizziness
- May also be without symptoms
- Diagonal earlobe crease

GENERAL CONSIDERATIONS

Atherosclerosis refers to the process that is the underlying pathology in a group of clinical entities collectively referred to as cardiovascular disease (CVD), including heart disease (atherosclerosis of the coronary arteries); coronary artery disease (CAD); and myocardial, pulmonary, and cerebral infarction. Despite a steady decline in the age-adjusted death toll since 1980, CVD remains the number one cause of death in the United States, where it is responsible for 1 of every 2.8 deaths. In 2006, more than 630,000 deaths were attributed to heart disease and nearly 140,000 deaths to stroke in the United States.

Understanding Atherosclerosis

To fully understand the important ways in which various natural measures described in this chapter affect the health of the arteries and treatment of CVD, it is necessary to examine closely the structure of an artery and the process of atherosclerosis.

Structure of an Artery

An artery is divided into three major layers:

- The intima, representing the endothelium or internal lining of the artery. It consists of a layer of endothelial cells. Glycosaminoglycans (GAGs) line the exposed endothelial cells to protect them from damage as well as to promote repair. Beneath the surface cells is the internal elastic membrane, composed of a layer of GAGs and other ground substance compounds, which supports the endothelial cells and separates the intima from the smooth muscle layer.
- The media consists primarily of smooth muscle cells. Interposed among the cells are GAGs and other ground substance structures that provide support and elasticity to the artery.
- The adventitia, or external elastic membrane, consists primarily of connective tissue including GAGs; it provides structural support and elasticity to the artery.

The Process of Atherosclerosis

The lesions of atherosclerosis are initiated in response to injury to or a disruption of the normal functioning of the arterial endothelium.[1] The progression of atherosclerosis is detailed as follows:

1. The initial step is damage or dysfunction of the vascular endothelium. Damage results from weakening of the GAG layer, which protects the endothelial cells, due to the same factors that ultimately damage the endothelial cells (insulin resistance, reactive oxygen and nitrogen species, impaired repair

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BOX 148-1 Major Risk Factors for Atherosclerosis

- Smoking
- Elevated blood cholesterol levels
- High blood pressure
- Diabetes
- Physical inactivity
- Other risk factors

processes, heavy metal toxicity, hyperhomocysteinemia, and inhibition of either nitric oxide production or availability).

2. Once the endothelial cells have been sufficiently damaged, sites of injury become more permeable to plasma constituents, especially lipoproteins. The binding of lipoproteins to GAGs leads to a breakdown in the integrity of the ground substance matrix and causes an increased affinity for cholesterol. Simultaneously, monocytes, T lymphocytes, and platelets adhere to the damaged area, where they release growth factors that stimulate smooth muscle cells to migrate from the media into the intima and replicate.
3. Local concentration of lipoproteins, monocytes, and platelets leads to the migration of smooth muscle cells from the media into the intima, where they undergo proliferation. Smooth muscle cells dump cellular debris into the intima, leading to the further development of plaque.
4. Formation of a fibrous cap (consisting of collagen, elastin, and GAGs) over the intimal surface occurs. Fat and cholesterol deposits accumulate.
5. Plaque continues to grow until eventually it either blocks the artery directly or ruptures to form a clot that travels the general circulation until it occludes a blood vessel. Plaque instability is associated with a significantly greater risk for myocardial infarction (MI) or stroke.[1] Thus, targeting plaque stabilization appears to be more clinically important than simply enlarging the lumen.

Causative Factors

Prevention of CVD involves reducing and, when possible, eliminating various risk factors. Risk factors are divided into two primary categories: major risk factors and other risk factors. Box 148-1 lists the major risk factors. Risk for a heart attack increases with the number of major risk factors, as Table 148-1 shows.

In addition to these well-accepted major risk factors, numerous others have occasionally been shown to be more significant. Box 148-2 lists these additional risk factors. It is also important to develop a strategic approach to plaque stabilization by addressing endothelial dysfunction as well as increased local and systemic inflammation, increased reactive oxygen species, the activation of mast cells, and the infiltration and activation of macrophages.

Determining a Patient's Risk

To help determine a patient's overall risk for having a heart attack or stroke, the following risk-determinant scale may prove useful. Although this risk assessment does not take into consideration several other important factors—such as the level of C-reactive protein, lipoprotein(a) or Lp(a), fibrinogen, and coping style—the score provides a good indication of a patient's risk for a heart attack or stroke (Table 148-2).

TABLE 148-1 **Association of Risk Factors with the Incidence of Atherosclerosis**

MAJOR RISK FACTORS	INCREASE IN INCIDENCE
Presence of one of the major risk factors	30%
High cholesterol and high blood pressure	300%
High cholesterol and a smoker	350%
High blood pressure and a smoker	350%
Smoker, high blood cholesterol, and high blood pressure	720%

BOX 148-2 Other Risk Factors for Atherosclerosis

- Insulin resistance
- Low thyroid function (see Chapter 177)
- Low antioxidant status
- Elevations of C-reactive protein
- Low levels of essential fatty acids
- Increased platelet aggregation
- Increased fibrinogen formation
- Low levels of magnesium and potassium
- Elevated levels of homocysteine
- "Type A" personality

Clinical Evaluation

The complete cardiovascular assessment can include the tests listed in Box 148-3.

Risk Factors

Smoking

Cigarette smoking is perhaps the most important risk factor for CVD, because statistical evidence reveals smokers have a 70% greater risk of death from CVD than nonsmokers.[2] The more cigarettes smoked and the longer the period of years a person has smoked, the greater the risk of dying from a heart attack or stroke. Overall, the average smoker dies 7 to 8 years sooner than the nonsmoker.

Tobacco smoke contains more than 4000 chemicals, of which more than 50 substances have been identified as carcinogens. These chemicals are extremely damaging to the cardiovascular system. Specifically, these chemicals are carried in the bloodstream on low-density lipoprotein cholesterol (LDL-C), where they either damage the lining of the arteries directly or they damage the LDL-C molecule, which then damages the arteries. An elevated LDL-C level worsens the effect of smoking on the cardiovascular system because more cigarette toxins travel through it. Smoking contributes to elevated cholesterol presumably by damaging feedback mechanisms in the liver, which control how much cholesterol is being manufactured.[3] Smoking also promotes platelet aggregation and elevated fibrinogen levels, two other important independent risk factors for CVD. In addition, it is a well-documented fact that cigarette smoking is a contributing factor to high blood pressure.[4]

Even passive exposure to cigarette smoke is damaging to cardiovascular health, because convincing evidence links environmental (secondhand or passive) smoke to heart disease mortality and morbidity. Analysis of ten epidemiologic studies indicates a consistent dose-response effect related to exposure.[5] Evidence indicates that

TABLE 148-2 **Risk-Determination Scale for Heart Disease and Stroke**

	Scale of Risk				
	1	2	3	4	5
Blood pressure (systolic)	<125	125-134	135-149	150-164	≥165
Blood pressure (diastolic)	<90	90-94	95-104	105-114	≥115
Smoking (cigarettes per day)	None	1-9	10-19	20-29	≥30
Heredity I*	None	>65	50-64	35-49	<35
Heredity II†	0	1	2	4	≥4
Diabetes duration (years)	0	1-5	6-10	11-15	>15
Total cholesterol (mg/dL)	<200	200-224	225-249	250-274	≥275
HDL-C (mg/dL)	≥75	65-74	55-64	35-54	<35
Total cholesterol/HDL-C ratio‡	<3	3-3.9	4-4.9	5-6.4	≥6.5
Exercise (hours per week)	>4	3-4	2-3	1-2	0.1
Supplemental EPA/DHA (mg) intake	>600	400-599	200-399	100-199	<100
Supplemental vitamin C (mg) and vitamin E (IU) intake	>400	251-499	250	125-249	0-124
Average daily servings of fruits and vegetables	>5	4-5	3	1-2	0
Age	<35	36-45	46-55	56-65	>65
Subtotals					

HDL-C, high-density-lipoprotein cholesterol.
*Age of patient when he or she had a heart attack or stroke.
†Number of immediate family members having had a heart attack before the age of 50.
‡The value of the total cholesterol is to be divided by the value of the HDL-C.
Risk = sum of all five columns; 14-20 = very low risk; 21-30 = low risk; 31-40 = average risk; 41-50 = high risk; ≥51 = very high risk.

BOX 148-3 **Assessment of the Cardiovascular System**

- Laboratory tests
- Total cholesterol
- Low-density-lipoprotein cholesterol
- High-density-lipoprotein cholesterol
- C-reactive protein
- Lipoprotein(a)
- Fibrinogen
- Homocysteine
- Ferritin (an iron-binding protein)
- Lipid peroxides
- Exercise stress test
- Electrocardiography
- Echocardiography

nonsmokers appear to be more sensitive to smoke, including its deleterious effects on the cardiovascular system. Environmental tobacco smoke actually has a higher concentration of some toxic constituents. Pathophysiologic and biochemical data after short- and long-term environmental tobacco smoke exposure show changes in the lining of the arteries and in platelet function as well as exercise capacity, similar to those in active smoking. In summary, passive smoking is a relevant risk factor for CVD. In the United States it is estimated that more than 37,000 coronary heart disease (CHD) deaths each year are attributable to environmental smoke.

The magnitude of risk reduction achieved by smoking cessation in patients with CVD is quite significant. Results from a detailed meta-analysis showed a 36% reduction in relative risk of mortality for patients with CAD who quit compared with those who continued smoking.[6]

Various measures—including nicotine-containing skin patches or chewing gum, acupuncture, and hypnosis—have all been shown to provide some benefit in helping patients to quit smoking, but not much. In a systematic review of the efficacy of interventions intended to help people to stop smoking, data were analyzed from 188 randomized controlled trials.[7] Encouragement to stop smoking by physicians during a routine office call resulted in a 2% cessation rate after 1 year. Supplementary measures such as follow-up letters or visits had an additional effect. Behavioral modification techniques such as relaxation, rewards and punishments, and avoiding trigger situations in group or individual sessions led by a psychologist had no greater effect than the 2% rate achieved by simple advice from a physician. Eight studies with acupuncture have produced an overall effectiveness rate of roughly 3%. Hypnosis has been judged to be ineffective even though trials have shown a success rate of 23%. Hypnosis was judged to be ineffective because no biochemical marker was used to accurately determine effectiveness. Nicotine replacement therapy (gum or patch) is effective in about 13% of smokers who seek help in quitting. All together, these results are not encouraging. It appears that the best results occur when people quit "cold turkey." Box 148-4 lists ten tips to help patients stop smoking.

Elevated Blood Cholesterol Levels

The evidence overwhelmingly demonstrates that elevated cholesterol levels greatly increase the risk of death due to CVD. It is currently recommended that the total blood cholesterol level be less than 200 mg/dL. In addition, it is recommended that the LDL-C be less than 130 mg/dL, the high-density-lipoprotein cholesterol (HDL-C) greater than 40 mg/dL in men and 50 mg/dL in women, and the triglyceride level less than 150 mg/dL.

Cholesterol is transported in the blood by lipoproteins. The major categories of lipoproteins are very-low-density lipoprotein (VLDL), LDL, and HDL. Because VLDL and LDL are responsible for transporting fats (primarily triglycerides and cholesterol)

BOX 148-4 Tips to Help Patients Stop Smoking

- List all the reasons why you want to quit smoking and review them daily.
- Set a specific day to quit, tell at least ten friends that you are going to quit smoking, and then . . . DO IT!
- Throw away all cigarettes, butts, matches, and ashtrays.
- Use substitutes. Instead of smoking, chew on raw vegetables, fruits, or gum. If your fingers seem empty, play with a pencil.
- Take one day at a time.
- Realize that 40 million Americans have quit. If they can do it, so can you!
- Visualize yourself as a nonsmoker with a fatter pocketbook, pleasant breath, unstained teeth, and the satisfaction that comes from being in control of your life.
- Join a support group. Call the local branch of the American Cancer Society and ask for referrals. You are not alone.
- When you need to relax, perform deep breathing exercises rather than reaching for a cigarette.
- Avoid situations that you associate with smoking.
- Each day, reward yourself in a positive way. Buy yourself something with the money you have saved or plan a special reward as a celebration for quitting.

from the liver to body cells, whereas HDL is responsible for returning fats to the liver, elevations of either VLDL or LDL are associated with an increased risk for developing atherosclerosis, the primary cause of a heart attack or stroke. In contrast, elevations of HDL-C are associated with a low risk of heart attacks.

The ratios of total cholesterol to HDL-C and LDL-C to HDL-C are referred to as the *cardiac risk factor ratios* because they reflect whether cholesterol is being deposited into tissues or broken down and excreted. The ratio of total cholesterol to HDL-C should be no higher than 4.2, and the ratio of LDL-C to HDL-C should be no higher than 2.5. The risk of heart disease can be reduced dramatically by lowering LDL-C while simultaneously raising HDL-C levels: For every 1% drop in the LDL-C level, the risk of a heart attack drops by 2%. Conversely, for every 1% increase in HDL-C level, the risk for a heart attack drops 3% to 4%.[8]

Further Refinement of Determining Risk. Although LDL-C is referred to as "bad cholesterol," there are some forms that are worse than others. For example, oxidized LDL-C is a persistent proinflammatory trigger for the progression of atherosclerosis and plaque rupture. LDL-C molecules of higher density are associated with greater risk than larger, less dense molecules. Small, dense LDL-C has a greater content of apolipoprotein CIII (apo CIII); in addition, apoB particles are more atherogenic than larger, less dense LDL-Cs and are markers for CVD risk.[9] In a small trial of nondiabetic subjects, researchers determined that these smaller particles were more heavily and preferentially glycated over the larger, more buoyant LDL-C particles, strongly suggesting an explanation for why these particles are more likely to participate in atherogenesis and highlighting the importance of avoiding hyperglycemia and excessive glycation.[10]

Another marker that deserves mention is Lp(a), a plasma lipoprotein whose structure and composition closely resemble those of LDL-C but with an additional molecule of an adhesive protein called apolipoprotein(a). Elevated plasma levels of Lp(a) are an independent risk factor for CHD, particularly in those patients with elevated LDL-C levels. In fact, in one analysis a high level of Lp(a) was shown to carry with it a ten times greater risk for heart disease than an elevated LDL-C level.[11] That is because LDL-C on its own lacks the adhesive apolipoprotein(a). As a result, LDL-C does not easily stick to the walls of the artery. Actually, a high LDL-C level carries less risk than a normal or even low LDL-C with a high Lp(a). Levels of Lp(a) below 20 mg/dL are associated with a low risk of heart disease; levels between 20 and 40 mg/dL are associated with a moderate risk; and levels above 40 mg/dL are associated with an extremely high risk of heart disease.

Elevations of Triglycerides. In the past, the relation between hypertriglyceridemia and CHD has been uncertain. However, a large body of accumulating evidence indicates that hypertriglyceridemia (HTG) is an independent risk factor for CVD. Multivariate analysis of 8-year follow-up data from the large-scale Prospective Cardiovascular Munster Study found HTG to be an independent risk factor for major coronary events after controlling for LDL-C and HDL-C.[12] HTG combined with elevated LDL-C and a high LDL-C:HDL-C (>5) increased the risk for a CHD event by approximately sixfold. Similarly, a large meta-analysis of 17 prospective trials reported HTG to be an independent risk factor for CVD.[13] In this study, an 88 mg/dL (1.0 mmol/L) increase in plasma triglyceride levels significantly increased the relative risk of CVD by approximately 30% in men and 75% in women; the corresponding rates were somewhat lower (14% and 37%, respectively) but still statistically significant after adjustment for HDL-C level.

This increased risk is mediated through the metabolic interrelationships between serum triglyceride (TG) levels and other risk factors, such as the atherogenic lipid profile (low high density lipoprotein-cholesterol levels and elevated small dense low density lipoprotein levels), insulin resistance, a prothrombotic propensity and low grade systemic inflammation. TG-lowering strategy in patients with HTG is an important clinical goal in reducing the risk of not only atherosclerosis but also the metabolic syndrome and diabetes.

Inherited Elevations of Cholesterol and Triglycerides. Elevations of blood cholesterol, triglycerides, or both can be due to genetic factors. These conditions are referred to as familial hypercholesterolemia (FH), familial combined hyperlipidemia (FCH), and familial hypertriglyceridemia (FHTG). Relatively speaking, these disorders are among the most common inherited diseases, affecting about 1 in every 500 people.

The basic problem in FH is a defect in the receptor protein for LDL-C in the liver. Normally, the LDL-C receptor is responsible for removing cholesterol from the blood. When the liver cell takes up the LDL-C after it has bound to the receptor, it signals the liver cell to stop making cholesterol. In FH, the defect in the LDL-C receptor results in the liver not receiving the message to stop making cholesterol.

Damage to the LDL-C receptor occurs with normal aging and in several disease states, among which diabetes is the most important owing to increased glycosylation of the receptor proteins. As a result of damage to the LDL-C receptor, cholesterol levels tend to rise with age. In addition, a diet high in saturated fat and cholesterol decreases the number of LDL-C receptors, thereby reducing the feedback mechanism that tells the liver cell that no more cholesterol is needed.

Fortunately lifestyle and dietary changes can increase the function or number of LDL-C receptors or both. The most dramatic effects are in people without inherited causes of elevated cholesterol or triglycerides or both, but even people with FH can benefit.

FCH and FHTG result in similar defects to FH. In FCH, the basic defect appears to be an accelerated production of VLDL in

the liver. These individuals may have only a high blood triglyceride level, only a high cholesterol level, or both. In FHTG there is only an elevation in blood triglyceride levels, and HDL-C levels tend to be low. The defect in FHTG is that the VLDL particles made by the liver are larger than normal and carry more triglycerides. FHTG is made worse by diabetes, gout, and obesity.

The recommendations given below, under "Therapeutic Considerations," for lowering lipids are also helpful for FCH and FHTG, although these conditions usually require more aggressive support.

Diabetes

Atherosclerosis is one of the key underlying factors in the development of many chronic complications of diabetes. Individuals with diabetes have a twofold to threefold higher risk of dying prematurely of heart disease or stroke than those who are not diabetic, and 55% of deaths in diabetic patients are caused by CVD. However, even mild insulin resistance and poor glucose control have both been shown to have a dramatic impact on the incidence and progression of CVD. For more information, see Chapter 161.

High Blood Pressure

Elevated blood pressure is often a sign of considerable atherosclerosis and a major risk factor for heart attack or stroke. In fact, the presence of hypertension is generally regarded as the most significant risk factor for stroke. For more information, see Chapter 174.

Physical Inactivity

A sedentary lifestyle is another major risk factor for CVD. *Physical activity* refers to "bodily movement produced by skeletal muscles that requires energy expenditure" and produces healthy benefits. Exercise, a type of physical activity, is defined as "a planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness." Physical inactivity denotes a level of activity less than that needed to maintain good health. Physical inactivity characterizes most Americans, because roughly 54% of adults report little or no regular leisure physical activity, and there is also a sharp decline in regular exercise among children and adolescents.[1]

Physical activity protects against the development of CVD and also favorably modifies other CVD risk factors including high blood pressure, blood lipid levels, insulin resistance, and obesity. Physical activity is also important in the treatment and management of patients with CVD or increased risk including those who have hypertension, stable angina, a prior MI, peripheral vascular disease, or heart failure or are recovering from a cardiovascular event.

Other Risk Factors

In addition to the major risk factors for CVD (i.e., smoking, elevations in cholesterol, elevated blood pressure, diabetes, and physical inactivity/obesity), a number of other factors have, on occasion, been shown to be more significant than the so-called major risk factors. In fact, more than 300 different risk factors have been identified, including those listed in Box 148-2.

Although there is considerable evidence that all of these risk factors and more can play significant roles in the pathogenesis of atherosclerosis, much of the current research has focused on the central roles of inflammatory processes and insulin resistance.[14] Inflammatory mediators influence many stages of atheroma development, from initial leukocyte recruitment to eventual rupture of the unstable atherosclerotic plaque. In particular, C-reactive protein (CRP), an acute-phase reactant that reflects different degrees of inflammation, has been identified as an independent risk factor for CAD. Although the CRP level has shown to be a stronger predictor of cardiovascular events than the LDL-C level, screening for both biological markers provides better prognostic information than screening for either alone.[15]

Elevations in CRP are closely linked to insulin resistance and the metabolic syndrome.[16] The diagnostic criteria for the metabolic syndrome comprise the presence of at least three of the following metabolic risk factors in one person:

- Central obesity (a waist-to-hip ratio >1 for men; >0.8 for women)
- Atherogenic dyslipidemia (mainly triglycerides >150 mg/dL and low HDL-C [<40 mg/dL in men and <50 mg/dL in women])
- Hypertension (≥130/85 mm Hg)
- Insulin resistance or glucose intolerance (fasting blood sugar levels >101 mg/dL)
- Prothrombotic state (e.g., high fibrinogen or plasminogen activator inhibitor in the blood)
- Proinflammatory state (e.g., elevated high-sensitivity CRP in the blood)

The metabolic syndrome has become increasingly common in the United States. It is now estimated that more than 60 million U.S. adults may have it. Insulin resistance and the metabolic syndrome are closely tied to obesity (particularly abdominal obesity), elevations in CRP, and a significant risk for CAD.



THERAPEUTIC CONSIDERATIONS—GENERAL GUIDELINES

Prevention of a heart attack or stroke involves reducing risk factors. The major risk factor of smoking was discussed earlier, while obesity, physical inactivity, diabetes, and hypertension are detailed in separate chapters. There is significant evidence that simply adopting a healthy diet and lifestyle dramatically reduces CVD-related mortality. In a prospective trial enrolling over 20,000 men and women, it was found that the combination of four healthy behaviors (nonsmoking, not physically inactive, moderate alcohol intake, and a plasma vitamin C indicative of at least 5 servings of fruit and vegetables per day) reduced total mortality fourfold compared with those who had none of these behaviors.[17]

In addition to these healthy lifestyle behaviors, the focus in this chapter is on improving blood cholesterol levels as well as highlighting factors that address some of the additional risk factors associated with atherosclerosis (e.g., antioxidant status, elevated CRP, fibrinogen levels).

Diet—General Guidelines

The dietary program detailed in Chapter 44 features a comprehensive dietary approach for both the prevention and treatment of CVD as well as the improvement of blood lipid profiles. In particular, it is important to reduce the intake of saturated fat and trans fatty acids while increasing the consumption of vegetables, fruit, dietary fiber, monounsaturated fats, and omega-3 fatty acids. An important dietary goal is to improve the structure and composition of cell membranes by making available essential structural components like the monounsaturated and omega-3 fatty acids and by preventing oxidative and free radical damage to these structures by consuming a high level of antioxidants and phytochemicals.

One of the most widely studied dietary interventions in CAD is the traditional "Mediterranean diet,"[18] which reflects food patterns

typical of some Mediterranean regions in the early 1960s, such as Crete, parts of the rest of Greece, and southern Italy.

Unfortunately, the modern Mediterranean diet has deviated significantly from its healthful origin.

The original Mediterranean diet had the following characteristics:

- Olive oil is the principal source of fat.
- The diet centers on an abundance of plant food (fruits; potatoes, beans, and other vegetables; breads; pasta; nuts; and seeds).
- Foods are minimally processed, and people focus on seasonally fresh and locally grown foods.
- Fresh fruit is the typical daily dessert, with sweets containing concentrated sugars or honey consumed only a few times a week at the most.
- Dairy products (principally cheese and yogurt) are consumed daily in low to moderate amounts.
- Fish is consumed regularly.
- Poultry and eggs are consumed in moderate amounts (up to four times a week) or not at all.
- Red meat is consumed in low amounts.
- Wine is consumed in low to moderate amounts, normally with meals.

In one study, the effect of the Mediterranean diet on endothelial function and vascular inflammatory markers was studied in patients with the metabolic syndrome.[19] Patients in the intervention group were instructed to follow the Mediterranean diet and received detailed advice on how to increase their daily consumption of whole grains, fruits, vegetables, nuts, and olive oil; patients in the control group followed the American Heart Association (AHA) diet. After 2 years, patients following the Mediterranean diet consumed more foods rich in monounsaturated fat, polyunsaturated fat, and fiber and had a lower ratio of omega-6 to omega-3 fatty acids. Compared with patients consuming the control diet, patients consuming the intervention diet had significantly reduced serum concentrations of CRP and other inflammatory mediators; improved endothelial function; and greater weight loss.

Although several components of the Mediterranean diet deserve special mention, it is important to stress that the total benefits reflect an interplay among many beneficial compounds rather than any single factor.[20]

In addition, it is critical to follow a low glycemic diet. A prospective trial with more than 48,000 participants highlighted the importance of good glycemic control for preventing CVD. Following a study population for an average of 8 years, researchers found that the consumption of foods with a high glycemic load increased the risk of CHD in women by 68%; women in the highest glycemic-load quartile had a relative risk of 2.2 for CHD compared with those in the lowest quartile.[21]

Olive Oil and Omega-3 Fatty Acids

One of the most important aspects of the Mediterranean diet may be the combination of olive oil (a source of monounsaturated fats and antioxidants) and the intake of omega-3 fatty acids. Olive oil consists not only of monounsaturated fatty acid (oleic acid) but also of several antioxidant agents that may also account for some of its health benefits. In addition to a mild effect in lowering LDL-C and triglycerides, olive oil increases the HDL-C level and helps prevent LDL-C from being damaged by free radicals.[22]

In addition to olive oil, the benefits of the longer-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahaexanoic acid (DHA) for cardiovascular health has been demonstrated in more than 300 clinical trials. These fatty acids exert considerable benefits in reducing the risk for CVD. Supplementation with EPA and DHA has little effect on cholesterol levels but does lower triglyceride levels significantly, as well as producing a myriad of additional beneficial effects including reduced platelet aggregation; improved endothelial function and arterial flexibility; improved blood and oxygen supply to the heart; and a mild effect in lowering blood pressure by vasodilation, and promotion of sodium excretion.[23]

The levels of EPA and DHA within red blood cells have been shown to be highly significant predictors of heart disease. This laboratory value has been termed the omega-3 index. An omega-3 index of 8% was associated with the greatest protection, whereas an index of 4% was associated with the least. In one analysis, the omega-3 index was shown to be the most significant predictor of CAD compared with CRP; total cholesterol, LDL-C, or HDL-C; and homocysteine. Researchers subsequently determined that a total of a combined 1000 mg of EPA and DHA daily is required to achieve or surpass the 8% target of the omega-3 index.[24,25]

The findings with the omega-3 index are not surprising, because a wealth of information has documented a clear relationship between dietary intake omega-3 fatty acids and the likelihood of developing CHD: the higher the omega-3 fatty acid intake, the lower the likelihood of CHD. It has been estimated that raising the levels of long-chain omega-3 fatty acids through diet or supplementation may reduce overall cardiovascular mortality by as much as 45%.[26,27]

In general, for preventive effects against CVD, the dosage recommendation is 1000 mg of EPA plus DHA a day; for lowering triglycerides, the dosage is 3000 mg. In a double-blind study, after 8 weeks of supplementation, a daily dosage of 3.4 g EPA plus DHA lowered triglycerides by 27%, while a lower dosage of 0.85 g had no effect. These results clearly indicate that the effective dosage for lowering triglycerides with fish oils requires dosages of 3 g EPA plus DHA a day.[28]

Although the longer-chain omega-3 fatty acids exert more pronounced effects than alpha-linolenic acid, the shorter omega-3 fatty acid from vegetable sources, it is important to point out that the two populations with the lowest rates of heart attack have a relatively high intake of alpha-linolenic acid: the Japanese who inhabit Kohama Island and the inhabitants of Crete.[29,30] Typically, Cretans have a threefold higher serum concentration of alpha-linolenic acid than members of other European countries, owing to their frequent consumption of walnuts and the vegetable purslane.[29] Of course, another important dietary factor in both the Kohamans and Cretans is their use of oleic acid–containing oils. However, although the oleic acid content of the diet offers some degree of protection, the rates of heart attack among the Kohamans and Cretans are much lower than those in populations that consume only oleic acid sources and little alpha-linolenic acid. The intake of alpha-linolenic acid is viewed as a more significant protective factor than oleic acid.

Nuts and Seeds

Higher consumption of nuts and seeds has been shown to significantly reduce the risk of CVD in large epidemiologic studies including the Nurses' Health Study, the Iowa Health Study, and the Physicians' Health Study.[31] Researchers estimate that substituting nuts for an equivalent amount of carbohydrates in an average diet resulted in a 30% reduction in heart disease risk. Researchers calculated an even more impressive risk reduction, 45%, when fat from nuts was substituted for saturated fats (found primarily in meat and dairy products). Nuts have a cholesterol-lowering effect, which partly explains this benefit, but they are also

a rich source of arginine. By increasing nitric oxide levels, arginine may help to improve blood flow, reduce blood clot formation, and improve blood fluidity (the blood becomes less viscous and therefore flows through blood vessels more easily).

Walnuts appear to be especially beneficial because they are also a rich source of both antioxidants and alpha-linolenic acid. In one study, hypercholesterolemic men and women were randomized to a cholesterol-lowering Mediterranean diet and a diet of similar energy and fat content in which walnuts replaced approximately 32% of the energy from monounsaturated fat (olive oil). Participants followed each diet for 4 weeks. Compared with the Mediterranean diet, the walnut diet improved endothelial cell function (it increased endothelium-dependent vasodilation and reduced levels of vascular cell adhesion molecule-1). The walnut diet also significantly reduced total cholesterol (–4.4%) and LDL-C (–6.4%).[32]

Vegetables, Fruits, and Red Wine

An important contributor to the benefits noted with the Mediterranean diet is the focus on carotene- and flavonoid-rich fruits, vegetables, and beverages (e.g., red wine). Numerous population studies have repeatedly demonstrated that a higher intake of dietary antioxidants significantly reduces the risk of heart disease and stroke. Higher blood levels of antioxidant nutrients are also associated with lower levels of CRP.[33] The importance of antioxidant intake in the prevention and treatment of CAD is discussed further later.

Two valuable sources of antioxidants in the Mediterranean diet are tomato products and red wine. Tomatoes are a rich source of the carotene lycopene. In large clinical studies evaluating the relationship between carotene status and heart attack (acute MI), lycopene but not beta-carotene was shown to be protective. Lycopene exerts greater antioxidant activity compared with beta-carotene in general but specifically against LDL-C oxidation.[34]

The cardiovascular protection offered by red wine is popularly referred to as the "French paradox." Because the French consume more saturated fat than people in the United States and the United Kingdom yet have a lower incidence of heart disease, red wine consumption has been suggested to be the reason. Presumably this protection is the result of flavonoids and other polyphenols in red wine that protect against oxidative damage to LDL-C as well as helping to reduce the levels of inflammatory mediators.[19,35] However, moderate alcohol consumption alone has also been shown to be protective in some studies by exerting positive effects on ratios of HDL-C to LDL-C and CRP as well as levels of fibrinogen, although red wine typically exerts the most significant effects.[36]

Importantly, the effects of alcohol on CVD risk, morbidity, and total mortality are counterbalanced by alcohol's addictive and psychological effects.

The major benefits of red wine consumption in protecting against CVD may ultimately be the effects that the polyphenols have on improving endothelial cell function. In one study, 30 male patients with CHD were randomly assigned to take a red grape polyphenol extract (600 mg) or placebo. Flow-mediated dilation was measured after fasting and 30, 60, and 120 minutes after intake of the grape extract or placebo. The intake of the red grape polyphenol extract caused an increase in flow-mediated dilation, peaking at 60 minutes, which was significantly higher than the baseline values and the corresponding values at 60 minutes after the intake of placebo (4.52% vs 2.64%).[37]

The consumption of green tea, like that of red wine, has also been shown in population studies to be associated with a reduced risk for CVD. As with red wine, much of the benefit of green tea consumption may be the result of several different mechanisms, including improving endothelial cell function. Green tea polyphenols (catechins) have been shown to decrease the oxidation of LDL-C, lower LDL-C levels, and improve the LDL-C:HDL-C ratio. In vitro studies have shown a dose-dependent response with green tea polyphenols in reducing several biomarkers associated with atherosclerosis and ischemia, including the inhibition of the endothelial cell–derived vascular cell adhesion molecule-1 as well as angiotensin II, platelet derived growth factor-BB, apolipoprotein E, and inducible nitric oxide synthase.[38]

Another mechanism of action for red wine and green tea polyphenols involves inhibiting the formation of new blood vessels within the vascular lesion. During the angiogenic process, new blood vessels develop from the existing microvascular bed. The initial event involves dilation of an existing blood vessel followed by an increase in vascular permeability and the degradation of extracellular matrices. This process allows endothelial cells to migrate into the lesion and proliferate, and these events are followed by the maturation of new blood vessels. The angiogenic process is controlled by two major proangiogenic factors: matrix metalloproteinases (MMPs), which degrade extracellular matrices, and vascular endothelial growth factor (VEGF), which strongly stimulates endothelial cell migration and proliferation and the formation of new blood vessels. Both red wine and green tea polyphenols have been shown to inhibit this process in vitro at concentrations conceivably achievable with oral intake.[38]

Foods and beverages rich in antioxidant content have shown benefit in fighting atherosclerosis. Pomegranate *(Punica granatum)* juice appears to be particularly useful. It is remarkably rich in antioxidants, such as soluble polyphenols, tannins, and anthocyanins. Animal research has indicated that components of pomegranate juice can retard atherosclerosis, reduce plaque formation, and improve arterial health. Human clinical studies have supported the role of pomegranate juice in benefiting heart health.[39-41]

In a randomized placebo-controlled double-blind study, the daily consumption of pomegranate juice for 3 months was evaluated for its effect on myocardial perfusion in 45 patients who had CHD and myocardial ischemia. Patients were randomly assigned into one of two groups: a pomegranate juice group (240 mL/day) or a placebo group, which drank a beverage of similar caloric content, amount, flavor, and color. Participants underwent electrocardiographic-gated myocardial perfusion single-photon emission computed tomographic scintigraphy at rest and during stress at baseline and 3 months. After 3 months, the extent of stress-induced ischemia decreased in the pomegranate group but increased in the control group. This benefit was observed without changes in cardiac medications, blood sugar, hemoglobin A_{1c}, weight, or blood pressure in either group.[39]

In another study, 10 patients with carotid artery stenosis (CAS) were evaluated to gauge the effect of pomegranate juice consumption on the progression of carotid lesions and changes in oxidative stress and blood pressure. The patients were supplemented with pomegranate juice (50 mL) for 1 year, and 5 continued for up to 3 years. In the control group (which did not consume pomegranate juice), common carotid intimal-medial thickness (IMT) increased by 9% during 1 year, whereas pomegranate juice consumption resulted in a significant IMT reduction, by up to 30%, after 1 year. Compared with values obtained before pomegranate juice consumption, the patients' serum paraoxonase 1 (PON 1) activity was increased by 83%, whereas serum LDL-C basal oxidative state and LDL-C susceptibility to copper ion–induced oxidation were both significantly reduced, by 90% and 59%, respectively, after 12 months. Furthermore, serum levels of antibodies against oxidized LDL-C were decreased by 19%; in

parallel, serum total antioxidant status was increased by 130% after 1 year of pomegranate juice consumption. Systolic blood pressure was reduced after 1 year of pomegranate juice consumption by 21%. For all studied parameters, the maximal effects were observed after 1 year of pomegranate juice consumption.[40]



THERAPEUTIC CONSIDERATIONS—LOWERING CHOLESTEROL

Lowering total cholesterol (TC), as well as LDL-C and triglycerides (TG), is clearly associated with reducing CVD risk. Most of the benefits noted with lowering LDL-C are based on a large number of randomized clinical trials involving the use of the HMG-CoA (3-hydroxy-3 methylglutaryl coenzyme A) reductase inhibitors known collectively as statin drugs. Statins owe their origin to red yeast *(Monascus purpureus)* fermented on rice. This traditional Chinese medicine has been used for its health-promoting effects in China for more than 2000 years. Red yeast rice is the source of a group of compounds known as monacolins (e.g., lovastatin, also known as monacolin K, one of the key monacolins in red yeast rice extract). The marketing of an extract of red yeast fermented on rice standardized for monacolin content as a dietary supplement in the United States caused controversy in 1997, because this agent contained a natural source of a prescription drug. The U.S. Food and Drug Administration (FDA) eventually ruled that red yeast rice products could be sold only if they were free of monacolin.

Although the data are clear that statin drugs can produce decreases in total mortality, cardiovascular events, hospitalizations, and the need for revascularization procedures in high-risk patients, the debate remains whether statin therapy represents the optimal treatment approach to the primary prevention of CAD in patients with only the risk factor of elevated LDL-C, especially in light of the growing acceptance of risk factors like CRP and the emerging role of nutrition.[42,43] For example, one interesting study compared the "portfolio diet," comprising plant-based cholesterol-lowering foods, to lovastatin.[44] The participants were randomly assigned to undergo one of three interventions on an outpatient basis for 1 month: a diet low in saturated fat, based on milled whole-wheat cereals and low-fat dairy foods; the same diet plus lovastatin, 20 mg/day; or a diet high in plant sterols (1 g/1000 kcal), soy protein (21.4 g/1000 kcal), viscous fibers (9.8 g/1000 kcal), and almonds (14 g/1000 kcal). The control, statin, and dietary portfolio groups had mean (SE) decreases in LDL-C of 8%, 30.9%, and 28.6%, respectively. Respective reductions in CRP were 10%, 33.3%, and 28.2%. This study and subsequent studies showed that by diversifying the cholesterol-lowering components in the same dietary portfolio, the effectiveness of diet as a treatment of hypercholesterolemia was increased. Moreover, results comparable with those of a statin drug (with lipid-lowering effects similar to statins in terms of both LDL-C and size of LDL-C) were produced.[45,46]

Whereas individual dietary changes may produce benefit in improving blood lipids, the best clinical approach is to incorporate a broad-spectrum dietary approach that incorporates a wide array of dietary components shown to have a positive impact on lipid levels. For example, although a meta-analysis of 27 randomized controlled trials in which isolated soy protein supplementation was the only intervention demonstrated that soy protein supplementation was associated with a significant dose-dependent reduction in mean serum total cholesterol, LDL-C, and triglycerides, the effect shown (–5.26 mg/dL, –4.25 mg/dL, and –6.26 mg/dL, respectively) was less than that noted above when the soy protein was used in conjunction with other dietary interventions.[47] In addition, the effects of isolated soy protein appear to be considerably less than those achieved by increasing soy food consumption in general. Much of the cholesterol-lowering effect of soy foods may relate more to the isoflavone and soluble fiber content rather than the protein. In an earlier meta-analysis based more on soy protein intake from other sources in addition to soy protein isolate, reductions were much more significant for total cholesterol (–23.2 mg/dL), LDL-C (–21.7 mg/dL), and triglycerides (–13.3 mg/dL) but still relatively modest from a clinical perspective.[47a] Although these results do support the recommendation to increase soy protein intake in the dietary approach to hypercholesterolemia, given the relatively small effect of soy protein on lipids, it is imperative that other dietary recommendations, such as reducing the dietary intake of saturated fat, trans fatty acids, and cholesterol as well as increasing the dietary intake of monounsaturated fats, soluble fiber, and nuts also be promoted.

Despite research documenting the benefits of nonpharmacologic approaches, it is unlikely that lowering LDL-C with statin drugs will be supplanted as the primary therapy in lipid management and the prevention of CAD at any time in the near future. In 2011, it was estimated that more than one of every six adults—nearly 40 million people—was taking a statin drug to lower LDL-C. Therefore, the focus with many patients will be on the support of statin therapy. For example, it appears that individuals taking statin drugs must supplement with coenzyme Q_{10} (CoQ_{10}). For the synthesis of cholesterol, not only HMG-CoA reductase but also CoQ_{10} is required. Thus, administration of these drugs might compromise the status of CoQ_{10} by decreasing its synthesis. Even modest dosages of various statins have been shown to lower serum levels of CoQ_{10}. Researchers have concluded that inhibition of CoQ_{10} synthesis by statin drugs could explain the most commonly reported adverse effects, especially fatigue and muscle pain, as well as more serious side effects such as rhabdomyolysis.[48,49] CoQ_{10} supplementation in subjects on statin drugs has also been shown to reduce markers of oxidative damage.

Statins are also gaining popularity as a prescription method to lower CRP. In one study, a group of 186 individuals with type 2 diabetes was selected to receive 10 mg of atorvastatin (Lipitor), 80 mg of atorvastatin, or a placebo for 30 weeks. In those given placebo, CRP levels increased by 6.6%, decreased by 15% in the 10-mg group, and by 47% in the 80-mg group. In a study with pravastatin, 40 mg daily lowered CRP levels by 13%.[50] Although many physicians appear to be aware of the effect of atorvastatin and pravastatin on CRP, they do not seem to be aware of the natural approaches to lowering CRP discussed below, including diet, niacin, vitamin E, and other measures.

The Importance of Soluble Dietary Fiber in Lowering Cholesterol

Chapter 52 provides a complete discussion of the benefits of dietary fiber. It is well established that the soluble dietary fiber found in legumes, fruit, and vegetables is effective in lowering cholesterol levels.[51] The greater the degree of viscosity or gel-forming nature, the greater the effect of a particular dietary fiber has on lowering cholesterol levels. New, highly viscous, soluble fiber blends are showing greater effect than previously used fiber sources, leading to more reasonable dosage recommendations (the cholesterol-lowering effect of soluble fiber is clearly dose-dependent).[52,53] Table 148-3 shows the average dosages and reductions noted in clinical trials with soluble fiber supplements.

TABLE 148-3 **Impact of Various Sources of Fiber on Serum Cholesterol Levels**

FIBER	DOSAGE (G)	TYPICAL REDUCTION IN TOTAL CHOLESTEROL
Oat bran (dry)	50-100	20%
Guar gum	9-15	10%
Pectin	6-10	5%
Psyllium	10-20	10-20%
Vegetable fiber	27	10%

TABLE 148-4 **Comparison of Niacin With Lovastatin**

LIPOPROTEIN	GROUP	WEEK 10	WEEK 18	WEEK 26
LDL-C reduction	Lovastatin	26%	28%	32%
	Niacin	5%	16%	23%
HDL-C increase	Lovastatin	6%	8%	7%
	Niacin	20%	29%	33%
Lp(a) lipoprotein reduction	Lovastatin	0%	0%	0%
	Niacin	14%	30%	35%

HDL-C, High-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol.

Many of the studies featured oat preparations containing either oat bran or oatmeal.[54] The overwhelming majority of these studies demonstrated that individuals with high cholesterol levels see significant reductions with frequent oatmeal or oat bran consumption. In contrast, individuals with normal or low cholesterol levels see little change. In individuals with high cholesterol levels (above 200 mg/dL), the consumption of the equivalent of 3 g of soluble oat fiber typically lowers total cholesterol by 8% to 23%. This is highly significant, because with each 1% drop in serum cholesterol level there is a 2% decrease in the risk of developing heart disease. In approximately one bowl of ready-to-eat oat bran cereal or oatmeal are 3 g of fiber. Although oatmeal's fiber content (7%) is less than that of oat bran (15% to 26%), it has been determined that the polyunsaturated fatty acids contribute as much to the cholesterol-lowering effects of oats as the fiber content. Although oat bran has a higher fiber content, oatmeal is higher in polyunsaturated fatty acids.

In an effort to lower cholesterol with dietary fiber, patients should be encouraged to eat 35 g of fiber daily from fiber-rich foods, a full listing of which can be found in Chapter 52. Achieving higher fiber intake is associated not only with lower cholesterol levels but also with lower inflammatory mediators like CRP.[55]

Natural Products to Lower Cholesterol Levels

In many cases, dietary therapy, although important, is not sufficient alone to reduce lipid levels to the desired ranges. Fortunately, several natural compounds can lower cholesterol levels and other significant risk factors for CAD. In fact, when all factors are considered (e.g., cost, safety, effectiveness), the natural alternatives presented here may offer significant advantages to the standard drug therapy.

Niacin

Since the 1950s niacin (vitamin B_3) has been known to be effective in lowering blood cholesterol levels. In the 1970s, the famed Coronary Drug Project demonstrated that niacin was the only cholesterol-lowering agent to actually reduce overall mortality. Niacin typically lowers LDL-C levels by 16% to 23% while raising HDL-C levels by 20% to 33%. These effects, especially the effect on HDL-C, compare quite favorably with those of conventional cholesterol-lowering drugs.[56,57]

It is now known that niacin does much more than lower total cholesterol. Specifically, niacin has been shown to lower LDL-C, the more harmful Lp(a) lipoprotein, as well as triglyceride, CRP, and fibrinogen levels while simultaneously raising levels of beneficial HDL-C. Although niacin has demonstrated better overall results in reducing risk factors for CHD compared with other cholesterol-lowering agents, physicians are often reluctant to prescribe niacin. The reason is a widespread perception that niacin is difficult to work with because of the bothersome flushing of the skin associated with its use. In addition, because niacin is a widely available "generic" agent, no pharmaceutical company stands to generate the huge profits that the other lipid-lowering agents have brought them. As a result, niacin does not benefit from the intensive advertising that focuses on the statin drugs. Despite the advantages of niacin over other lipid-lowering agents, it accounts for less than 10% of all cholesterol-lowering prescriptions. Niaspan (Abbott Laboratories, Abbott Park, Ill.), a prescription niacin product, accounted for 952,000 prescriptions in 2002, translating in to sales of $145.7 million—a dramatic 73% increase from 2001 levels. The increasing sales of niacin reflect a growing physician awareness of the advantages of niacin over statin drugs.

Several studies have compared niacin with standard lipid-lowering drugs including the statin drugs. These studies have shown significant advantages for niacin. In the first published clinical study comprising 136 patients, niacin was compared with lovastatin directly in the following groups of subjects: (1) those with LDL-C levels greater than 160 mg/dL and CHD, (2) those with more than two CHD risk factors, (3) those with both elevated LDL-C levels and more than two CHD risk factors, (4) those with LDL-C levels greater than 190 mg/dL and without CHD, and (5) those with fewer than two CHD risk factors.[58] This controlled randomized open-label, 26-week study was performed at five lipid clinics. Patients were first placed on a 4-week diet run-in period, after which eligible patients were randomly assigned to receive treatment with either lovastatin (20 mg/day) or niacin (1.5 g/day). On the basis of the LDL-C response and patient tolerance, the doses were sequentially increased to 40 and 80 mg/day of lovastatin or 3 and 4.5 g/day of niacin after 10 and 18 weeks of treatment, respectively. In the two patient groups, 66% of patients treated with lovastatin and 54% of patients treated with niacin underwent full dosage titration. Table 148-4 shows the results.

These results indicate that, although lovastatin produced a greater reduction in LDL-C, niacin provided better overall results despite the fact that fewer patients were able to tolerate a full dosage of niacin because of skin flushing. The percentage increase in HDL-C, a more significant indicator for CHD, was dramatically in favor of niacin (33% vs. 7%). Equally impressive was the percentage decrease in Lp(a) for niacin. Although niacin produced a 35% reduction in Lp(a) levels, lovastatin did not produce any effect. Niacin's effect on Lp(a) in this study confirmed a previous study showing that niacin (4 g/day) reduced Lp(a) levels by 38%. Moreover, a subsequent study showed similar reductions in Lp(a) in patients with diabetes.[59,60]

Another comparative study evaluated the lipoprotein responses to niacin, gemfibrozil, and lovastatin in patients with normal total cholesterol levels but low levels of HDL-C.[61] The first phase of the

TABLE 148-5 **The Effects of Atorvastatin (Lipitor) and Niacin on Lipid Profiles**

	Atorvastatin		Niacin		Atorvastatin + Niacin	
PARAMETER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
Total LDL-C (mg/dL)	110	56	111	89	123	55
LDL-C peak diameter	251	256	253	263	250	263
Lipoprotein(a) (mg/dL)	45	44	37	23	54	35
HDL-C (mg/dL)	42	43	38	54	38	54
HDL2-C (%)	30	42	29	43	32	37
Triglycerides (mg/dL)	186	100	194	108	235	73

HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol.

study compared lipoprotein responses with lovastatin and gemfibrozil in 61 middle-aged men with low levels of HDL-C. In the second phase, 37 patients agreed to take niacin; 27 patients finished this phase at a dose of 4.5 g/day. In the first phase, gemfibrozil therapy increased HDL-C levels by 10% and lovastatin did so by 6%. In the second phase, niacin therapy was shown to raise HDL-C by 30%.

Another comparative study involved niacin versus atorvastatin (Lipitor).[62] The average dosage was 3000 mg with niacin and 80 mg for atorvastatin. The patients selected had abnormal particle size of LDL-C in that the molecules were small and dense—these LDL-C molecules are considerably more atherogenic than larger, less dense LDL-Cs. The patients selected also had low levels (<40%) of a specific fraction of HDL-C associated with a greater protective effect than HDL-C alone. Although atorvastatin reduced total LDL-C levels substantially more than niacin, niacin was more effective in increasing LDL-C particle size and raising HDL-C and HDL2-C than atorvastatin (Table 148-5).

Because taking niacin at higher dosages (e.g., ≥3000 mg) can impair glucose tolerance, many physicians have avoided niacin therapy in diabetic patients, but newer studies with slightly lower dosages (1000 to 2000 mg) of niacin have not shown it to adversely affect blood sugar regulation.[63] For example, during a 16-week double-blind placebo-controlled trial, 148 patients with type 2 diabetes were randomized to placebo or 1000 or 1500 mg/day of niacin; in the niacin-treated groups there was no significant loss of glycemic control, and the favorable effects on blood lipids were still apparent.[64] Other studies have actually shown hemoglobin A_{1C} to drop, indicating improvement in blood sugar control.[65]

The most common blood lipid abnormality in patients with type 2 diabetes is elevated triglyceride levels; decreased HDL-C levels; and a preponderance of smaller, denser LDL-C particles. Niacin has been shown to address all of these areas much more significantly than the statins or other lipid-lowering drugs.

In addition to lowering cholesterol and triglycerides, niacin exerts additional benefits in battling atherosclerosis. Specifically, niacin produces beneficial lipid-altering effects on particle distribution in patients with CAD that are not well reflected in typical lipoprotein analysis. In addition, systemic markers of inflammation decrease in patients receiving niacin. In one study, when a modest dosage of niacin (1000 mg daily) was added to existing therapy for 3 months in 54 subjects with stable CAD, there was a 32% increase in large-particle HDL-C, an 8% decrease in small-particle HDL-C, an 82% increase in large-particle LDL-C, and a 12% decrease in small-particle LDL-C.[66] Niacin therapy also decreased lipoprotein-associated phospholipase A2 and CRP levels (20% and 15%, respectively). No significant changes from baseline were seen in any tested parameter in subjects who received placebo. These results indicate that the addition of niacin to existing medical regimens for patients with CAD and already well-controlled lipid levels improves the distribution of lipoprotein particle sizes and inflammatory markers in a manner expected to improve protection against a cardiovascular event.

Although niacin exerts significant benefit on its own, it does not appear to enhance the benefits of statins in well-controlled patients. The AIM-HIGH study funded by the National Heart, Lung, and Blood Institute recruited 3400 patients who were at risk for heart trouble despite the fact that their LDL-C was under control (<70 mg/dL) with the use of a statin drug (simvastatin [Zocor]). The study ended 18 months early because no additional cardiovascular benefit was found in those taking niacin despite increases in HDL-C and reductions in triglycerides.[67] Nonetheless, other studies are under way to determine the effect of niacin combined with a statin in patients with very low HDL-C levels and/or poorly controlled LDL-C levels.

The Side Effects of Niacin. The side effects of niacin are well known. The most common and bothersome side effect is the skin flushing that typically occurs 20 to 30 minutes after the niacin is taken. Other occasional side effects of niacin include gastric irritation, nausea, and liver damage. In an attempt to combat the acute reaction of skin flushing, several manufacturers began marketing "sustained-release," "timed-release," or "slow-release" niacin products. These formulations allow the niacin to be absorbed gradually, thereby reducing the flushing reaction. However, although these forms of niacin reduce skin flushing, earlier timed-release preparations were proved to be more toxic to the liver than regular niacin. In one analysis, 52% of the patients taking the earlier sustained-release niacin preparations developed liver toxicity while none of the patients taking immediate-release niacin did so.[68] The newer timed-released preparations now on the market, referred to as "intermediate-release," appear to have solved this problem, as relatively large clinical trials have shown them to be extremely well tolerated even when combined with statin drugs.[69-71]

The safety and tolerability of intermediate-release niacin preparation have been evaluated in a multicenter study of 566 patients.[72] The target dose was achieved by 65% of patients. Flushing was the most common side effect (42%), as expected, and 9.7% withdrew because of this. Other drug-related adverse reactions occurred at low frequency (18.6%), and 8.7% withdrew for an adverse reaction other than flushing. Most adverse reactions were mild or moderate in severity. There was no hepatotoxicity or serious adverse event involving muscle. The researchers concluded that intermediate-release nicotinic acid was well tolerated, and these results support its use in the management of patients at elevated cardiovascular risk due to low HDL-C.

Another safe form of niacin is inositol hexaniacinate. This form of niacin has long been used in Europe to lower cholesterol levels and also to improve blood flow in intermittent claudication. It yields slightly better clinical results than standard niacin but is much better tolerated in terms of both flushing and, more importantly, long-term side effects.[73,74]

Regardless of the form of niacin being used, periodic checking (at least every 3 months) of cholesterol and liver function is indicated. Niacin should not be used in patients with preexisting liver disease or elevations in liver enzymes. For these patient groups, policosanol, garlic, or pantethine are recommended.

For best results, niacin should be taken at night, because most cholesterol synthesis occurs during sleep. If pure crystalline niacin is being used, it should begin with a dosage of 100 mg a day and be carefully increased over 4 to 6 weeks to the full therapeutic dosage of 1.5 to 3 g/day. If a timed-released preparation or inositol hexaniacinate is being used, a 500-mg dose should be given at night and increased to 1500 mg after 2 weeks. If after 1 month of therapy the dosage of 1500 mg/day fails to effectively lower LDL-C, the dosage should be increased to 3000 mg.

Plant Sterols and Stanols

Phytosterols and phytostanols are structurally similar to cholesterol and can act in the intestine to lower cholesterol absorption by displacing cholesterol from intestinal micelles. Because phytosterols and phytostanols are poorly absorbed themselves, blood cholesterol levels will likely drop owing to increased excretion. These compounds are showing up in functional foods (e.g., margarine and other spreads, orange juice), as well as in dietary supplements.[75]

Phytosterols and phytostanols are effective in lowering LDL-C in some people. A meta-analysis of 41 trials showed that a daily intake of 2 g of stanols or sterols reduces LDL-C by 10%.[75] Administration of higher dosages produced little additional benefit. Effects of phytosterols and phytostanols are additive with diet or drug interventions: Eating foods low in saturated fat and cholesterol and high in stanols or sterols can reduce LDL-C by 20%; adding sterols or stanols to statin medication is more effective than doubling the statin dose alone. Individuals most likely to respond have been identified as having high cholesterol absorption and low cholesterol biosynthesis. Phytosterols and phytostanols have been shown to have antiplatelet and antioxidant effects as well.[76-79]

Phytosterol or phytostanol intake at higher dosages may reduce carotenoid absorption. Human subjects consuming 6.6 g/day phytosterols showed cholesterol-adjusted plasma reduction of alpha- and beta-carotene levels (–19% to –23%), lutein (–14%), and lycopene (–11%). However, this effect was partially reversed by increased fruit and vegetable intake.[80]

Pantethine

Pantethine is the stable form of pantetheine, the active form of vitamin B_5 or pantothenic acid. Pantothenic acid is the most important component of coenzyme A (CoA). This enzyme is involved in the transport of fats to and from cells, as well as to the energy-producing compartments within the cell. Without coenzyme A, the cells' fats could not be metabolized to energy.

Pantethine has significant lipid-lowering activity, whereas pantothenic acid has little if any effect in lowering cholesterol and triglyceride levels owing to pantethine's ability to be converted to cysteamine. Pantethine administration (standard dosage 900 mg/day) has been shown to significantly reduce serum triglyceride (-32%), total cholesterol (-19%), and LDL-C (-21%) levels while increasing HDL-C (+23%) levels.[81,82] It appears to be especially useful in lowering blood lipids in diabetic patients.[83-85]

The lipid-lowering effects of pantethine are most impressive when its toxicity (virtually none) is compared with that of conventional lipid-lowering drugs. Its mechanism of action is due to the inhibition cholesterol synthesis and acceleration of the use of fat as an energy source.

Garlic (Allium sativum) and Onion (Allium cepa)

Garlic appears to be an important protective factor against heart disease and stroke via its ability to affect the process of atherosclerosis at so many steps. A major area of interest has been garlic's ability to offer significant protection against heart disease and stroke by lowering blood cholesterol levels even in apparently healthy individuals. According to the results of numerous double-blind placebo-controlled studies in patients with initial cholesterol levels above 200 mg/dL, supplementation with commercial preparations providing a daily dose of at least 10 mg of alliin or a total allicin potential of 4000 mg can lower total serum cholesterol levels by about 10% to 12% and LDL-C by about 15%; HDL-C usually increases by about 10% and triglyceride levels typically drop by 15%. However, most trials not using products that can deliver this dosage of allicin fail to produce a lipid-lowering effect.[86-90]

Although the effects of supplemental garlic preparations on cholesterol levels are modest, the combination of lowering LDL-C and raising HDL-C can greatly improve the HDL-C:LDL-C ratio, a significant goal in the prevention of heart disease and stroke. Garlic preparations have also demonstrated blood pressure–lowering effects, inhibition of platelet aggregation, reduction of plasma viscosity, promotion of fibrinolysis, prevention of LDL-C oxidation, and an ability to exert positive effects on endothelial function, vascular reactivity, and peripheral blood flow (see Chapter 63 for more information).

Comparing Natural Cholesterol-Lowering Agents

Numerous natural compound products can effectively improve cholesterol and triglyceride levels. Of the several described earlier, niacin produces the best overall effect. However, the others do have a place in the clinical management of hyperlipidemia and the prevention of atherosclerosis (Table 148-6).

Typically, along with dietary and lifestyle recommendations, niacin (1500 mg to 3000 mg at night) reduces total cholesterol by 50 to 75 mg/dL within the first 2 months in patients with initial total cholesterol levels above 250 mg/dL. In patients with initial cholesterol levels above 300 mg/dL, it may take 4 to 6 months before cholesterol levels begin to reach recommended levels. Once cholesterol levels are reduced below 200 mg/dL, the dosage of niacin is reduced by 500 mg for 2 months. If the cholesterol levels creep up above 200 mg/dL, the dosage of niacin is raised back up to previous levels. If the cholesterol level remains below 200 mg/dL, then the niacin is dropped by another 500 mg and the cholesterol levels are rechecked in 2 months, with niacin therapy at previous levels if levels have exceeded 200 mg/dL. Continue with this reduction in dosage until niacin can be stopped entirely and cholesterol levels remain below 200 mg/dL.

Pantethine is recommended primarily to patients who have HTG, especially patients with diabetes. As stated earlier, pantethine has demonstrated excellent effects in diabetics. It not only improves cholesterol and triglyceride levels but also normalizes platelet lipid composition and function as well as blood viscosity.

With regard to elevations in Lp(a), both niacin and vitamin C have shown an ability to reduce Lp(a) levels dramatically (35% and 27% reductions, respectively). In addition, it is important to

TABLE 148-6 **Comparative Effects on Blood Lipids of Several Natural Compounds**

	NIACIN	GARLIC	POLICOSANOL	PANTETHINE
Total cholesterol (% decrease)	18	10	24	19
LDL-C (% decrease)	23	15	25	21
HDL-C (% increase)	32	31	15	23
Triglycerides (% decrease)	26	13	5	32

HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol.

rule out low thyroid function (hypothyroidism) in all cases of elevated blood lipids, especially elevated Lp(a).

It is well established that patients with overt hypothyroidism are prone to CAD because of increased LDL-C and decreased HDL-C. What is not so well established is the significance of "subclinical" hypothyroidism in terms of risk for cardiovascular mortality. A recent study indicates that the risk may be greater than previously suspected. The study demonstrated that patients with subclinical hypothyroidism (defined in this study as normal T3 and free thyroxine index with a raised TSH) were shown to have not only significantly elevated levels of LDL-C but also elevated Lp(a).[91] For more information, see Chapter 175.

THERAPEUTIC CONSIDERATIONS—ANTIOXIDANT STATUS

Dietary antioxidant nutrients like lycopene, lutein, selenium, vitamin E, and vitamin C have been shown in epidemiologic studies to offer significant protection against the development of CVD. Fats and cholesterol are particularly susceptible to free radical damage. When damaged, fats and cholesterol form lipid peroxides and oxidized cholesterol, which can then damage the artery walls and accelerate the progression of atherosclerosis. Antioxidants block the formation of these damaging compounds.

Although diets rich in antioxidant nutrients have consistently shown tremendous protection against CVD, clinical trials using antioxidant vitamins and minerals have produced inconsistent results.[92,93] This failure may be due to several factors, most importantly the fact that the human antioxidant system represents a complex scenario of interacting components. It is unlikely that any single antioxidant would be proved to be effective, especially in the absence of a supporting cast. Most antioxidants require some sort of "partner" antioxidant, allowing them to work more efficiently. The most salient example of this is the partnership between the two primary antioxidants in the human body—vitamins C and E. Vitamin C is an "aqueous phase" antioxidant, while vitamin E is a "lipid phase" antioxidant. Although some studies have shown that supplementation with these nutrients reduces atherosclerotic lesions, more protection is likely required to ensure optimal effect.[94]

In addition to vitamin C, vitamin E also requires selenium and CoQ_{10} to work efficiently (discussed in more detail later). Further adding to the shortcomings of many of the studies on antioxidant nutrients is the lack of consideration of the importance of phytochemicals and plant-derived antioxidants that, in addition to exerting benefit on their own, are well known to potentiate the activities of vitamin and mineral antioxidants. Phytochemicals like carotenes (especially lycopene and lutein) and flavonoids are especially important in fighting against free radical damage. Importantly, most scientific reviews on antioxidant supplements devote significant attention to the studies using beta-carotene, because they have involved more than 70,000 subjects, but such studies fail to differentiate the facts that synthetic beta-carotene was used and that beta-carotene is of little importance in protecting against LDL-C oxidation. (Unlike lycopene and lutein, beta-carotene does not become incorporated into LDL-C effectively, although it may help protect the endothelium.)

TABLE 148-7 **Effect of Increasing Doses of Vitamin E on Oxidation Parameters**

DOSAGE (mg/day)	LAG TIME*	PROPAGATION RATE†
0	94	7.8
25	99	8
50	100	7.9
100	106	7.7
200	111	7.5
400	116	6.8
800	120	6.5

*The time before oxidation occurs after the addition of an oxidizing agent. The higher the number, the greater the beneficial effect.
†The rate at which lipid peroxidation progresses. The lower the number, the greater the beneficial effect.

Lutein may turn out to be the most significant carotene in the battle against atherosclerosis. On the basis of analysis of the different subtypes of LDL-C, lycopene, beta-carotene, and cryptoxanthin were mainly located in the larger, less dense LDL-C particles, whereas lutein and zeaxanthin were found preferentially in the smaller, denser LDL-C particles.[95] Because the smaller, denser LDL-C subtype is most easily oxidized, lutein and zeaxanthin are particularly important in protecting against damage to LDL-C.

The support of nonantioxidant vitamins and minerals may also be important in supporting the effectiveness of antioxidants. Taking a multivitamin/multimineral supplement seems appropriate. In one double-blind study, CRP levels were significantly lower in the multivitamin group than in the placebo group, with the reduction in CRP levels most evident in patients who had elevated levels (≥1 mg/L) at baseline.[96] Researchers found that serum vitamin B_6 and vitamin C levels were inversely associated with CRP level.

Vitamin E

Although clinical studies have shown inconsistent effects, it is clear that vitamin E does play a role in the protection against oxidation of LDL-C because of its ability to be easily incorporated into the LDL-C molecule (Table 148-7). Furthermore, there is a clear-cut dosage effect (i.e., the higher the dosage of vitamin E, the greater the degree of protection against oxidative damage to LDL-C). Although dosages as low as 25 mg were originally shown to offer some protection, it appears that doses of greater than 400 IU are required to produce clinically significant effects.[97-99]

TABLE 148-8 **Intervention Trials With Vitamin E for Secondary Prevention**

STUDY	NUMBER OF SUBJECTS	DOSAGE	DURATION	OUTCOME
HOPE (2000)	9541	400 IU (d-alpha)	4.5 years	No effect
SPACE (2000)	196	800 IU (d-alpha)	1.4 years	-70%
GISSI (1999)	11,324	300 IU (synthetic)	3.5 years	-35% (vs. placebo)
CHAOS (1996)	9541	400-800 IU (d-alpha)	1.4 years	-47%

CHAOS, Cambridge Heart Antioxidant Study; HOPE, Heart Outcomes Protection Evaluation Trial; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; SPACE, Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease.

Improvements have also been noted in insulin sensitivity and plasma lipids in non–insulin-dependent diabetic patients.

Several large population studies have demonstrated that vitamin E levels may be more predictive of incipient heart attack or stroke than total cholesterol levels.[98-101] Although the consumption of red wine has been suggested as the reason behind the French paradox, described earlier, higher vitamin E levels provide at least as good an explanation.[98-100]

Vitamin E may offer additional benefit in protecting against heart disease and strokes by its ability to do the following:

- Reduce LDL-C peroxidation and increase plasma LDL-C breakdown
- Inhibit excessive platelet aggregation
- Increase HDL-C levels
- Increase fibrinolytic activity
- Reduce CRP levels
- Improve endothelial cell function
- Improve insulin sensitivity

Two early large-scale studies with relatively low dosages of vitamin E supplementation demonstrated a significant reduction in the risk of heart attack or stroke. The Nurses' Health Study of 87,245 nurses concluded that those who took 100 IU of vitamin E daily for more than 2 years had a 41% lower risk of heart disease compared with nonusers of vitamin E supplements.[100] The Physicians' Health Study of 39,910 male health care professionals found similar results: a 37% lower risk of heart disease with the intake of more than 30 IU of supplemental vitamin E daily.[101] Subsequent studies have been equivocal.[92]

Large-scale studies examining the impact of vitamin E supplementation in patients with existing CAD have also shown somewhat conflicting results.[93,94] Some of the disappointing results may have been due to the choice of synthetic vitamin E (D,L-alpha tocopherol) in one of the large studies versus the more active natural form (D-alpha tocopherol). There is also the problem of the interference by statin drugs in vitamin E and CoQ_{10} metabolism, thereby increasing the needs for both compounds (Table 148-8).

Vitamin E and CoQ_{10} work synergistically, and each is required for the regeneration of the other. For example, CoQ_{10} is present in the blood in both oxidized (inactive) and reduced (active) forms. During times of increased oxidative stress or low vitamin E levels, more CoQ_{10} will be converted to its oxidized (inactive form). Thus, by providing higher levels of vitamin E, the biological activity and function of CoQ_{10} are enhanced, and vice versa. Several studies in humans and animals have shown that the combination of vitamin E and CoQ_{10} works better than either alone. For example, in a study in baboons, where supplementation with vitamin E alone reduced CRP levels, co-supplementation with CoQ significantly enhanced this effect of vitamin E. Similar results have been seen in other animal studies on other factors associated with atherosclerosis, including LDL-C oxidation and lipid peroxide content within the aorta.[101-104]

In addition to CoQ_{10}, vitamin E also requires adequate selenium status for optimal antioxidant effects. Selenium functions primarily as a component of the antioxidant enzyme glutathione peroxidase. This enzyme works closely with vitamin E to prevent free radical damage to cell membranes. Studies looking only at vitamin E's ability to reduce cancer and heart disease are often faulty because they fail to factor in the critical partnership between selenium and vitamin E, not to mention the interrelationship between vitamin E and CoQ_{10}. Several studies have clearly demonstrated that low selenium status is significantly associated with CAD.[105,106] Failure to co-supplement with selenium as well as vitamin C and CoQ_{10} may be a major reason for the inconsistent results in intervention trials with vitamin E supplementation alone.

Vitamin C

Vitamin C works as an antioxidant in aqueous (water) environments in the body—both outside and inside human cells. It is the first line of antioxidant protection in the body. Its primary antioxidant partner is vitamin E, as this antioxidant is fat-soluble. Along with CoQ_{10}, vitamin C is also responsible for regenerating oxidized vitamin E in the body, thus potentiating the antioxidant benefits of vitamin E.[107] Vitamin C also works along with antioxidant enzymes such as glutathione peroxidase, catalase, and superoxide dismutase. Vitamin C has been shown to be extremely effective in preventing LDL-C from being oxidized, even in smokers.[108] Vitamins C and E supplementation, 500 mg and 272 IU daily, respectively, for 6 years has been shown to reduce the progression of carotid atherosclerosis by 53% in men and 14% in women.[109]

A high dietary intake of vitamin C has been shown to significantly reduce the risk of death from heart attacks and strokes, as well as all other causes including cancer in numerous population studies.[110] One of the most detailed studies providing insight analyzed the vitamin C intake of 11,348 adults over 5 years and divided them into three groups: (1) less than 50 mg dietary intake daily; (2) greater than 50 mg daily dietary intake with no vitamin C supplementation; and (3) greater than 50 mg dietary intake a day plus vitamin C supplementation (estimated to be ≥ 300 mg).[110] Analysis showed that the standardized mortality ratio, a comparison with the average death rate, was up to 48% lower in the high vitamin C intake group than in the low-intake group for CVD and overall mortality. These differences correspond to an increase in longevity of 5 to 7 years for men and 1 to 3 years for women.

Dozens of observational and clinical studies have shown that vitamin C levels correspond to total cholesterol and HDL-C.[111-113] In one of the best-designed studies, it was shown that the higher the vitamin C content of the blood, the lower the total cholesterol and triglycerides and the higher the HDL-C.[113] The benefits for HDL-C were particularly impressive. For each

0.5 mg/dL increase in vitamin C content of the blood, there was an increase in HDL-C of 14.9 mg/dL in women and 2.1 mg/dL in men. This study is significant in having demonstrated that the association of vitamin C and HDL-C levels persists even in well-nourished individuals with normal serum levels of vitamin C who supplement their diets with additional vitamin C.

Recent studies have focused on the effects of vitamin C therapy in reducing CRP and Lp(a) and its positive effects on the fibrinolytic system.

In summary, vitamin C lowers the risk of CVD by doing the following[107-115]:

- Acting as an antioxidant
- Strengthening the collagen structures of the arteries
- Lowering total cholesterol, Lp(a), and blood pressure
- Raising HDL-C levels
- Inhibiting platelet aggregation
- Promoting fibrinolysis
- Reducing markers of inflammation

Grape Seed and Pine Bark Extracts

One of the most beneficial groups of plant flavonoids are the proanthocyanidins (also referred to as procyanidins or procyanidonic oligomers [PCOs]). Although PCOs exist in many plants as well as in red wine, commercially available sources of PCO include extracts from grape seeds and the bark of the maritime (Landes) pine.[116] These extracts offer protection via several different mechanisms, including their antioxidant activity and effects on endothelial cells. For more information, see Chapter 117.

THERAPEUTIC CONSIDERATIONS—MISCELLANEOUS RISK FACTORS

Platelet Aggregation

Excessive platelet aggregation is another independent risk factor for heart disease and stroke. Once platelets aggregate, they release potent compounds that dramatically promote the formation of the atherosclerotic plaque, or they can form a clot that can lodge in small arteries and produce a heart attack or stroke. The adhesiveness of platelets is determined largely by the types of fats in the diet and the level of antioxidants. Although saturated fats and cholesterol increase platelet aggregation, omega-3 oils (both short-chain and long-chain) and monounsaturated fats have the opposite effect.[117,118]

In addition to the monounsaturated and omega-3 fatty acids, antioxidant nutrients, and flavonoids, vitamin B_6 also inhibits platelet aggregation and lowers blood pressure and homocysteine levels.[119,120] In one study, the effect of vitamin B_6 (pyridoxine HCl) supplementation on platelet aggregation, plasma lipids, and serum zinc levels was determined in 24 healthy male volunteers (19 to 24 years old) given either pyridoxine at a dosage of 5 mg/kg body weight or a placebo for 4 weeks.[119] Results demonstrated that pyridoxine inhibited platelet aggregation by 41% to 48%, while there was no change in the control group. Pyridoxine prolonged both bleeding and coagulation time but not over the physiologic limits. It had no effect on platelet count. Pyridoxine was also shown to lower total plasma lipids and cholesterol levels considerably from pretreatment levels. Total plasma lipids were reduced from 593 to 519 mg/dL, and total cholesterol was reduced from 156 to 116 mg/dL. HDL-C increased from 37.9 to 48.6 mg/dL. Serum zinc levels increased from 96 to 138 mg/dL.

In another study, a significant inverse graded relation was observed between the serum level of pyridoxal-5-phosphate (P5P) and both CRP and fibrinogen.[121] The odds ratio for CAD risk related to low P5P concentrations after adjustments for the major classic CAD risk factors, including CRP and fibrinogen, was 1.89. In addition, the CAD risk as a result of low P5P was additive when considered in combination with elevated CRP concentrations or with an increased LDL-C:HDL-C ratio.

These results provide clear evidence of the possible role of vitamin B_6 supplementation in reducing the risk of atherosclerotic mortality.

Garlic preparations standardized for alliin content as well as garlic oil have also demonstrated inhibition of platelet aggregation. In one study, 120 patients with increased platelet aggregation were given either 900 mg/day of a dried garlic preparation containing 1.3% alliin or a placebo for 4 weeks.[122] In the garlic group, spontaneous platelet aggregation disappeared, the microcirculation of the skin increased by 47.6%, plasma viscosity decreased by 3.2%, diastolic blood pressure dropped from an average of 74 to 67 mm Hg, and fasting blood glucose concentration dropped from an average of 89.4 to 79 mg/dL.

Fibrinogen

Elevated fibrinogen levels are another clear risk factor for CVD. Early clinical studies stimulated detailed epidemiologic investigations into the possible link between fibrinogen and CVD.[123] The first such study was the Northwick Park Heart Study in the United Kingdom. This large study involved 1510 men 40 to 64 years of age who were randomly recruited and tested for a range of clotting factors including fibrinogen. At the 4-year follow-up, there was a stronger association between cardiovascular deaths and fibrinogen levels than that for cholesterol. This association has now been confirmed in at least five other prospective epidemiologic studies.

Natural therapies designed to promote fibrinolysis include exercise, omega-3 oils, niacin, garlic, and nattokinase. In addition, the Mediterranean diet alone significantly reduces fibrinogen and other markers of inflammation.[124] Adherence to the Mediterranean diet was shown to be associated with a 20% lower CRP level, 17% lower interleukin-6 level, 15% lower homocysteine level, and 6% lower fibrinogen level.

Natto is a traditional Japanese food prepared from fermented soybeans by *Bacillus subtilis*. Nattokinase is a serine proteinase isolated from natto that has potent fibrinolytic and thrombolytic activity. An open-label self-controlled clinical trial was conducted on subjects of the following groups: healthy volunteers (healthy group), patients with cardiovascular risk factors (cardiovascular group), and patients undergoing dialysis (dialysis group). All subjects ingested two capsules of nattokinase (2000 fibrinolysis units per capsule) daily orally for 2 months. The laboratory measurements were performed on the screening visit and then regularly after the initiation of the study. After 2 months of administration, fibrinogen, factor VII, and factor VIII decreased by 9%, 14%, and 17%, respectively, for the healthy group; 7%, 13%, and 19%, respectively, for the cardiovascular group; and 10%, 7%, and 19%, respectively, for the dialysis group. These results highlight the potential of nattokinase as a natural fibrinolytic.[125]

Homocysteine

Homocysteine is an intermediate in the conversion of the amino acid methionine to cysteine. If a person is functionally deficient in folic acid, vitamin B_6, or vitamin B_{12}, there will be an increase in

homocysteine. Elevated homocysteine levels are an independent risk factor for developing a heart attack, stroke, or peripheral vascular disease. Elevations in homocysteine are found in approximately 20% to 40% of patients with heart disease and are significantly associated with CAD.[126-128] A meta-analysis found that for each increase of 5 µmol/L in homocysteine, the risk of CHD events increased by approximately 20%, independently of traditional CHD risk factors.[129]

A number of interrelated atherogenic mechanisms are thought to be involved with hyperhomocyteinemia. These include advanced thickening and smooth muscle cell proliferation of endothelial vessel wall intima, enhanced lipid deposition in the vessel wall, forced detachment of endothelial cells, activation of leukocytes and thrombocytes, increased LDL-C oxidation, initiation of platelet thromboxane synthesis, enhanced oxidative stress induced by peroxide formation during homocysteine oxidation, and prothrombotic coagulation interference. Homocysteine is thought to promote atherosclerosis by directly damaging the artery, reducing the integrity of the vessel wall, and interfering with the formation of proper collagen.

Although folic acid supplementation (400 mcg daily) alone can reduce homocysteine levels in many subjects, given the importance of vitamins B_{12} and B_6 to proper homocysteine metabolism, all three should be used together. In one study, the suboptimal levels of these nutrients in men with elevated homocysteine levels were 56.8%, 59.1%, and 25% for folic acid, vitamin B_{12}, and vitamin B_6, respectively, indicating that folic acid supplementation alone would not lower homocysteine levels in many cases.[130] In other words, folic acid supplementation will lower homocysteine levels only if there are adequate levels of vitamins B_{12} and B_6. This fact could reduce the effect of the folic acid fortification of food.

In 1998, the FDA mandated the fortification of food products with folic acid. Although homocysteine levels have decreased modestly since then, the effect on mortality has been minor at best.[131] This indicates the importance of more aggressive supplementary measures to reduce homocysteine-associated cardiovascular risk.

"Type A" Personality

"Type A" behavior is characterized by an extreme sense of time urgency, competitiveness, impatience, and aggressiveness. This behavior carries with it a twofold increase in CHD compared with non–type A behavior.[132–134] Particularly damaging to the cardiovascular system is the regular expression of anger. In one study, the relationship between habitual anger coping styles, especially anger expression, and serum lipid concentrations were examined in 86 healthy subjects.[133] Habitual anger expression was measured on four scales: aggression, controlled affect, guilt, and social inhibition. A positive correlation between serum cholesterol level and aggression was found. The higher the aggression score, the higher the cholesterol level. A negative correlation was found between the ratio of LDL-C to HDL-C and controlled affect score—the greater the ability to control anger, the lower this ratio. In other words, those who learn to control anger experience a significant reduction in the risk for heart disease, while an unfavorable lipid profile is linked with a predominantly aggressive (hostile) anger coping style.

Anger expression also plays a role in CRP levels. In one study, greater anger and severity of depressive symptoms, separately and in combination with hostility, were significantly associated with elevations in CRP in apparently healthy men and women.[135] Other mechanisms explaining the link between the emotions, personality, and CVD include increased cortisol secretion, endothelial dysfunction, hypertension, and increased platelet aggregation and fibrinogen levels.[119]

These associations are independent of potential confounding factors.

Ten tips that can help patients improve their coping strategies follow:

1. Do not starve your emotional life. Foster meaningful relationships. Provide time to give and receive love in your life.
2. Learn to be a good listener. Allow the people in your life to really share their feelings and thoughts uninterruptedly. Empathize with them; put yourself in their shoes.
3. Do not try to talk over somebody. If you find yourself being interrupted, relax; do not try to outtalk the other person. If you are courteous and allow someone else to speak, eventually (unless he or she is extremely rude) he or she will respond likewise. If not, explain that he or she is interrupting the communication process. You can do this only if you have been a good listener.
4. Avoid aggressive or passive behavior. Be assertive, but express your thoughts and feelings in a kind way to help improve relationships at work and at home.
5. Avoid excessive stress in your life as best you can by avoiding excessive work hours, poor nutrition, and inadequate rest. Get as much sleep as you can.
6. Avoid stimulants like caffeine and nicotine. Stimulants promote the fight-or-flight response and tend to make people more irritable in the process.
7. Take time to build long-term health and success by performing stress-reduction techniques and deep breathing exercises.
8. Accept gracefully those things over which you have no control. Save your energy for those things that you can do something about.
9. Accept yourself. Remember that you are human and will make mistakes from which you can learn along the way.
10. Be more patient and tolerant of other people. Follow the golden rule.

Other Nutritional Factors

Magnesium and Potassium

Magnesium and potassium are absolutely essential to the proper functioning of the entire cardiovascular system. Their critical roles in preventing heart disease and strokes are now widely accepted. In addition, there is a substantial body of knowledge demonstrating that magnesium or potassium supplementation or both are effective in treating a wide range of CVDs, including angina, arrhythmias, congestive heart failure, and high blood pressure. In many of these applications, magnesium or potassium supplementation or both have been used for more than 50 years.

Because the role of potassium in the cardiovascular system is described in detail in Chapter 174, the focus here is on magnesium. Most Americans do not consume enough of this important mineral. The average intake of magnesium by healthy adults in the United States ranges from 143 to 266 mg/day. This level is well below even the recommended daily allowance (RDA) of 350 mg for men and 300 mg for women. Food choices are the main reason. Because magnesium occurs abundantly in whole foods, most nutritionists and dietitians assume that most Americans get enough magnesium in their diets. But most Americans are not eating whole, natural foods. They are consuming large quantities of processed foods. Because food processing refines a large

portion of magnesium, most Americans are not getting the RDA for magnesium.

The best dietary sources of magnesium are tofu, legumes, seeds, nuts, whole grains, and green leafy vegetables. Fish, meat, milk, and most commonly eaten fruits are quite low in magnesium. Most Americans consume a low-magnesium diet because their diet is high in low-magnesium foods such as processed foods, meat, and dairy products.

People dying of heart attacks have been shown to have lower heart magnesium levels than people of the same age dying of other causes.[136] Low magnesium levels contribute to atherosclerosis and CVD via many mechanisms including the promotion of endothelial dysfunction by generating a proinflammatory, prothrombotic, proatherogenic environment.[137]

Intravenous magnesium therapy has now emerged as a valued treatment measure in acute MI.[138-140] The major obstacle to its becoming the preferred method for saving a person's life may be a financial interest. Magnesium is cheap compared with new high-tech, high-priced, genetically engineered drugs currently being promoted by drug companies. The treatment of acute MI is big business in the United States. Each year more than 1.5 million U.S. citizens experience acute MI. Although many other parts of the world are now using magnesium therapy for acute MI because of its effectiveness, low cost, safety, and ease of administration, it plays second fiddle to the high-tech drugs in the United States.

During the past decade, eight well-designed studies involving more than 4000 patients have demonstrated that intravenous magnesium supplementation during the first hour of admission to a hospital for acute MI produces a favorable effect in reducing immediate and long-term complications as well as death rates. The beneficial effects of magnesium in acute MI relate to its ability to do the following:

- Improve energy production within the heart
- Dilate the coronary arteries, resulting in improved delivery of oxygen to the heart
- Reduce peripheral vascular resistance, resulting in reduced demand on the heart
- Inhibit platelets from aggregating and forming blood clots
- Reduce the size of the infarct (blockage)
- Improve heart rate and arrhythmias

Vitamin D Deficiency

Data from more than 8000 individuals enrolled in the NHANES 2001-2004 study indicate that individuals with vitamin D (25-OH) levels below 30 ng/mL were more likely to be at high risk for CVD (OR 1.32), for CHD (OR 1.48), and for both CHD and heart failure (OR 3.52).[141] A prospective cohort study of more than 3000 men and women found that those in the lowest quartile of 25-hydroxy vitamin D had a hazard ratio of 2.22 for cardiovascular mortality and 2.08 for all-cause mortality.[142]



THERAPEUTIC CONSIDERATIONS—PREVENTING A RECURRENT HEART ATTACK

People who have experienced a heart attack or stroke and live through it are extremely likely to experience another. The primary prevention of subsequent cardiovascular events is to control the major cardiac risk factors (e.g., hyperlipidemia, hypertension, cigarette smoking, diabetes, physical inactivity). The most popular "secondary" recommendation to reduce the risk of a subsequent heart attack being given by most physicians is low-dose aspirin (e.g., 325 mg/day or every other day). However, there may be effective alternatives, especially for those who cannot tolerate aspirin therapy. It is becoming standard to recommend dosages of aspirin lower than 325 mg (e.g., 50 to 150 mg/day or every other day). To date these lower dosages have not been shown to be effective in reducing CVD mortality.

Aspirin

Aspirin has been shown to decrease the risk of CVD events in both primary and secondary trials. The first primary prevention study was the Physicians' Health Study, a randomized double-blind placebo-controlled trial of 22,071 apparently healthy men. The study was terminated early owing principally to a statistically extreme 44% reduction in the risk of a first MI with the use of 325 mg of aspirin every other day. Since this study, three additional randomized trials including both men and women have shown aspirin to be effective in the primary prevention of MI: the Thrombosis Prevention Trial, the Hypertension Optimal Treatment Study, and the Primary Prevention Project. Among the 55,580 subjects, aspirin use was associated with a statistically significant 32% reduction in the risk of a first MI and a significant 15% reduction in the risk of all other important vascular events, but it had no significant effects on nonfatal stroke or vascular death. Evaluation of the data from the Physicians' Health Study indicated that those with the highest CRP had the greatest decrease in risk, 55.7%, versus 13.9% in those with the lowest CRP. It seems reasonable to reserve the use of aspirin as a primary prevention strategy for individuals with high CRP values.[143]

Regarding the secondary prevention of MI, there have been seven prospective randomized placebo-controlled trials involving almost 15,000 survivors of heart attack that have examined the use of aspirin to reduce the incidence of recurrent heart attack and death. These trials have used several doses of aspirin, ranging from 325 to 1500 mg/day and enrolled patients at various intervals after infarction ranging from 4 weeks to 5 years. None of the studies demonstrated a statistically significant reduction in mortality with aspirin use. However, when all the results from these studies were pooled, aspirin was shown to reduce the mortality rate from all causes as well as cardiovascular deaths. The mortality rate for all causes in the aspirin group was 5.8%, compared with 8.3% in the placebo group, indicating a reduction in mortality by 30% with aspirin.[144,145]

Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) are associated with a significant risk of peptic ulcer. However, most studies documenting the relative frequency of peptic ulcers as a consequence of NSAIDs have focused on their use in the treatment of arthritis and headaches. The risk of gastrointestinal bleeding due to peptic ulcers has been evaluated for aspirin at daily dosages of 300, 150, and 75 mg, respectively. Essentially there is an increased risk of gastrointestinal bleeding due to peptic ulcers at all dosage levels. However, the dosage of 75 mg/day was associated with a 40% reduction in ulcers compared with 300 mg/day and 30% compared with 150 mg/day.[146]

Because it is unknown whether 75 mg/day of aspirin is helpful in preventing a second heart attack, most physicians recommend at least 300 mg. To prevent stroke, the dosage necessary appears to be 900 mg. These dosage recommendations carry with them a significant risk for developing a peptic ulcer but may be appropriate for high-risk patients unwilling to adopt the natural approach.

Dietary Alternatives to Aspirin

The best approach to preventing subsequent heart attacks may not be low-dose aspirin, especially in aspirin-sensitive patients. The first

alternative to aspirin to be examined is one too often overlooked by many physicians—diet. Several studies have shown that dietary modifications are not only more effective in preventing recurrent heart attack than aspirin but can also reverse the blockage of clogged arteries. In addition to the studies with the Mediterranean diet, three famous studies deserve special mention. The first was the Lifestyle Heart Trial conducted by Dean Ornish.[147] In this study, subjects with heart disease were divided into a control group and an experimental group. The control group received regular medical care while the experimental group was asked to eat a low-fat vegetarian diet for at least 1 year. The diet included fruits, vegetables, grains, legumes, and soybean products. Subjects were allowed to consume as many calories as they wished. No animal products were allowed except egg whites and 1 cup of nonfat milk or yogurt daily. The diet contained approximately 10% fat; 15% to 20% protein; and 70% to 75% carbohydrates—that is, predominantly complex carbohydrates from whole grains, legumes, and vegetables.

The experimental group was also asked to perform stress reduction techniques such as breathing exercises, stretching exercises, meditation, imagery, and other relaxation techniques for an hour each day and to exercise for at least 3 hours each week. At the end of the year, the subjects in the experimental group showed significant overall regression of atherosclerosis of the coronary blood vessels. In contrast, subjects in the control group who were being treated with regular medical care and following the standard AHA diet actually showed progression of their disease. Ornish stated: "This finding suggests that conventional recommendations for patients with CHD (such as a 30% fat diet) are not sufficient to bring about regression in many patients."

Two other famous studies showing that diet can prevent further heart attacks in patients suffering a first heart attack highlight the importance of omega-3 fatty acids and again show the ineffectiveness of the AHA's dietary recommendations. As stated previously, numerous population studies have demonstrated that people who consume a diet rich in omega-3 oils from either fish or vegetable sources have a significantly reduced risk of developing heart disease. Two famous intervention trials upheld this protective effect. In the Dietary and Reinfarction Trial (DART), it was only when the intake of omega-3 fatty acids (from fish) was increased that future heart attacks were reduced.[148] In another study, the Lyon Diet Heart Study, increasing the intake of omega-3 fatty acids from plant sources (alpha-linolenic acid) was found to offer the same degree of protection as increased fish intake.[149]

Preventing a Subsequent Stroke

To prevent a subsequent stroke and promote recovery from a stroke, *Ginkgo biloba* extract should be added to the program described earlier for preventing a subsequent heart attack. The extract of *G. biloba* leaves standardized to contain 24% ginkgo flavonglycosides and 6% terpenoids has been the subject of more than 300 published scientific papers and more than 40 double-blind studies in the treatment of decreased blood supply to the brain (cerebrovascular insufficiency). *G. biloba* extract has also been shown to enhance stroke recovery (see Chapter 93 for more information).

Other Considerations

Angiography, Coronary Artery Bypass Surgery, or Angioplasty

A significant challenge for the clinician is determining when a patient should be referred for angiography, coronary artery bypass surgery, or angioplasty. As is fully discussed in Chapter 145, these procedures are used far more frequently than is justified by objective evaluation of their appropriateness and efficacy. Chapter 145 also gives advice for patient care when angiography, coronary artery bypass surgery, or angioplasty is unavoidable.

Intravenous Chelation Therapy

The clinician is also asked for recommendations concerning the efficacy of the far less invasive intravenous ethylenediamine tetraacetic acid chelation therapy. This useful yet controversial procedure is also discussed fully in Chapter 145.

Earlobe Crease

The presence of a diagonal earlobe crease has been recognized as a sign of CVD since 1973. More than 30 studies have been reported in the medical literature. The earlobe is richly vascularized, and a decrease in blood flow over an extended period of time is believed to result in collapse of the vascular bed. This leads to a diagonal crease.[150,151]

In one study, angiographs performed on 205 consecutive patients showed an 82% accuracy in predicting heart disease, with a false-positive rate of 12% and a false-negative rate of 18%. In another study of 112 consecutive patients, the earlobe crease was highly correlated with demonstrable heart disease and less strongly with previous MI.[151]

The crease is seen more commonly with advancing age, until the age of 80, when the incidence drops dramatically. However, the association with heart disease is independent of age. Although the presence of an earlobe crease does not prove heart disease, it strongly suggests it, and examination of the earlobe is an easy screening procedure. The correlation does not hold with Asians, Native Americans, or children with Beckwith's syndrome.[151]

THERAPEUTIC APPROACH

There is little doubt that in most cases atherosclerosis is directly related to diet and lifestyle. Treatment and prevention include reducing all known risk factors. For many patients this goal requires a major change in diet and lifestyle. Because so many factors are known to be involved in atherosclerosis, any treatment plan must be individualized to assure optimal results. What follows is a general approach that must be tailored according to the clinical picture and the patient's willingness to adopt it.

Dietary Recommendations

Follow the dietary guidelines given in Chapter 44 (a modified version of the Mediterranean diet). Table 148-9 provides additional guidance in dietary selections, and Box 148-5 lists foods to avoid because of their trans-fatty acid content. Specifically, it is important to do the following:

- Eat less saturated fat and cholesterol by reducing or eliminating the amounts of animal products in the diet.
- Increase the consumption of fiber-rich plant foods (fruits, vegetables, grains, legumes, and raw nuts and seeds).
- Increase the consumption of monounsaturated fats and omega-3 fatty acids.
- Follow a low-glycemic diet.

Lifestyle Recommendations

- Achieve ideal body weight.
- Exercise aerobically on a regular basis.
- Do not smoke.

TABLE 148-9 **Food Choices for Lowering Cholesterol**

DECREASE CONSUMPTION OF THE FOLLOWING:	SUBSTITUTE WITH THE FOLLOWING:
Red meat	Fish and white-meat poultry
Hamburgers and hot dogs	Soy-based alternatives
Eggs	Egg Beaters and similar products, tofu
High-fat dairy products	Low-fat or nonfat dairy products
Butter, lard, and other saturated fats	Vegetable oils
Ice cream, pies, cake, cookies, etc.	Fruits
Refined cereals, white	Whole grains, whole wheat bread, etc.
Fried foods, fatty snack foods	Vegetables, fresh salads
Salt and salty foods	Low-sodium foods, light salt
Coffee and soft drinks	Herbal teas, fresh fruit, and vegetable juices

BOX 148-5 **Foods Typically Containing Partially or Totally Hydrogenated Vegetable Oils and Trans Isomers**

- Virtually all refined and processed foods
- Margarine
- Cakes
- Cookies
- Candies
- Doughnuts
- Bread
- Canned soups
- Crackers
- Processed cheese
- Canned foods
- Cereals
- Snack foods
- Salad oils, except olive oil, which is recommended

Supplements

- High-potency multivitamin and mineral formula
- Vitamin C: 250 to 500 mg three times a day
- Vitamin E (mixed tocopherols): 100 to 400 IU/day
 - Grape seed or pine bark extract: 100 mg/day
 - Fish oil supplement: minimum 1000 mg of EPA+DHA
- Vitamin D: 1000 to 4000 IU/day

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CHAPTER 149

Atopic Dermatitis (Eczema)

Michael T. Murray, ND, and Michael Traub, ND, DHANP, FAB

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DIAGNOSTIC SUMMARY

- Chronic, pruritic, inflammatory skin
- Dry, hyperkeratotic skin
- Lesions include excoriations, papules, eczema (patches of erythema, exudation, and scaling with small vesicles formed within the epidermis), and lichenification (hyperpigmented plaques of thickened skin with accentuated furrows)
- Scratching and rubbing lead to lichenification, most commonly in the antecubital and popliteal flexures
- Personal or family history of atopy

GENERAL CONSIDERATIONS

Atopic dermatitis (eczema) is a common condition with a prevalence of 2.4% to 7% of the population. The current etiopathogenesis of atopic dermatitis (AD) involves the interplay of the following:

- Cutaneous barrier dysfunction and mutations in genes coding for skin proteins (filaggrin)
- Dysregulation of the immune system and the role of thymic stromal lymphopoietin in allergic inflammation
- Environmental factors

Filaggrin and Epidermal Barrier Dysfunction

A genetic basis for AD has long been recognized. Family history of atopic disease is a major risk factor. Before characterization of the human genome, heritability studies combined with family-based linkage studies supported the understanding of AD as a complex trait, in that interactions between genes and environmental factors and the interplay between multiple genes contributed to disease manifestation. More than 100 published reports on genetic association studies through mid-2009 implicated 81 genes, in 46 of which at least 1 positive association with AD had been demonstrated. Of these, the gene encoding filaggrin (FLG) has been most consistently replicated. Most candidate gene studies to date have focused on adaptive and innate immune response genes, but there is increasing interest in genes governing skin barrier dysfunction.[1]

Filaggrin is a protein that facilitates the aggregation of keratin filaments; it is otherwise known as filament aggregating protein. It binds cytokeratin into tonofilaments and, when proteolyzed, forms small hygroscopic molecules including amino acids, which comprise natural moisturizing factor (NMF). NMF is responsible for hydration of the stratum corneum. Robust associations of filaggrin mutations have been replicated in several populations, especially in those with northern European ancestry, and it is now accepted that 15% of cases of AD are attributable to such mutations.[2] If an individual is born with one filaggrin mutation, the risk of AD is 40%.

But additional acquired stressors to the skin barrier are required to initiate inflammation. Sustained hapten access through a defective barrier stimulates a Th1-to-Th2 shift in immunophenotype, which in turn further impairs the barrier. Secondary *Staphylococcus aureus* colonization not only amplifies inflammation but also further stresses the barrier in AD. These observations suggest a new "outside-to-inside, back

to outside" paradigm for the pathogenesis of AD. This new concept is providing impetus for the development of new categories of "barrier repair" therapy.[3]

Immune Dysregulation, Thymic Stromal Lymphopoietin, and Allergic Inflammation

IgE is elevated in up to 80% of patients with AD. It is clear that activation of type 2 T-helper (Th2) cells in response to antigens plays a major role in AD. Thymic stromal lymphopoietin (TSLP) is an IL-7–like cytokine secreted by barrier-defective skin and is found at high levels in skin biopsies from lesional AD patients.[4] TSLP profoundly triggers Th2 commitment and is increased when stimulated by phthalates.[5] Phthalates are used in a large variety of products, from enteric coatings of pharmaceutical pills and nutritional supplements to viscosity control agents, gelling agents, film formers, stabilizers, dispersants, lubricants, binders, emulsifying agents, and suspending agents. End applications include adhesives and glues, agricultural uses, building materials, personal care products, medical devices, detergents and surfactants, packaging, children's toys, modeling clay, waxes, paints, printing inks and coatings, pharmaceuticals, food products, and textiles. Phthalates are also frequently used in soft plastic fishing lures, caulk, paint pigments, and sex toys made of "jelly rubber." Phthalates are used in a variety of household applications such as shower curtains, vinyl upholstery, adhesives, floor tiles, food containers and wrappers, and cleaning materials. Pervasive exposure to phthalates may therefore play a role in the pathogenesis of AD. TSLP sensitizes the lungs to allergens, and may help to explain the frequently observed evolution of AD to asthma, known as the "atopic march."

Gastric *Helicobacter pylori* directly stimulates epidermal cells to secrete TSLP, and *H. pylori* antibody is positive in up to 70% of AD patients.[6] One study has shown that treatment of infection, demonstrated by a reduction in C-urea breath test and anti-*H. pylori* antibody titers, resulted in partial improvement in patients with AD.[7]

Environmental Factors: Atopic Dermatitis and Allergy

Sensitization to foods triggers isolated skin symptoms in about 30% of children. These symptoms include immediate reactions within minutes after ingesting food without exacerbation of AD and early and late exacerbations of AD. It is important to identify clinically relevant sensitizations to foods using skin-prick tests, specific IgE and IgG4 blood tests, and food challenges to initiate appropriate dietary interventions and avoid unnecessary dietary restrictions. A defective skin barrier and increased intestinal permeability appear to facilitate allergen sensitization. Appropriate skin care to maintain skin barrier function and dietary avoidance of highly allergenic foods during infancy may help to prevent allergen sensitization, thereby reducing the severity of AD and food allergies.[8]

Predictors of Severity

One longitudinal study of children examined a number of risk factors that may predict the severity of AD in children.[9] This study surveyed 137 children and followed them through four visits over a period of 1½ years. Parameters such as age at onset, social class, ethnic group, child's atopy, family history of atopy, and other potential risk factors were recorded. This study revealed the following: (1) Children with AD whose eczema started during the first year of life were more likely to have severe disease than were those whose eczema started later; (2) a history of atopy (asthma, hay fever, or both) was associated with severe AD; and (3) children with eczema who lived in an urban area were at increased risk of severe disease compared with their counterparts who lived in a rural environment. This urban environmental risk was independent of ethnicity.

Other factors such as breastfeeding, family size, sex, birth weight, gestational age, child's age, and any atopy (hay fever, asthma, or eczema) in parents and siblings were found to have no significant association with disease severity in this study. The lack of a protective effect from breastfeeding is not consistent with other studies (see later). Although the authors of this study did mention the possibility of environmental allergens, there was no mention of diet history or food associations regarding severity. Not examining the relationship of this condition to food was a major omission. Subsequent studies evaluating risk factors should include diet diaries and food association studies.

THERAPEUTIC CONSIDERATIONS

The myriad of prescription and over-the-counter medications commonly used to treat AD fail to address the root cause of the condition. Topical medications used to treat AD include emollients, corticosteroids, antibiotics, and calcineurin inhibitors. Oral antihistamines are used for pruritus. Severe eczema has also been treated with systemic immodulatory agents (cyclosporine) and systemic corticosteroids. None of these medications has shown effective long-term ability to cure AD. Side effects such as growth retardation, cutaneous complications, sedation, and allergic reactions are a major concern.[10] Furthermore, a number of these medications can result in a rebound flareup that is usually worse than the primary lesions.

Naturopathic medicine generally attempts to understand the underlying causes of AD and thus attends to additional factors including those affecting the digestive system, such as food allergies and candidal overgrowth. Although no one treatment option may be universally effective, patient-specific combination therapeutics acting in synergy are encouraged for optimal efficacy.

Food Allergy, Gut Permeability, and Candidal Overgrowth

Numerous studies have documented the role of food allergy in AD (also see Chapter 15). Studies have also shown that breastfeeding offers significant prophylaxis against AD as well as allergies in general.[11]

One study of 100 infants demonstrated that breastfeeding should be promoted for the primary prevention of allergy.[12] Interestingly, further studies by the same group suggest that breastfed infants with allergies should be treated by allergen avoidance; in some cases breastfeeding cessation is recommended in order to avoid traces of food antigens in breast milk.[13] However, the development of AD in breastfed infants is usually the result of the transfer of allergic antigens in the breast milk, in which case mothers should be instructed to avoid the common food allergens (especially milk, eggs, and peanuts and, to a lesser extent, fish, soy, wheat, citrus, and chocolate).[14] Maternal avoidance of these common allergens is associated with complete resolution in the majority of cases. We recommend that further studies regarding breastfeeding and food allergies examine maternal food allergy restrictions in an attempt to more accurately evaluate the underlying causes of infantile eczema.

In older or formula-fed infants, milk, eggs, and peanuts appear to be the most common food allergens inducing AD. In one study,

these three foods were implicated in 81% of all cases of childhood AD,[15] whereas in another study 60% of children with severe AD had a positive food challenge to one or two of the following: egg, cow's milk, peanut, fish, wheat, or soybean. One randomized controlled trial found that in those individuals with a positive radioallergosorbent test to eggs, an egg-free diet was associated with an improvement in the severity of AD, with the greatest effect seen in those most severely affected.[16] Although eggs are a major suspect, virtually any food can be the offending agent.[17]

Diagnosis of food allergy is usually best achieved via the elimination diet and challenge method. This approach is especially useful in childhood eczema. Elimination of milk products, eggs, peanuts, tomatoes, and artificial colors and preservatives results in significant improvement in at least 75% of cases.[15,17,18] If laboratory methods are used to identify food allergies in eczema, the most useful method appears to be the enzyme-linked immunosorbent assay (ELISA) IgE and IgG_4 (see Chapter 15).[19]

The presence of food allergies is thought to be partially responsible for children with AD having a "leaky gut."[20] As a result of this increased gut permeability, there is an increased antigen load on the immune system, which subsequently overwhelms the immune system and increases the likelihood of developing additional allergies. Permeability studies using urinary mannitol and lactulose confirm that hypoallergenic diets do decrease gut permeability and are associated with improvements in atopic eczema. It is essential to identify offending foods as soon as possible to avoid increasing gut permeability. Trying to deal with multiple food allergies is often a difficult task for the patient, as the diet is often unrealistically restrictive. The elimination of allergenic foods and restoration of normal intestinal permeability appear to stop the development of new allergies.[21]

Patients should be encouraged to find out whether, if they can avoid offending foods for a period of 6 to 12 months, their antibody levels to allergens will decrease to the point that they can tolerate the reintroduction of some foods at least twice a week. The loss rate of food allergy in patients with AD after 1 year was 26% for the five major allergens (egg, milk, wheat, soy, and peanut) and 66% for other food allergens.[22]

Candida albicans

An overgrowth of the common yeast *Candida albicans* in the gastrointestinal tract has been implicated as a causative factor in allergic conditions including AD. Elevated levels of anticandidal antibodies are common in atopic individuals. Furthermore, the severity of lesions tends to correlate with the level of IgE antibodies in relation to candidal antigens. Appropriate anticandidal therapy (see Chapter 51) may result in significant clinical improvement of AD.[23,24]

Nutritional Supplements

Probiotics

Because the intestinal flora plays a major role in the health of the host, especially regarding AD, probiotic therapy is especially indicated. Studies evaluating the administration of the probiotic *Lactobacillus rhamnosus* strain GG alone or in conjunction with *Lactobacillus reuteri* to infants with AD and cow's milk allergy demonstrated significant reduction of the severity of eczema.[25-28]

However, the one randomized controlled trial[27] that prescribed both probiotic strains used a skim milk powder preparation for the placebo group. Patients were also allowed to continue corticosteroid treatment. Both of these factors may have confounded any beneficial results, because it was noted that corticosteroid use increased in the placebo group during the active treatment period, possibly indicating an allergic reaction to the milk proteins in the placebo. Another interesting note is the finding in this study that the positive therapeutic effect of probiotics was more pronounced in patients with an allergic constitution, as evidenced by positive responses to the skin-prick test and increased IgE levels. This suggests that these tests may be useful in forecasting who may be most responsive to probiotic therapy. Although more study is warranted, it seems reasonable to include probiotics in a therapeutic regimen given their safety and overall health benefits.

Essential Fatty Acids

In the past it was thought that supplementing the diet of AD patients with evening primrose, borage, or black currant oil (commercial sources of gamma-linolenic acid) might prove helpful. In fact, several double-blind studies with evening primrose oil (typically using dosages of at least 3000 mg daily, providing 270 mg of gamma-linolenic acid) did show benefit.[29-31] The benefit of omega-6 oils are primarily in skin barrier function. However, overall the therapeutic results appear to be more favorable with omega-3 oil supplementation, than with evening primrose oil. Several studies with evening primrose oil failed to demonstrate any therapeutic benefit over a placebo. In the largest of these studies and one of the highest in methodologic quality, no benefit of evening primrose oil could be demonstrated.[32] Similarly, one study of 140 people, including 69 children, showed few beneficial effects of borage oil for AD.[33]

Dietary enrichment with "fish oil" supplements providing EPA and DHA or simply eating more fatty fish (e.g., mackerel, herring, salmon) results in significant incorporation of omega-3 fatty acids into the membrane phospholipid pools. Flaxseed oil, which contains alpha-linolenic acid, the precursor omega-3 fatty acid, may benefit patients with AD. However, because the degree of clinical improvement correlates with the increase in concentration of DHA in serum phospholipids, and fish oils tend to be more effective in raising DHA levels than flaxseed oil, supplementation with EPA/DHA or increasing the consumption of cold-water fish is likely to produce better overall results in AD than flaxseed oil.[34]

Epidemiologic studies have found protective associations between fish intake in pregnancy, lactation, infancy, and childhood and atopic outcomes. Similar studies of fish oil supplements have also found protective and therapeutic effects.[35]

Vitamin E

One single-blind analysis evaluated 96 patients given either 400 international units of vitamin E or a placebo daily for 8 months. Significant improvement was reported in approximately 60% of the treatment group (compared with 2% among the placebo group), with significant reductions in serum IgE levels.[36]

Botanical Medicines

The use of botanical medicines in AD can be generally divided into two categories: internal and external. Licorice *(Glycyrrhiza glabra)* appears to be useful in either application. Internally, licorice preparations can exert significant antiinflammatory and antiallergic effects (see Chapter 96). These benefits are perhaps best exemplified in several double-blind studies featuring a licorice-containing Chinese herbal formula.[37] In addition to licorice, the formula contained the following:

- *Ledebouriealla seseloides*
- *Potentilla chinensis*
- *Clematis chinensis*
- *Clematis armandi*
- *Rehmania glutinosa*
- *Paeonia lactiflora*

- *Lophatherum gracile*
- *Dictamnus dasycarpus*
- *Tribulus terrestris*
- *Schizonepeta tenuifolia*

Interest in this formula by a group of researchers began after a patient with AD experienced tremendous improvement after taking a decoction prescribed by a Chinese doctor.

Several double-blind studies have confirmed this benefit. In one study, 40 adult patients with long-standing, refractory, widespread AD were randomized to receive 2 months' treatment of either the active formula or a placebo decoction, followed by a crossover to the other treatment after a 4-week washout period.[38] The treatment group demonstrated significant superiority over the placebo in clinical evaluation. In addition, of the 31 patients completing the study, 20 preferred the active formula, whereas only 4 preferred the placebo. There was also a subjective improvement in itching and sleep during the active treatment phase. No side effects were reported, although many complained about the poor palatability of the decoction.

Similar results were demonstrated in a double-blind study in children.[39] These positive preliminary studies will hopefully be followed by more extensive investigations to determine proper dosages and perhaps different forms of administration (e.g., pills, tablets, or capsules vs. decoctions).

Licorice undoubtedly plays a major role in the effectiveness of the Chinese herbal formula. At this time, until the benefits of the other components can be confirmed, it makes the most sense to base the dosage level on the level of delivered licorice.

With regard to using licorice topically, the best results are likely to be obtained by using commercial preparations featuring pure glycyrrhetinic acid. Several studies have shown glycyrrhetinic acid to exert an effect similar to that of topical hydrocortisone in the treatment of eczema, contact and allergic dermatitis, and psoriasis. In one study, 9 of 12 patients with intractable eczema noted marked improvement, and 2 noted mild improvement when an ointment containing glycyrrhetinic acid was applied topically. In another study, 93% of the patients with eczema applying glycyrrhetinic acid demonstrated improvement compared with 83% using cortisone.[40]

Other Therapeutic Considerations

Endocrine Factors

Hypothyroid patients with eczema respond well to thyroid hormone supplementation.[41]

Scratching Cessation

Scratching is extremely detrimental in AD because it breaks the skin, which aids bacterial ingress, and promotes barrier dysfunction and lichenification. Factors that limit itching therefore promote healing and prevent recurrence. Some behavior modification techniques have proved valuable in reducing the exacerbation of AD symptoms caused by scratching.[10]

Wet wraps are an effective barrier to scratching while also increasing hydration as well as penetration of medication and emollients and promoting more restful sleep and using them is simple. After applying medication and emollient, the affected areas are wrapped in warm, wet gauze or, as an alternative, 100% cotton socks with the toe portion cut off. Apply a dry layer over the wet layer, and leave it on overnight for 5 to 14 days.

Psychological Approach

Emotional tension can provoke and aggravate itching in patients with AD, and, according to a number of studies, AD patients show higher levels of anxiety, hostility, and neurosis than matched controls.[42] Studies employing psychotherapeutics have shown promising results, with one study showing reductions in the use of corticosteroids for up to 2 years.[10]

ENVIRONMENTAL CONSIDERATIONS

Dust Mite Exposure

In patients with dust mite sensitization and eczema, sublingual immunotherapy has shown benefit.[43] Paradoxically, lower levels of eczema have been found in children with higher levels of dust mite exposure, so that reducing house dust in early infancy could increase the risk of AD.[44]

Microwave Exposure

One fascinating study of cell phone use continuously for an hour showed significant increases in allergic response to dust and pollen in adults with eczema.[45] Microwave radiation exposure also increased plasma levels of substance P and vasoactive intestinal peptide in patients with AD. This study raises the concern that microwave radiation emitted from cell phones may actually increase sensitivity to specific allergens in some patients.

THERAPEUTIC APPROACH

Effective management requires relief from and prevention of itching while the underlying abnormalities are being treated. Barrier dysfunction must be addressed. Food allergens must be detected and controlled, pthalates should be avoided and detoxification carried out, and the presence of *H. pylori* should be determined and treated.

Diet

The patient should begin a 4-day rotation diet and eliminate all major allergens (milk, eggs, and peanuts account for the offending food in approximately 81% of cases). As the patient improves, allergens can slowly be reintroduced and a stringent rotation diet can be modified. Cold water fish such as wild salmon, mackerel, herring, sardine, and halibut should be included and other animal products should be limited.

Supplements

- High potency multiple vitamin and mineral formula
- Vitamin E: 400 international units daily (mixed tocopherols)
- Fish oil: 1000 to 3000 mg EPA+DHA daily
- Flaxseed oil: 1 tbsp daily
- Probiotics: 5 to 10 billion viable *Lactobacillus acidophilus* and *Bifidobacterium bifidum* cells daily

Topical Treatments

- Ceramide-containing emollients can be used to reduce transepidermal water loss: these include CeraVe, Nature Pure's Hippophae-Ceramide Cream, Hippophae Oil (sea buckthorn), ceramides, squalane, olive oil, beeswax, extracts of St. John's wort, gingko biloba, calendula, and chamomile.
- Glycyrrhetinic acid–containing commercial preparations may be helpful. Chamomile, feverfew, oatmeal, and cardiospermum preparations are also popular and their use is supported in the scientific literature.[46,47]

- Atopiclair Rx contains glycyrrhetinic acid, shea butter, bisabolol (chamomile), vitamin E, aloe vera, and grape seed.
- 1% feverfew (parthenolide-free extract: Aveeno Daily Moisturizer, Ultra-Calming)
- Colloidal oatmeal contains starches and beta glucans that have protective and water-holding functions, polyphenols (avenanthramides) are antioxidant, antiinflammatory, and UV absorbers.
- Saponins have a cleansing activity (Aveeno Overnight Itch Relief Cream).[48,49]

Patients should also try to take the following measures:

- Avoid sweating and rough-textured clothing.
- Wash clothing with mild soaps only and rinse thoroughly.
- Avoid exposure to chemical irritants and any other agent that might cause skin irritation.

Psychological Approach

It should be determined whether the patient is experiencing significant levels of anxiety, hostility, or neurosis. If so, he or she may be helped to resolve these problems or referred to a counselor for more extensive assistance.

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CHAPTER 150

Attention Deficit Hyperactivity Disorder

Michael Lyon, BSc, MD, and Michael T. Murray, ND

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DIAGNOSTIC SUMMARY

- A neurobehavioral disorder that begins in early childhood with persistence into adolescence and adulthood
- Typified by one or more symptoms of disabling inattentiveness, hyperactivity, and impulsivity
- Commonly accompanied by comorbid conditions, such as mood disorders or learning disabilities

GENERAL CONSIDERATIONS

Attention deficit hyperactivity disorder (ADHD) is defined by the *Diagnostic and Statistical Manual, Fourth Edition* as a condition characterized by developmentally appropriate inattention and impulsivity with or without hyperactivity. ADHD has three subtypes:

Predominantly hyperactive-impulsive:

- Most symptoms (six or more) are in the hyperactivity-impulsivity categories.
- Fewer than six symptoms of inattention are present, although inattention may still be present to some degree.

Predominantly inattentive:

- The majority of symptoms (six or more) are in the inattention category and fewer than six symptoms of hyperactivity-impulsivity are present, although hyperactivity-impulsivity may still be present to some degree.
- Children with this subtype are less likely to act out or have difficulties getting along with other children. They may sit quietly, but they are not paying attention to what they are doing. Therefore, the child may be overlooked, and parents and teachers may not notice that he or she has ADHD.

Combined hyperactive-impulsive and inattentive:

- Six or more symptoms of inattention and six or more symptoms of hyperactivity-impulsivity are present.

To be diagnosed with ADHD, a child must have symptoms for 6 or more months and to a degree that is greater than other children of the same age.

Children who have symptoms of inattention may:

- Be easily distracted, miss details, forget things, and frequently switch from one activity to another
- Have difficulty focusing on one thing
- Become bored with a task after only a few minutes, unless they are doing something enjoyable
- Have difficulty focusing attention on organizing and completing a task or learning something new
- Have trouble completing or turning in homework assignments, often losing things (e.g., pencils, toys, assignments) needed to complete tasks or activities
- Not seem to listen when spoken to
- Daydream, become easily confused, and move slowly
- Have difficulty processing information as quickly and accurately as others
- Struggle to follow instructions

Children who have symptoms of hyperactivity may:

- Fidget and squirm in their seats
- Talk nonstop
- Dash around, touching or playing with anything and everything in sight

- Have trouble sitting still during dinner, school, and story time
- Be constantly in motion
- Have difficulty doing quiet tasks or activities.

Children who have symptoms of impulsivity may:

- Be very impatient
- Blurt out inappropriate comments, show their emotions without restraint, and act without regard for consequences
- Have difficulty waiting for things they want or waiting their turns in games
- Often interrupt conversations or others' activities.

ADHD characteristics are frequently associated with difficulties in school, both in learning and behavior. If not intensively managed, a child with ADHD will likely experience academic impairment, increased risk of injuries, and problems with self-esteem and socialization. Later in adolescence and adulthood, those with ADHD have a high risk of experiencing depression or anxiety, substance abuse and addictions, traffic accidents, financial problems, vocational underachievement, and social problems. Nevertheless, ADHD is a condition that can be transcended, because many with ADHD have achieved a high level of personal success.

Depending on the region and the investigator, ADHD has been found in 5% to 15% of school-aged children or about 10 million children in the United States. Clinical observation and epidemiologic surveys typically report a greater incidence in boys than girls (approximately 2:1). Over 5.5 million children in the United States take prescription drugs for ADHD every day. Onset is usually by 3 years of age, although the diagnosis is often not made until later when the child is in school.[1]

Etiology

The behavioral and cognitive manifestations of ADHD arise from evidence associating this disorder with diminished function of polysynaptic dopaminergic circuits belonging to executive centers within the brain's prefrontal cortex.[2,3] These executive centers are largely inhibitory in nature and are responsible for impulse control and the ability to maintain sustained attention.[4]

Evidence from studies using magnetic resonance imaging, positron emission tomographic scanning, single-photon emission computed tomographic scan imaging, and electroencephalograms (EEGs) suggested that the brains of those with ADHD exhibit differences both morphologically and metabolically from normal controls, particularly with regard to the prefrontal executive centers.[5,6] Various disturbances in dopaminergic activity within these brain centers have remained the primary molecular defects implicated in ADHD, although other neurotransmitters (particularly norepinephrine) have also been incriminated. Decreased sensitivity of the dopaminergic (D4) receptor and heightened dopamine reuptake by the presynaptic dopamine transporter were both suggested to result in diminished dopaminergic activity within executive centers. However, all of these defects are not necessarily permanent, because as children with ADHD grow up, the brain develops a normal level of dopamine activity, and their anatomic variations lessen. In addition, ADHD symptoms also tend to improve.[7]

Genetic factors may play a significant role in the etiology of ADHD.[8] For example, studies identified differences in genes encoding for both the D2 and the D4 dopamine receptors in ADHD. Other studies associated ADHD with genetic polymorphisms associated with increased activity of the presynaptic dopamine transporter (which would result in increased uptake of dopamine). Other genetic factors contributing to ADHD may include inherited tendencies toward allergic states, decreased immune competence, and various genetic polymorphisms, resulting in diminished capacity to detoxify drugs, heavy metals, and xenobiotics. In other words, although there is little doubt that genetics are a predisposing factor, like most health conditions, environmental and dietary factors appear to play a significant role in how and whether these genetic factors manifest to produce ADHD in an individual.

THERAPEUTIC CONSIDERATIONS

The role of nutritional and environmental factors as the underlying cause of ADHD has been increasingly recognized. Despite significant advances in the use of nutritional therapies for ADHD, the prevailing conventional approach to the treatment of ADHD relies almost entirely on amphetamine drugs for purely symptomatic relief. These drugs, like Ritalin (methylphenidate), Adderall (amphetamine and dextroamphetamine), Concerta (methylphenidate), and Vyvanse (lisdexamfetamine dimesylate), improve ADHD symptoms primarily by potentiating the neurotransmitter dopamine within all brain regions, including those affected in ADHD. These medications reportedly improved behavior and cognitive functioning in approximately 75% of children in formal placebo-controlled trials. However, the success of treatment when studied in actual clinical practice might be significantly lower. Furthermore, follow-up studies failed to demonstrate long-term benefits with these stimulant medications. Additionally, these drugs are associated with a high prevalence of adverse effects, such as decreased appetite, sleep problems, anxiety, and irritability. Some of the long-term effects of these drugs could be extremely detrimental to both brain function and behavior.[9-11]

Nonstimulant drugs like atomoxetine (Strattera) have been promoted as a safe alternative to parents. However, the drug has its own set of problems, including studies that showed that children and teenagers who took atomoxetine were more likely to have suicidal thoughts than children and teenagers with ADHD who did not take it.[12]

The bottom line is that every effort should be made to treat ADHD without the long-term reliance on medications.

One of the primary goals in many cases of ADHD treatment is to enhance cognitive function. Perhaps up to 50% of people with ADHD have definable learning disabilities, and most have measurable cognitive disturbances. Particularly disabling is the diminishment in nonverbal working memory exhibited by most ADHD patients.[13,14] This feature of ADHD results in a diminished sense of time, as well as a decreased ability to hold events or tasks in the mind. Tardiness, missed appointments, procrastination, poor task planning, and failure to meet deadlines are all examples of how diminished working memory can result in serious consequences, particularly in adulthood.

ENVIRONMENTAL NEUROTOXINS

Environmental factors that contribute to the development of ADHD may begin at or even before conception. Maternal-to-fetal transport of various neurotoxins can occur readily during pregnancy. A woman who has an ongoing exposure to or a significant body burden of neurotoxic substances (e.g., heavy metals like lead and mercury, solvents, pesticides, polychlorinated biphenyls [PCBs], alcohol, or other drugs of abuse) may herself exhibit features consistent with ADHD and give birth to a child who presents with symptoms of ADHD. In such cases, it might be assumed that ADHD is inherited when it is actually acquired. Children remain susceptible to neurotoxins after birth, and some

of these agents have been shown to be common among children in North America.[15,16]

Maternal tobacco and drug use has been associated with a higher risk of ADHD.[17-19] One study suggested that up to 25% of all behavioral disorders in children can be attributed to exposure to cigarette smoking during pregnancy.[17] In addition, long-term, low-level lead intoxication in North American children was reported to exist in an alarmingly high incidence.[16,20]

The Centers for Disease Control and Prevention estimated that about 2% of American children younger than age 6 currently meet the criteria for lead toxicity at a level that has been associated with cognitive deficits and behavioral disturbances (more than 10 mg/dL whole blood lead).[20] Low-level lead intoxication has also been associated with addictive behaviors and impulsivity, suggesting neurologic changes consistent with the reward deficiency syndrome, as described earlier.[21] In keeping with these data, pilot studies demonstrated improvement in ADHD behaviors in some children with moderate elevations in blood lead levels who were treated with intravenous ethylenediaminetetraacetic acid chelation.[22]

In addition to lead, other heavy metals, such as mercury, cadmium, and aluminum, as well as pesticides and PCBs, are nearly ubiquitous contaminants arising from dental amalgams, food, air, and drinking water, and these agents may act synergistically to impair neurologic function and development in susceptible children. The Consumer's Union of the United States recently conducted the largest study to date looking at the level of human exposure to a wide range of pesticides in the U.S. food supply. In this startling report, it was demonstrated that human exposure to pesticides is far greater than ever previously estimated, and that children are at particularly high risk for neurotoxic effects from regular inadvertent pesticide exposure from common foods.[23]



FOOD ADDITIVES, SUGAR, AND THE FEINGOLD HYPOTHESIS

The hypothesis that food additives can cause hyperactivity in children stemmed from the research of Benjamin Feingold, MD, and is commonly referred to as the "Feingold Hypothesis." According to Feingold, many hyperactive children, perhaps 40% to 50%, are sensitive to artificial food colors, flavors, and preservatives.[24]

Feingold's claims were based on his experience with over 1200 cases in which food additives were linked to learning and behavior disorders. Since Feingold's presentation to the American Medical Association in 1973, the role of food additives as a contributing cause of hyperactivity has been hotly debated in the scientific literature. In actuality, however, researchers focused on only 10 food dyes versus the 3000 food additives with which Feingold was concerned.

At first glance, it appears that the majority of the double-blind studies designed to test the hypothesis showed essentially negative results. However, upon closer examination of these studies and further investigation into the literature, it becomes evident that food additives do play a major role in hyperactivity.[25-27] Overwhelming evidence was produced in several of these studies.

In the most recent study, 153 3-year-old and 144 8- to 9-year-old children from the general population (in other words, the study was not conducted on children with the specific diagnosis of ADHD) were challenged with either a drink that contained sodium benzoate and an artificial food coloring mix or a placebo mix. The main outcome measure was a global hyperactivity aggregate, based on observed behaviors and ratings by teachers and parents, plus, for the 8- to 9-year-old children, a computerized test of attention. The results showed that the children given the artificial food coloring agents definitely had a statistically significant adverse reaction on hyperactivity and behavior. The results were so clear that the authors concluded that "Artificial colours or a sodium benzoate preservative (or both) in the diet result in increased hyperactivity in 3-year-old and 8/9-year-old children in the general population."[28]

It is interesting to note that, although the U.S. studies were largely negative, the reports from the United Kingdom, Australia, and Canada were more supportive. Feingold contended that there is a conflict of interest on the part of the Nutrition Foundation, an organization supported by the major food manufacturers—Coca Cola, Nabisco, General Foods, and so forth. It appears significant that the Nutrition Foundation financed most of the negative studies. The conflict of interest arises because these companies would suffer economically if food additives were found to be harmful. Other countries have significantly restricted the use of artificial food additives because of the possible harmful effects.

In looking at all of the data on the role of food additives in ADHD, the following conclusions can be made: virtually every study (both negative and positive) demonstrated that some hyperactive children consistently react with behavioral problems when challenged by specific food additives. Critics of the hypothesis ignore the significance of the clear (reproducible under double-blind conditions) individual results. The bottom line is that some children definitely react quite strongly to food additives, warranting the exclusion of these compounds for at least 10 days to judge their significance in all cases of ADHD.

In addition to eliminating food additives, there appears to be an interrelationship between sugar consumption and artificial food dyes. One study demonstrated that destructive-aggressive and restless behavior significantly correlated with the amount of sugar consumed.[29] The higher the sugar intake, the worse the behavior. In another study, researchers performed 5-hour oral glucose tolerance tests on 261 hyperactive children, with the result that 74% displayed abnormal glucose tolerance or hypoglycemia.[30]

Essential Fatty Acids

Numerous studies have shown that children with ADHD have a measurable reduction in tissue levels of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) compared with age-matched controls. Omega-3 (EPA+DHA) supplementation in ADHD has been studied extensively and is considered a sensible intervention even by many mainstream physicians. Of particular importance is the recognition that omega-3 fatty acid supplementation improves many symptoms of ADHD, including impulsive-oppositional behavior, a symptom not typically helped by the pharmaceutical treatment of ADHD.[31]

Because these omega-3 fatty acids are critical in the structure and function of brain cells, it is thought that low levels play a key role in ADHD. The nerve endings in the areas of the brain affected in ADHD should be rich in DHA, because they are highly fluid and should be composed of approximately 80% DHA. DHA deficiency has also been shown to result in increased permeability of the blood–brain barrier in animal studies, and is thought to play a critical role in protecting the brain from an influx of neurotoxic compounds.[32,33]

Human breast milk is also rich in DHA, and several studies suggested that children who are formula fed are at twice the risk of developing ADHD as those who are breastfed.[34] The role of DHA in brain development, intelligence, and possible protection against

ADHD finally led to its inclusion in many infant formulas and other foods.

Individual Nutrients and Attention Deficit Hyperactivity Disorder

Beside fatty acids, inadequate provision of other nutrients during fetal development and early childhood may also play a significant role in the development of ADHD as well as its treatment.[35,36] In addition, children with ADHD often show multiple nutrient deficiencies, highlighting the importance of broad-spectrum nutritional support. In particular, the following minerals are critical supplements in the management of ADHD.

Magnesium: Magnesium levels in serum, red blood cells, and hair were all shown to be low in the majority of children with ADHD.[37] These children also demonstrated improved behavior when administered magnesium supplements.[38]

Zinc: Both hair and serum zinc levels were shown to frequently accompany ADHD.[39] Those children with low serum zinc were also more frequently found to have lower free fatty acid levels, suggesting that abnormalities in fatty acid metabolism may, at least in part, result from zinc deficiency.[40] It was also shown that lower hair zinc levels correlated with a poorer response to treatment with amphetamines. Several clinical trials demonstrated positive effects of zinc supplementation in hyperactive children.[41,42]

Iron: Anemia from iron deficiency is estimated to affect approximately 20% of infants, and many more are thought to have milder iron deficiencies without anemia, leaving them at risk for impairment of brain development.[43,44] Iron deficiency was found to be even much more common in children with ADHD. One study demonstrated that iron supplementation in nonanemic children with ADHD resulted in diminished ADHD symptoms within 30 days.[45] A more recent study demonstrated improvement in ADHD symptoms in children with ADHD and low iron stores.[46]

Food Allergy

There is a very strong relationship between allergies and ADHD, including food allergies.[47-51] In one study, demonstrable brainwave EEG changes occurred immediately after ingestion of a previously identified food allergy.[51] Food allergies and other allergic disorders were also associated with a higher incidence of recurrent ear infections (otitis media).[52] In turn, recurrent otitis media were associated with an increased risk of ADHD.[53] Both food allergy and ADHD were associated with sleep disturbances, which may, in turn, contribute to a worsening of ADHD symptoms. Heavy snoring and sleep apnea are particularly prevalent in allergic children and may significantly contribute to ADHD symptoms.[54,55] Studies demonstrated improved sleep in children with ADHD during a low-allergy potential (oligoantigenic) diet. Food allergy elimination or desensitization can be as effective as drug therapy in reducing ADHD symptoms.[56-60]

Obstructive Sleep Apnea

It has been repeatedly demonstrated that attentional deficits are exceedingly common (95%) in both children and adults with obstructive sleep apnea (OSA).[61] Likewise, OSA is found in up to 30% of children diagnosed with ADHD, and this may be central to the etiology of their attentional problems. In children, chronic nasal or tonsillar/pharyngeal congestion is the most common etiologic factor leading to OSA, although childhood obesity is also becoming a leading cause. OSA should be carefully considered in all children with ADHD, and health care providers should be familiar with the signs and symptoms suggestive of OSA as well as the local resources available for diagnosis and treatment. Children and parents will usually be unaware of the presence of OSA. However, clues such as nocturnal mouth breathing, snoring, enuresis, daytime urinary incontinence, and daytime drowsiness should strongly suggest a need to rule out OSA, usually by referring the patient for nocturnal oximetry testing or polysomnography. Because questionnaires and physical examination are relatively insensitive to pick up OSA in children, a high index of suspicion is essential. OSA results in severe sleep fragmentation and frequent hypoxic episodes, which, in turn, reduces a child's intellectual capacity, reduces attentional performance, and diminishes their quality of life. Children with sleep disordered breathing should be treated. Efforts should be made to reduce nasal congestion and decrease recurrent upper respiratory infections. However, in those children with OSA who do not clearly respond to conservative measures, tonsilloadenoidectomy has been proved to have a substantial and sustainable benefit (to ADHD symptoms and comorbidities). Parents need to be made aware of the substantial risks of untreated OSA versus the risks and/or benefits of this surgery.[62]

Dysbiosis, Gastrointestinal Permeability, and Intestinal Parasites

Probiotic supplementation with *Bifidobacteria* and *Lactobacilli* may be helpful in the treatment of ADHD. These organisms function as part of the first line of defense in gut immunity and have been shown to restore the altered gut permeability due to food allergies.[63,64] In addition, a stool analysis to rule out parasitic infection or altered bacterial flora appears advisable due to disturbances in gut mucosal immunity (discussed in the following).

IMMUNE SYSTEM IMPAIRMENT

It has been shown that subtle immune dysfunction may be a prominent problem in ADHD. Both cellular and humoral immunity was shown to be abnormal in children with ADHD compared with age-matched controls.[65] Plasma complement levels were found to be lower in children with ADHD.[66] Immune dysfunction in ADHD may be either directly inherited or it may be a result of nutritional, toxicologic, or atopic factors. ADHD may also be, in part, an autoimmune disorder. Antineural antibodies were found in the blood and cerebrospinal fluid in ADHD.[67,68] Gut mucosal immunity may also be significantly impaired in ADHD, leading to increased susceptibility to gut pathogens and food allergies.

COGNITIVE BEHAVIORAL THERAPIES

All children exhibiting symptoms suggestive of ADHD should undergo thorough neurobehavioral and cognitive assessment. Many of the features often associated with gifted children can be mistaken for symptoms of ADHD. Likewise, children with mood disorders, learning disabilities, and those from abusive environments or who have suffered serious trauma may benefit from specific psychological or cognitive behavioral interventions and may not respond appropriately to ADHD-specific pharmacotherapy. In addition, cognitive behavioral therapies that can be implemented in schools and in the home environment have been shown to be efficacious in the treatment of ADHD.[69]

NEUROFEEDBACK

In neurofeedback (EEG biofeedback) treatment, individuals are provided with real-time feedback about their brainwave activity through electronic instrumentation. This feedback allows the subject to learn self-regulation of brainwave intensity and frequency. Measurements of brain activity in many individuals with ADHD demonstrate cortical slowing and diminished brainwave intensity in the prefrontal region and frontal lobes. Neurofeedback treatment is designed to train individuals to increase the production of brainwave patterns that reduce or eliminate this cortical slowing and thus reduce or eliminate many associated ADHD symptoms. Evidence supporting neurofeedback as an effective treatment in ADHD is accumulating, including studies showing cessation of methylphenidate (Ritalin) in children without loss of treatment effect.[70-74]

Recently, rapid transcranial magnetic stimulation, a treatment used in many centers as a safer alternative to electroconvulsive therapy, has begun to show promise in the treatment of a variety of neuopsychiatric conditions. This treatment may hold promise in the treatment of ADHD, particularly in those children with more severe forms of the disorder, with serious comorbidities, or in those who are resistant to treatment.[75]

BOTANICAL MEDICINES

Procyanidolic Oligomers

Extracts from grape seed skin and the bark of the maritime pine such as Pycnogenol are rich sources of procyanidolic oligomers—one of the most beneficial groups of plant flavonoids. These extracts may prove useful in the treatment of ADHD due to their broad-spectrum antioxidant effects alone, because increased oxidative damage is believed to be a central factor in ADHD.

To date, four studies have been conducted in ADHD with Pycnogenol. In two of the studies, children with ADHD supplemented with Pycnogenol (1 mg/kg body weight per day) showed improved antioxidant status.[76,77] A third study not only confirmed this antioxidant effect, but also showed improvements in hyperactivity.[78] In the most detailed study, 61 children with ADHD supplemented with 1 mg/kg/day Pycnogenol or placebo over 4 weeks showed that 1-month Pycnogenol administration caused a significant reduction of hyperactivity and improved attention and visual-motor coordination and concentration of children with ADHD.[79] No positive effects were found in the placebo group. These results point to an option to use grape seed or pine bark extract as a nutritional adjunct in ADHD.

Ginkgo biloba Extract

Two pilot studies, one in children (in combination with American ginseng) and the other in adults, showed some beneficial effects attributed to supplementation with *Gingko biloba* extract.[80,81] Specifically, these studies showed improvements in inattentiveness, hyperactivity, and socialization.

L-Theanine

L-theanine, an amino acid found in green tea, shows promise in improving sleep quality in children with ADHD. This amino acid is known to reduce anxiety, increase concentration, improve sleep quality, and stabilize mood without sedation.[82,83] It also improves cerebral dopaminergic activity. In a recently completed double-blind, placebo-controlled trial on L-theanine in ADHD, 90 boys with ADHD were found to have significant improvements in sleep quality as measured by nocturnal actigraphy with 400 mg L-theanine a day.[84]

THERAPEUTIC APPROACH

A plethora of alternative and complementary therapies have been offered for the treatment of ADHD in children and adults. Some have good evidence for safety and efficacy, whereas the evidence for others is still lacking. A reasonable approach with a high probability of success will be multimodal and will address as many contributing factors as are practical. A basic workup ruling out common disorders that may manifest as ADHD is prudent, because these may require specific treatments, and delay of treatment may be harmful. Celiac disease, depression, lead poisoning, sleep apnea, and visual or auditory problems are some of the problems that should be included in the differential diagnosis. Other contributory factors, such as increased intestinal permeability; food allergies or intolerances; and iron, magnesium, zinc, and omega-3 fatty acid deficiencies, may be assessed through laboratory testing or simply treated empirically if financial constraints prevent ordering noninsured tests.

In general a stepwise, rational approach is often successful.

Step 1

Assisting parents in eliminating junk foods, fast foods, and food additives from the diet (especially sugary foods and beverages, white flour products, and deep-fried foods) while increasing the quantity of whole foods is an important first step. If a child consumes more whole grains, fruits, vegetables, clean protein sources, pure water, and fiber, health benefits are inevitable. In some cases, converting to a whole foods–based diet can result in marked improvements in behavior and cognitive performance.

Step 2

Nutritional supplementation is often helpful and usually includes a pharmaceutic grade fish oil supplement or DHA/EPA concentrate; high-potency multivitamin/trace mineral supplement; additional calcium, magnesium, and zinc (additional iron is also beneficial in children and adolescents if anemia or low iron stores are documented); and potent antioxidant support (e.g., pine bark [Pycnogenol] or grape seed extract). Although there is evidence to support each of these interventions, when combined, as well as in the context of a whole-foods diet, the results are usually significant.

Step 3

Gastrointestinal rehabilitation is a concept familiar to practitioners of natural medicine. This involves therapeutic steps to reduce intestinal permeability, improve nutrient absorption, and increase immune response to gut pathogens while diminishing hypersensitivities. A useful approach follows the mnemonic "ANT PIE" (Abstain, Nourish, Toxins/detoxification, Probiotics, Identify, Eliminate).

Abstain from junk foods, deep-fried foods, sugary drinks, and other foods that harm or irritate the gut, as well as unnecessary drugs or excessive alcohol.

Nourish the digestive tract with nutrients that support gut healing. Functional foods that combine low allergy potential protein

and a number of nutrients helpful for gastrointestinal healing are readily available.

Toxins/detoxification refers to the avoidance of pesticides by eating organic foods and consuming nutrients that improve the efficiency of detoxification processes such as L-glutamine, *N*-acetylcysteine, dietary fiber, and cruciferous vegetables. Regular exercise and stress reduction are also important parts of this step.

Probiotics are therapeutic bacteria (and some yeasts) that may improve the gastrointestinal microecology, improve immune response toward gut pathogens, reduce immune hypersensitivities, and stimulate gut repair.

Identify allergenic or intolerant foods and gut pathogens. Food allergies (type I or immediate hypersensitivity food reactions) can be identified by skin-prick testing, radioallergosorbent testing, or enzyme-linked immunosorbent assay testing for immunoglobulin-E antifood antibodies. Patients with evidence of type I hypersensitivity food allergies (e.g., postprandial swelling of the lips, urticaria, wheezing) should be referred to an allergist for definitive testing, because serious anaphylaxis could occur without proper avoidance. Delayed hypersensitivity reactions (usually type III mediated) are best identified with a properly conducted elimination test diet, followed by carefully observed reintroductions of individual food items eliminated in the test diet. Immunoglobulin-G antifood antibodies may also be tested but only before any dietary manipulation occurs.

Intestinal parasites, yeast, and pathogenic bacteria may also be identified by stool testing, *Candida* and *Helicobacter pylori* serology, breath testing, and urinary organic acids.

Eliminate foods found to be allergic or intolerant with elimination test diet or laboratory testing. Gut pathogens, parasites, and *Candida* overgrowth may be treated.

This approach to gut rehabilitation follows a rational order that provides for optimal physiologic responses to treatment. The results of following this program to its completion in children with ADHD can be quite dramatic.

Step 4

Nutraceuticals can often provide additional improvements in behavior and cognition and may be a necessary intervention earlier on if parents are pressured to submit their child to drug intervention. For example, *Ginkgo biloba* extract and/or L-theanine may provide some benefit.

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CHAPTER 151

Bacterial Sinusitis

Michael T. Murray, ND

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DIAGNOSTIC SUMMARY

- History of acute viral respiratory infection, dental infection, or nasal allergy
- Nasal congestion and purulent discharge
- Fever, chills, and frontal headache
- Pain, tenderness, redness, and swelling over the involved sinus
- Transillumination showing opaque sinus
- Chronic infection often producing no symptoms other than mild postnasal discharge, a musty odor, or a nonproductive cough

GENERAL CONSIDERATIONS

The most common predisposing factor in acute bacterial sinusitis is viral upper respiratory infection (the common cold). Allergic rhinitis and other factors that interfere with normal protective mechanisms may precede the viral infection and therefore are the more likely predisposing factors. Any factor that induces edema of the mucous membranes may result in obstruction of meatal drainage. The transudate that is produced serves as a suitable medium for bacterial overgrowth, with streptococci, pneumococci, staphylococci, and *Haemophilus influenzae* being most commonly cultured.

In chronic bacterial sinusitis an allergic background is commonly present, and in 25% of cases of chronic maxillary sinusitis there is an underlying dental infection. Although vasoconstrictors and antihistamines cause transient relief, their chronic use is contraindicated because there is usually a reflex reaction following continual administration.

THERAPEUTIC CONSIDERATIONS

Antibiotics

Although antibiotic therapy is the dominant treatment of acute and chronic bacterial sinusitis, it is of limited value.[1] A detailed analysis to determine the evidence for the effectiveness of antibiotic treatment in acute maxillary sinusitis in adults by assessing the methodologic quality of placebo-controlled double-blind randomized trials concluded: "The effectiveness of antibiotic treatment in acute maxillary sinusitis in a general practice population is not based sufficiently on evidence."[2] Nonetheless, in severe or unresponsive cases, antibiotics may be appropriate. In a Cochrane review it was shown that, although 80% of participants treated without antibiotics improve within 2 weeks, antibiotics have a small treatment effect in patients with uncomplicated acute sinusitis in a primary care setting with symptoms for more than 7 days. Newer, more potent antibiotics (e.g., lactam antibiotics) appear to be more effective than penicillin, amoxicillin, and other less potent antibiotics.[3]

In children, there is even less evidence that antimicrobial therapy is of significant benefit.[4] Overuse of antibiotics in children with sinusitis or otitis media is a growing concern, as it is leading to antibiotic-resistant strains of bacterial pathogens.

In chronic sinusitis, antibiotics are also of little or no benefit.[5] Clearly, the most rational approach seems to be to address the underlying cause of chronic sinusitis (e.g., respiratory or food allergens) along with providing supportive therapy (e.g., saline nasal sprays, immune-enhancing herbs, natural decongestants).

Allergy

Studies indicate that most patients with chronic sinusitis, perhaps as many as 84%, have allergies.[6,7] Patients with chronic sinusitis should be aggressively screened for environmental and food allergies. Environmental control requires the elimination of dust mites (warm-water washing at a temperature of least 58°C), use of air-filtering vacuum cleaners, installation of an air cleaner with a high-efficiency particulate air filter, and whatever methods are necessary to maintain the humidity under 50%. Some particularly sensitive patients may need to have all pets removed, along with carpeting and featherbedding.[8]

Mucolytics

Airway mucociliary clearance depends on the properties and volume of secreted mucus, ciliary function, and mucociliary interactions. In chronic sinusitis, mucus viscoelasticity is higher than the optimal values for mucociliary clearance. Mucolytic agents such as *N*-acetylcysteine (NAC) and proteolytic enzymes can reduce viscoelasticity and promote mucociliary clearance.[9]

NAC is the most commonly used mucolytic agent. The free sulfhydryl group of NAC interacts with the disulfide bonds of mucus glycoproteins, thereby breaking the protein network into less viscous strands. Although NAC is often used as a 10% solution by dilution with saline, sodium bicarbonate, and sterile water, it can also be used orally for sinusitis, as it has been shown to be effective for chronic bronchitis.[10]

Proteolytic enzymes may break down complex proteins at the site of inflammation, exert some antimicrobial effects, or act directly on the naked peptide region of mucus glycoproteins. Trypsin, chymotrypsin, *Serratia* peptidase, bromelain, and streptokinase are the proteolytic enzymes that can break down mucus glycoproteins and other proteins when they are administered topically. When *Serratia* peptidase was given at a dose of 30 mg/day for 4 weeks to patients with chronic sinusitis, it significantly reduced the viscosity but not the elasticity of nasal mucus.[11]

It has been reported that the ratio of the viscosity to the elasticity is an important determinant of mucociliary transport. When *Serratia* peptidase was administered at the same dose to patients with chronic bronchitis, it significantly increased mucociliary clearance.[12] A multicenter double-blind placebo-controlled study of 193 subjects suffering from various acute or chronic ear, nose, or throat disorders, including sinusitis, demonstrated a greater efficacy and rapid action of the peptidase against all the symptoms examined.[13] Orally administered bromelain has also shown benefit in the treatment of chronic sinusitis.[14]

Pelargonium Sidoides (South African Geranium)

Extracts from the rhizomes and tubers of *P. sidoides* have been shown to exert a number of effects beneficial in upper respiratory tract infections, particularly acute bronchitis, an indication for which it is an approved drug in Germany (see Chapter 153, "Bronchitis and Pneumonia"). *P. sidoides* has demonsrated immune-enhancing effects as well as antibacterial and antiviral effects and the ability to prevent adhesion of bacteria to epithelial cells.[15] In one double-blind placebo-controlled trial, 103 patients with acute rhinosinusitis of presumably bacterial origin were given an ethanolic extract of *P. sidoides* (EPs 7630) or matching placebo at a dose of 3 mL three times daily for a maximum 22 days.[16] The mean decrease in the Sinusitis Severity Score was 5.5 points in the EPs 7630 group compared with 2.5 points in the placebo group, a difference of 3.0 points. This result was confirmed by all secondary parameters, indicating a more favorable course and a faster recovery in the EPs 7630 group.

THERAPEUTIC APPROACH

In acute sinusitis, the immediate therapeutic goals are to reestablish drainage and clear the acute infection. Various measures can be used: local application of heat, local use of volatile oils and botanicals with antibacterial properties, and immune system support (see Chapter 56).

Because chronic bacterial sinusitis is often secondary to allergy, long-term control depends on isolation and elimination of the food or airborne allergens and correction of the underlying problem that allowed the allergy to develop. During the acute phase, elimination of common food allergens (milk, wheat, eggs, citrus, corn, and peanuts) is indicated until a more definitive diagnosis can be made.

Local applications of heat have been shown to be effective in alleviating both the short- and long-term symptoms of allergic rhinitis.[17]

Supplements

- Vitamin C: 500 mg three times a day
- Bioflavonoids: 1000 mg/day
- Vitamin A: 5000 IU/day or beta-carotene: 25,000 IU/day
- NAC: 200 mg three times a day

Serratia Peptidase or Bromelain

- Bromelain (1200 to 1800 MCU): 250 mg three times a day
- *Serratia* peptidase (enteric coated): 50 mg three times a day between meals

Botanicals

Echinacea sp

- Dried root (or as tea): 0.5 to 1 g
- Freeze-dried plant: 325 to 650 mg
- Juice of aerial portion of *Echinacea purpurea* stabilized in 22% ethanol: 2 to 3 mL
- Tincture (1:5): 2 to 4 mL (1/2 to 1 Tsp)
- Fluid extract (1:1): 2 to 4 mL (1/2 to 1 Tsp)
- Solid (dry powdered) extract (6.5:1 or 3.5% echinacoside): 150 to 300 mg

Hydrastis Canadensis

The dosage should be based on berberine content. As there is a wide range of quality in goldenseal preparations, standardized extracts are recommended. Three-times-a-day dosages follow:

- Dried root or as infusion (tea): 2 to 4 g
- Tincture (1:5): 6 to 12 mL (1.5 to 3 tsp)
- Fluid extract (1:1): 2 to 4 mL (0.5 to 1 tsp)
- Solid (powdered dry) extract (4:1 or 8% to 12% alkaloid content): 250 to 500 mg

Pelargonium Sidoides

Dosage recommendations for EPs 7630 or equivalent preparation:

Adults: 3 mL three times a day or two 20-mg tablets three times a day for up to 14 days

Children: ages 7 to 12 years, 30 drops (1.5 mL) three times a day; age 6 years or less, 10 drops (0.5 mL) three times a day

Local Treatment

- Intranasal douche with saline water or *Hydrastis* tea
- Swabbing of passages with oil of bitter orange
- Menthol or eucalyptus packs over sinuses (care should be taken to avoid irritation)

Physical Therapy

- Local applications of hot packs
- Diathermy: 30 minutes (discontinue if pain increases without drainage)

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*For references on botanical recommendations, see Chapters 86 and 97.

CHAPTER 152

Benign Prostatic Hyperplasia

Geovanni Espinosa, ND, LAc, and Michael T. Murray, ND

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DIAGNOSTIC SUMMARY

- Symptoms of bladder outlet obstruction (progressive urinary frequency, urgency and nocturia, hesitancy, and intermittency with reduced force and caliber of urine)
- Enlarged nontender prostate
- Uremia with prolonged obstruction

GENERAL CONSIDERATIONS

Benign prostatic hyperplasia (BPH) is the fourth most common diagnosis in older men.[1] More than 50% of men over age 50 years are affected and 90% of men will have an enlarged prostate by the time they are 80 years old. Progression to urinary retention may occur, with an accompanying risk of recurrent urinary tract infections, bladder calculi, and occasionally renal insufficiency. Management options for BPH include exercise, low-fat diet, supplementary medications, minimally invasive therapies, and prostate surgery.

The most common symptoms of BPH are lower urinary tract symptoms (LUTS), such as frequent urination, urgency to urinate, nocturia, weak urinary stream, incomplete bladder emptying, straining to void, and an intermittent stream. A patient may have multiple symptoms but be bothered primarily by one. Prostate cancer, bladder cancer, overactive bladder, urinary tract infections, prostatitis, urethral stricture, and bladder stones can also cause LUTS and must be ruled out before a diagnosis of BPH is made.[2]

Abdominal obesity and genetic factors appear to be the main risk factors for the development of BPH, which appears to run in families. If one or more first-degree relatives are affected, an individual is at greater risk of developing this disorder.[1] Waist size, body mass index, and increases in body weight appear to increase the volume of the prostate gland.[3]

Hormones and Benign Prostatic Hyperplasia

The role of androgens in the development of prostate enlargement is evident, owing to the fact that BPH does not develop in men who have been castrated before puberty and therefore have greatly depleted levels of circulating androgens. Furthermore, in men with BPH, medical or surgical castration has been shown to lead to a reduction in prostate volume.[4]

For testosterone to have any effect on the prostate, it must be converted to dihydrotestosterone (DHT) by the enzyme 5-alpha reductase.[5] DHT has twice as great an effect on the prostate as testosterone.[6]

Although testosterone levels decline with age, DHT concentrations remain similar to those in young men in the prostate even if serum levels are low.[4] Circulating DHT, by virtue of its low serum plasma concentration and tight binding to plasma proteins, is of diminished importance as a circulating androgen affecting prostate growth.[7]

Most of the research on BPH and its pharmaceutical treatment has focused on modulating DHT by inhibiting the enzyme 5-alpha reductase. Other intriguing and accumulating research has illustrated the effects of estrogen or, more importantly the estrogen:testosterone ratio in aging men and it effects on BPH.

In animal models, estrogen has shown molecular changes in the prostate of the aging dog.[8] The evidence is less clear in humans. Estrogens in the male are

predominantly the products of peripheral aromatization of testicular and adrenal androgens.[9] Although the testicular and adrenal production of androgens declines with aging, levels of total plasma estradiol do not decline. In fact, estradiol remains relatively constant or even increases with age in men. This increase has been attributed to increased aromatase activity in the aging male, who often also has an increased accumulation of body fat. Fat cells contain aromatase, an enzyme that converts certain androgens to estrogen. The resulting disproportion in the estrogen:testosterone ratio may increase up to 40% in some men.[10]

By limiting aromatase or inhibiting the binding of estrogen to prostate cells, it may be possible to reduce BPH or slow its progression. More research is needed.

DIAGNOSTIC CONSIDERATIONS

International Prostate Symptom Score

A useful subjective assessment tool for BPH patients is the International Prostate Symptom Score (IPSS). The IPSS is a modification of the American Urological Association (AUA) Symptom Index adding a single question assessing the quality of life or bother score based on the patient's perception of the problem. The IPSS is a questionnaire that assesses the degree of LUTS and the quality of life of patients with BPH.

Patients can fill out the IPSS form before their examinations, but as little as possible interference from the health care provider and personnel is recommended (Figure 152-1). A score of 7 or less is considered mildly symptomatic, 8 to 19 points as moderate, and a score of 20 to 35 points as severely symptomatic. Both the AUA index and IPSS questionnaire—although not specific for BPH, prostate volume, urinary flow rate, postvoid residual volume, or bladder outlet obstruction—have been validated and are sensitive enough to be to be used in evaluating symptoms and selecting treatment.[11]

A good physical examination should include a digital rectal examination (DRE) to determine the approximate consistency and shape of the patient's prostate and abnormalities suggestive of prostate cancer, BPH, or prostatitis. The approximate size of the prostate can be determined with a DRE, however, inadvertent misestimations can be made even by physicians who are highly experienced. Prostate size can be determined most accurately by a transrectal ultrasound scan.

Urine and Blood Tests

Patients with suspected BPH should undergo dipstick urinalysis testing or microscopic urinalysis to screen for infection and hematuria, proteinuria, pyuria, glycosuria, and ketonuria. If a urine dipstick is positive, a urine culture may be necessary to determine whether the patient's LUTS is independent of BPH.

Prostate-Specific Antigen

Because the symptoms of BPH and prostate cancer can be similar, measurement of prostate-specific antigen (PSA) is often used to differentiate BPH from prostate cancer. Recent studies show there are high levels of false-positive and false-negative PSA test results; therefore, the benefits and risks of such test should be discussed with the patient. PSA testing is one of the tools used to assess for prostate cancer and its severity, along with imaging, PSA density, staging, and Gleason score. This remains a controversial test, however, owing to its lack of specificity, which can lead to the overdiagnosis and overtreatment of indolent prostate cancers.[12,13] One European study showed that it takes 1 of 48 men treated for prostate cancer to be saved from prostate cancer death over a 10-year period.[12]

PSA and BPH

PSA is a glycoprotein secreted by the glands of the prostate; it is released in the serum with disruption of normal prostatic tissue due to prostate cancer, inflammation, BPH, or trauma.

Finasteride (5-mg dose) and dutasteride (0.5-mg dose), both of which are 5-alpha reductase inhibitors used for the treatment of BPH and male-pattern baldness (1-mg dose of finasteride), will lower PSA levels by approximately 50% regardless of the dose.[14] Ejaculation and DRE have been reported to increase PSA levels, but studies have shown the effects to be variable or insignificant.[15,16] Prostate biopsy, however, will usually cause a substantial elevation of PSA levels. Therefore, after biopsy, PSA testing should be postponed for at least 3 to 6 weeks.[17] Although an elevated level indicates prostate cancer in about 90% of cases, it must be kept in mind that midrange elevations in PSA can be caused by BPH and that in some instances there may be prostate cancer without an elevation of PSA levels. One approach to distinguish the two conditions when PSA is elevated is to perform a free-to-total PSA ratio: more free PSA than complexed PSA suggests BPH rather than prostate cancer. A ratio of around 20% or greater for free PSA is considered more likely to represent BPH than cancer.[18]

PSA density (PSAD) can be used to differentiate between prostate cancer and BPH in men with PSAs between 4 and 10 ng/mL and normal DRE results. PSAD should be higher in men with prostate cancer than in those with benign disease, because cancer causes a greater elevation in PSA per prostate volume in comparison with BPH. To determine PSAD, the patient's PSA can be divided by prostate volume (as determined by a transrectal ultrasound examination). Studies show that a PSAD greater than 0.15 may mean a higher risk of prostate cancer. A lower PSAD would likely indicate the patient has BPH. This method should not conclusively determine whether a patient has BPH or prostate cancer, but it can be one piece of the puzzle.[19]

THERAPEUTIC CONSIDERATIONS

Left untreated, BPH eventually obstructs the bladder outlet, leading to the retention of urine and eventual kidney damage. Because this situation is potentially life-threatening, proper surgical treatment is crucial. Surgery may also be indicated in patients who have failed medical therapy or have recurrent infections, hematuria, or renal insufficiency. In the past, medical treatment involved a procedure called transurethral resection of the prostate. Because this surgery is associated with the risk of considerable morbidity (sexual dysfunction, incontinence, and bleeding)[20] and often makes matters worse, it should be avoided unless absolutely necessary. Surgical procedures that use thermal microwave or laser to reduce hyperplastic tissue are also available. Generally, these newer procedures are less expensive than transurethral resection of the prostate and have fewer complications, although subsequent therapies are often required.[21]

Lifestyle/Exercise

There is an inverse association between physical activity[22] and BPH and a positive one between abdominal obesity and BPH.[21]

The ingestion of more calories may encourage abdominal obesity and sympathetic nervous system activity, both of which can increase the risk of BPH. Increased sympathetic activity,

A
B
C

International Prostate Symptom Score (I-PSS)

Patient Name: _____ **Date of birth:** _____ **Date completed** _____

In the past month:	Not at all	Less than 1 in 5 times	Less than half the time	About half the time	More than half the time	Almost always	Your score
1. Incomplete emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	**1 Time**	**2 Times**	**3 Times**	**4 Times**	**5 Times**	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS score							

Score 1–7: *Mild* 8–19: *Moderate* 20–35: *Severe*

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

FIGURE 152-1 From Bope E, Kellerman R, Rkel, R. Conn's current therapy 2011, Saunders 2011. International Prostate Symptom Score (IPSS) questionnaire, available from the urological Sciences Research Foundation at http://www.usrf.org/questionnaires/UA_SymptomScore.html. Accessed September 26, 2011. Used with permission.

which is the "fight or flight" arm of the autonomic nervous system, may cause the prostate's smooth muscle to contract, resulting in a worsening of lower urinary tract symptoms. However, a higher caloric intake does not seem to increase BPH risk when accompanied by increased physical activity.[22]

It is then possible that physical activity may serve a threefold purpose:

1. It may increase blood flow to the area, allowing the body to remove wastes efficiently.
2. It can decrease sympathetic stress responses, thus relaxing prostatic tissue.
3. It can reduce excess abdominal weight, which increases overall lower body pressure, thus relaxing the prostate/rectal region and improving blood flow into and out of the area.

Dietary and Nutritional Factors

Diet appears to play a critical role in the health of the prostate. Diets high in overall fat (not specific to the type of fat) are associated with an increase risk of BPH, as are diets high in red meat (whether conventional meats were used in comparison with the grass-fed kind in unknown.) Conversely, according to a recent

large randomized trial, diets high in protein and vegetables are associated with a decreased risk.[21]

It is particularly important to avoid pesticides, increase fruit consumption,[23] increase the intake of zinc and essential fatty acids, decrease coffee consumption,[24] decrease butter consumption, avoid margarine,[23] and keep cholesterol levels below 200 mg/dL. A moderate intake of alcohol can possibly benefit BPH but make LUTS worse.[25]

High-Protein Diet

Research evaluating protein intake and BPH is mixed. Some evidence shows that a high-protein diet (total calories: 44% protein, 35% carbohydrate, 21% fat) can inhibit 5-alpha reductase, whereas a low-protein diet (10% protein, 70% carbohydrate, and 20% fat) may stimulate the enzyme.[26] On the other hand, an 8-year study of 3523 men with BPH found that total protein intake is positively associated with BPH, with the association being slightly stronger for animal protein intake than vegetable protein.[21] A study of Chinese farmers also revealed a correlation between a higher intake of animal protein and the incidence of BPH (91.1% in those eating diets high in animal protein vs. 11.8% in those not eating animal protein).[27]

A possible theoretical reason why high protein intake may not be helpful relates to a greater osmolar load, which may influence urinary output and thus impose an undue extra burden on an already taxed system.[6] Therefore, we recommend against ingesting excess animal protein as a means to increase total protein intake. Instead, high-quality, plant-derived protein and protein from coldwater fish in moderate amounts is probably a reasonable recommendation until we know more about the relationship between protein intake and BPH.

Zinc

Studies conducted in the 1970s showed that zinc supplementation reduced the size of the prostate and the symptomatology of BPH in the majority of patients.[28] A more recent randomized trial comprising 4770 participants indicates a possible protective role of zinc against BPH. In that investigation, BPH was assessed over 7 years and defined in terms of medical or surgical treatment or repeated elevation (above 14) on the IPSS questionnaire. Diet, alcohol, and the use of supplements were assessed via a food frequency questionnaire. Higher zinc intake was associated with a significantly reduced risk for BPH.[22] The mechanism probably involves zinc's ability to inhibit 5-alpha reductase[29] and/or by its ability to inhibit prolactin.[30] Prolactin has been shown to increase the uptake of testosterone by the prostate, thereby leading to increased levels of DHT by providing additional substrate.[31]

Alcohol

Although only beer raises prolactin levels, higher alcohol intake may be associated with BPH. In a 17-year study of 6581 men in Hawaii, it was noted that an alcohol intake of at least 25 ounces per month was directly correlated with the diagnosis of BPH.[32]

The association was most significant for beer, wine, and sake and less so for distilled spirits. Most other recent studies confirm a protective effect of alcohol with regard to BPH but not LUTS.[22]

Amino Acids

The combination of glycine, alanine, and glutamic acid (in the form of two 6-grain capsules administered three times daily for 2 weeks and one capsule three times daily thereafter) has been shown in several studies to relieve many BPH symptoms. In a controlled study of 45 men, nocturia was relieved or reduced in 95%, urgency reduced in 81%, frequency reduced in 73%, and delayed micturition alleviated in 70%.[33] These results have also been reported in other controlled studies.[34] The mechanism of action is unknown but is likely related to the amino acids acting as inhibitory neurotransmitters and reducing the feeling of a full bladder. In other words, amino acid therapy is only palliative.

Cholesterol

The association with cholesterol, BPH, and LUTS has been mixed. High levels of serum lipids have been associated with cardiovascular disease and include elevated serum LDL cholesterol, decreased serum HDL cholesterol, and increased serum triglycerides. In the case of BPH, however, as described by Parsons, no positive association has been shown for cholesterol.[35]

Beta Sitosterol

Beta sitosterol is one of several plant sterols (cholesterol is the main animal sterol) found in almost all plants. High levels are found in rice bran, wheat germ, corn oil, and soybeans. Peanuts and their products—such as peanut oil, peanut butter, and peanut flour—as well as *Serenoa repens*, avocados, pumpkin seed, *Pygeum africanum*, and cashew fruit. The ability of beta sitosterol and other phytosterols to lower cholesterol has been well documented.[36] Beta sitosterol has also been shown to improve BPH. One double-blind study comprised 200 men receiving beta sitosterol (20 mg) or placebo three times daily.[37] The beta sitosterol group experienced an increase in maximum urinary flow rate from a baseline of 9.9 to 15.2 mL/s and a decrease in mean residual urinary volume of 30.4 from 65.8 mL.

In yet another study, 177 patients with benign prostate enlargement were randomized.[38] Patients received 130 mg of beta sitosterol each day and were monitored for over 6 months. Measurements of the IPSS, urinary flow, and residual urine in the bladder after voiding were recorded.

On average, urinary flow values increased by 4.5 mL/s whereas residual urinary volumes decreased by a substantial 33.5 mL. The IPSS showed a statistically significant improvement.[38]

Vitamin D

Krystal and colleagues showed that vitamin D supplementation was associated with a reduced risk of BPH, but the dosage was imprecise. The association in this 4770-subject trial was observed only among men who used both multivitamins and single vitamin D supplements. There were no associations of supplement use with BPH risk with the exception of a trend toward decreased BPH risk with increased intake of supplemental vitamin D.[22] Although this study lacked data on the frequency, dose, and duration of vitamin D use, the results are intriguing enough to support further research addressing whether high-dose supplementation will have any benefit for BPH. Numerous studies have shown that vitamin D_3 may have protective effects against prostate cancer.[39]

The mechanism of vitamin D's favorable effect on BPH is by attaching this molecule to vitamin D receptors on the prostate and bladder and inhibiting prostate growth, lowering excessive contractility, and reducing inflammation.[40]

Cadmium

Although cadmium is a known antagonist of zinc and increases the activity of 5-alpha reductase, its concentration in the prostate and its effects are unclear. Several studies have produced conflicting results.[41,42]

Botanical Medicines

Botanical medicines in the treatment of BPH has been a popular recommendation in Europe for decades.[43] The chance of clinical success with any of the botanical treatments of BPH appears to be determined by the degree of obstruction, as indicated by the volume of residual urine. For levels less than 50 mL, the results are usually excellent. For levels between 50 and 100 mL, the results are usually quite good. With residual urine levels between 100 and 150 mL, it will be tougher to produce a significant improvement within the customary 4- to 6-week period. If the volume of residual urine is greater than 150 mL, saw palmetto extract and other botanical medicines alone are unlikely to produce any significant improvement.

Serenoa repens (Saw Palmetto)

The liposterolic extract of the fruit of this palm tree (also known as *Sabal serrulata*), native to Florida, has been shown to significantly improve the signs and symptoms of BPH in numerous clinical studies (see Chapter 122). The mechanism of action is related to inhibition of DHT binding to both the cytosolic and nuclear androgen receptors, inhibition of 5-alpha reductase, and interference with intraprostatic estrogen receptors. Owing to these effects, the results of most randomized trials have been excellent. Systematic literature reviews and meta-analyses of clinical trials report excellent results using *Serenoa*, comparing quite favorably with those of finasteride (Proscar) and tamsulosin (Flomax) in terms of efficacy but with a better side-effect profile. It appears that the effect of *Serenoa* extract is most obvious in the early stages of BPH (i.e., in cases of mild to moderate hypertrophy), because the clinical research has clearly shown that roughly 90% of men with mild to moderate BPH experience improvement in symptoms during the first 4 to 6 weeks after starting *Serenoa* extract (320 mg per day of the liposterolic extract). However, it is likely that *Serenoa* extract may show little if any clinical benefit in more advanced cases of BPH. Chapter 122 offers a complete discussion of the pharmacology of *Serenoa*.

Furthermore, although *Serenoa* is often very effective on its own, better results may be achieved by combining *Urtica dioca* root extract (discussed below) with *Serenoa* extract. One double-blind study involving 431 patients found this combination to produce clinical benefit equal to that of finasteride.[44] In a more recent long-term study, the efficacy and tolerability of this combination was investigated in elderly male patients suffering from lower urinary tract symptoms (LUTS) caused by BPH.[45] A total of 257 patients were randomized to treatment with the combination (320 mg of *Serenoa* and 240 mg of *Urtica* extracts per day) or placebo. A 24-week double-blind treatment was followed by an open control period of 24 weeks during which all patients were given the *Serenoa* and *Urtica* combination. Patients treated with the botanical combination exhibited a substantially greater reduction in their total IPSS scores after 24 weeks of double-blind treatment than did patients of the placebo group. This applied to obstructive as well as to irritative symptoms and to patients with moderate symptoms as well as those with severe symptoms at baseline. Patients randomized to placebo showed a marked improvement in LUTS (as measured by the IPSS) after being switched to the botanical combination. Like the extract of *Serenoa, Urtica* extract appears to interact with the binding of DHT to cytosolic and nuclear receptors.[46] In vitro studies also show that lignans found in *Urtica* may modulate hormonal effects owing to their affinity for sex hormone–binding globulin.[45]

Cernilton

Cernilton, an extract of rye-grass flower pollen, has been used to treat prostatitis and BPH in Europe for more than 35 years.[47] It has been shown to be quite effective in several double-blind clinical studies in the treatment of BPH,[48,49] where the overall success rate is about 70%.[50] Patients who respond typically experience less nocturia and diurnal frequency (a reduction of about 70%) as well as significant reductions in residual urine volume.[44] The extract has been shown to exert some antiinflammatory action and to produce a contractile effect on the bladder while simultaneously relaxing the urethra. In addition, Cernilton contains a substance that inhibits the growth of prostate cells.[46]

In one study, the clinical efficacy of Cernilton in the treatment of symptomatic BPH was examined over a 1-year period.[48] Seventy-nine men averaging 68 years of age (range 62 to 89) with a mean baseline prostatic volume of 33.2 cm^2 were given 63 mg Cernilton pollen extract twice daily for 12 weeks. As a result, their average urinary maximum flow rate increased from 5.1 to 6 mL/s. Average flow rate increased from 9.3 to 11 mL/s. Residual urine volume decreased from 54.2 mL to less than 30 mL. Clinical efficacy, based on symptoms, was as follows:

- Urgency or discomfort: improved by 76.9%
- Dysuria: improved by 71.4%
- Nocturia: improved by 56.8%
- Incomplete emptying: improved by 66.2%
- Prolonged voiding: improved by 64.1%
- Delayed voiding: improved by 62.2%
- Intermittency: improved by 60.6%
- Postvoid dribbling: improved by 42.7%

Overall, 85% of the test subjects experienced benefit: 11% reporting "excellent," 39% "good," 35% "satisfactory," and 15% "poor" results.

A summary review of two placebo-controlled studies, two comparative trials (both lasting 12 to 24 weeks), and three double-blind studies of 444 men showed that, although Cernilton did not improve urinary flow rates, residual volume, or prostate size compared with placebo or the comparative study agents, it did improve self-rated urinary symptom scores and reduced nocturia compared with placebo and an amino acid mixture.[46] Clearly, more long-term studies of Cernilton need to be conducted in order to elucidate the terms of its usefulness as an alternative or adjunct to *Serenoa*.

Last, a study by Preuss and associates illustrates the potential value of a combination of nutrients used for BPH. In this randomized trial, 144 subjects were randomized to cernitin, saw palmetto, B sitosterol, vitamin E, or placebo. After 3 months, the combination group had significantly less nocturia, frequency, and overall BPH symptoms without any adverse side effects.[51]

Pygeum africanum

The bark of *P. africanum,* an evergreen tree native to Africa, has historically been used in the treatment of urinary tract disorders. The major active components of the bark are fat-soluble sterols and fatty acids. Virtually all of the research on *Pygeum* has featured a *Pygeum* extract standardized to contain 14% triterpenes, including beta-sitosterol and 0.5% *n*-docosanol. This extract has been extensively studied in both experimental animals and humans in clinical trials (see Chapter 118). A study on rat prostatic cells suggests that the therapeutic effect of *Pygeum* may be due in part to the inhibition of growth factors EGF, bFGF, and IGF-I, which are responsible for prostatic overgrowth.[52]

Numerous clinical trials with more than 600 patients have shown *Pygeum* extract to be effective in reducing the symptoms and clinical

signs of BPH, especially in early cases.[53] However, in a double-blind study that compared *Pygeum* extract with extract of saw palmetto, the latter produced a greater reduction of symptoms and was better tolerated.[54] In addition, the effects on objective parameters, especially urine flow rate and residual urine content, were better in the clinical studies with saw palmetto. However, there may be circumstances in which *Pygeum* is more effective than saw palmetto. For example, saw palmetto has not been shown to produce some of Pygeum's effects on prostate secretion. Of course the two extracts have somewhat overlapping mechanisms of action and can be used in combination.

Urtica dioica (Stinging Nettle)

Extracts of the root of *U. dioica* have also been shown to be effective in the treatment of BPH. Three double-blind studies have shown it to be more effective than placebo.[55,56] The most recent study, conducted in Iran, was a 6-month double-blind placebo-controlled randomized partial crossover comparative trial of *Urtica* with placebo in 620 patients.[57] Both groups continued the medication up to 18 months and only those who continued the therapy, had favorable results. No side effects were identified in either group.

THERAPEUTIC APPROACH

Therapeutic goals for BPH are aimed at doing the following:

- Normalize prostate nutrient levels
- Restore steroid hormones to normal levels
- Inhibit excessive conversion of testosterone to DHT
- Inhibit DHT-receptor binding
- Reduce inflammation
- Eliminate excess estradiol production
- Limit promoters of the hyperplastic process (e.g., prolactin)

Severe BPH resulting in significant acute urinary retention may require catheterization for relief; a sufficiently advanced case may not respond rapidly enough to therapy and may require the short-term use of an alpha$_1$ antagonist by itself or combined with a 5-alpha reductase medication or surgical intervention.

Lifestyle

Patients should exercise more, between 4 to 6 times a week, and properly stretch the prostate/urogenital area to increase blood flow.

Diet

Initially, the diet should be higher in vegetable protein, low in carbohydrate, low in animal fats, and high in unsaturated oils. After the patient responds, a less strict whole-foods, balanced approach can be used. The patient should limit alcohol and coffee intake, avoid drug-, pesticide- and hormone-contaminated foods, and limit cholesterol-rich foods. Soy foods should be used regularly.

Supplements

- Zinc: 30 to 45 mg/day (picolinate preferred, maximum of 6 months; reduce dosage to 15 to 30 mg/day after 6 months and consider monitoring copper status in long-term therapy)
- Glycine: 200 mg/day
- Glutamic acid: 200 mg/day
- Alanine: 200 mg/day
- Vitamin D3: 2000 to 5000 IU/day

Botanicals

- Liposterolic extract of saw palmetto *(S. repens)* (standardized at 85% to 95% fatty acids and sterols): 160 mg two times a day
- Flower pollen extract (e.g., Cernilton): 63 mg two to three times a day
- *Pygeum africanum* extract (14% triterpene content): 50 to 100 mg/day
- *Urtica dioica* extract: 120 to 150 mg two times a day
- Beta-sitosterol: 60 to 130 mg/day

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CHAPTER 153

Bronchitis and Pneumonia

Michael T. Murray, ND

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GENERAL CONSIDERATIONS

Bronchitis is inflammation of the mucous membranes of the bronchi, the airways that carry airflow from the trachea into the lungs. Pneumonia is inflammation of the lungs. Both acute bronchitis and pneumonia are characterized by the development of a cough with or without the production of sputum. Acute bronchitis often occurs during the course of an acute viral illness such as the common cold or influenza. Viruses cause about 90% of cases of acute bronchitis.

Although pneumonia may appear in healthy individuals, it is usually seen in those who are immune-compromised, particularly drug and alcohol abusers. The growing population of those with chronic lung diseases and other debilitating illnesses and a history of the use of respiratory therapy, immunosuppressive drugs, and other such technologies have contributed to the further increase of nosocomial and opportunistic pneumonias, which have high mortality rates. Acute pneumonia is the seventh leading cause of death in the United States.[1] It is particularly dangerous in the elderly.

In healthy individuals, pneumonia most often follows an insult to the host defense mechanisms: viral infection (especially influenza), cigarette smoke and other noxious fumes, impairment of consciousness (which depresses the gag reflex, allowing aspiration), neoplasms, and hospitalization (Table 153-1). In immunocompetent, nonelderly adults, cigarette smoking is the strongest independent risk factor for invasive pneumococcal disease.[2]

The airway distal to the larynx is normally sterile owing to several protective mechanisms, both mechanical and humoral. The mucus-covered ciliated epithelium that lines the lower respiratory tract propels sputum to the larger bronchi and trachea, evoking the cough reflex. The respiratory secretions contain substances that exert nonspecific antimicrobial actions: alpha$_1$ antitrypsin, lysozyme, and lactoferrin. At the level of the alveoli, potent defense mechanisms are present, including alveolar macrophages, a rich vasculature capable of rapidly delivering lymphocytes and granulocytes, and an efficient lymphatic drainage network.

DIAGNOSTIC SUMMARY: BRONCHITIS

The diagnosis of acute bronchitis is usually made by ruling out other causes of an acute cough—such as pneumonia, the common cold, acute asthma, or an exacerbation of chronic obstructive pulmonary disease.

In patients with the presumed diagnosis of acute bronchitis, viral cultures, serologic assays, and sputum analyses should not be routinely performed because the responsible organism is rarely identified in clinical practice.

In patients with acute cough and sputum production suggestive of acute bronchitis, the absence of the following findings reduces the likelihood of pneumonia sufficiently to eliminate the need for a chest radiograph: (1) heart rate greater than 100 beats per minute; (2) respiratory rate greater than 24 breaths per minute; (3) oral body temperature above 38° C; and (4) chest examination findings of focal consolidation, egophony, or fremitus.

DIAGNOSTIC SUMMARY: PNEUMONIA

The diagnosis of pneumonia is usually made by physical examination and confirmed by a chest x-ray. Common physical examination findings include the following:

TABLE 153-1 **Etiologies of Common Pneumonias**

TYPE	PERCENTAGE
Viral (influenza)	20 (3)
Mycoplasmal	10-20
Bacterial	12
Bacterial superimposed on viral	6
Chlamydia	10
Unknown cause (Legionnaires' disease, toxic)	38

Data from Branch WT Jr. Office practice of medicine. Philadelphia: Saunders, 1982:57-76.

- Rales (a bubbling or crackling sound). Rales on one side of the chest and rales heard while the patient is lying down are strongly suggestive of pneumonia.
- Rhonchi (abnormal rumblings indicating the presence of thick fluid).
- Percussion. A dull thud instead of a healthy hollow-drum–like sound, indicates certain conditions that suggest pneumonia, including the following:
 - Consolidation (a condition in which the lung becomes firm and inelastic)
 - Pleural effusion (fluid buildup in the space between the lungs and the lining around it)

Examination of the sputum suggestive of infection includes the presence of blood; thick, opaque sputum colored yellow, green, or brown and a positive Gram stain. Sputum culture and sensitivity are not always helpful in identifying the cause of pneumonia due to contamination of the sample with throat or mouth bacteria.

A urine test (Binax NOW, Binax Inc., Scarborough, Maine) can detect *Streptococcus pneumonia* or *Legionella pneumophila* antigens within 15 minutes. It may identify up to 77% of pneumonia cases and may rule out the infection in 98% of patients who do not have *S. pneumoniae*. However, the test is not very useful in diagnosing *S. pneumoniae* as a cause of pneumonia in children, since the organism is so common in this population whether or not they have pneumonia. *L. pneumophila* is the bacterium that causes Legionnaires' disease and sometimes pneumonia.

A chest x-ray is nearly always taken to confirm a diagnosis of pneumonia, but it is not imperative that it be positive to make the clinical diagnosis. A positive chest x-ray for pneumonia may reveal lung infiltrates or complications of pneumonia such as pleural effusions.

Special Considerations with Pneumonia

There are more than 100 types of bacteria, viruses, and fungi known to cause bronchitis or pneumonia. The three most common forms of pneumonia are the viral, mycoplasmal, and pneumococcal types.

Viral Pneumonia

Viral pneumonia is most often caused by one of several viruses: adenovirus, influenza, parainfluenza, and respiratory syncytial virus. Viral pneumonia is responsible for about 30% of cases of pneumonia and will often develop as a complication to an upper respiratory infection caused by one of the viruses. People who are at risk for more serious viral pneumonia often are immunocompromised. Antibiotics are of no value in viral pneumonia.

Clinical Summary for Viral Pneumonia

- People who are at risk for more serious viral pneumonia are often immunocompromised.
- Antibiotics are of no value in viral pneumonia.
- Symptoms of viral pneumonia often begin slowly and may not be severe at first.
- The most common symptoms of viral pneumonia are
 - Cough (with some pneumonias patients may cough up mucus or even bloody mucus)
 - Fever, which may be mild or high
 - Shaking chills
 - Shortness of breath (may only occur when on merely climbing stairs)

Mycoplasmal Pneumonia

Mycoplasmal pneumonia is caused by *Mycoplasma pneumoniae*. *Mycoplasma* is a genus of bacteria that lack cell walls. Various studies suggest that *M. pneumoniae* is responsible for 15% to 50% of all cases of pneumonia in adults and even more than those in school-age children. It is often referred to as "walking pneumonia." Antibiotics are usually not necessary but may speed recovery. Effective classes of antibiotics that may be effective against *M. pneumoniae* include macrolides, quinolones, and tetracyclines.

Clinical Summary for Mycoplasmal Pneumonia

- Most commonly occurs in children or young adults
- Insidious onset over several days
- Nonproductive cough, minimal physical findings, temperature generally less than 102° F
- Headache and malaise are common early symptoms
- White blood cell count is normal or slightly elevated
- X-ray pattern is patchy or inhomogeneous

Pneumococcal pneumonia

Pneumococcal pneumonia (due to *Streptococcus pneumoniae*) is the most common bacterial pneumonia and the most common cause of pneumonia requiring hospitalization. Careful clinical judgment is necessary in determining the severity of the disease and the status of the patient's immune system because it is often necessary to administer antibiotics or to refer for hospitalization, especially for elderly or immunocompromised patients.

Unfortunately, most reports show an increase not only of resistance rates to antibiotic therapy but also of the proportion of highly resistant strains.[3-5] In two multinational studies, the worldwide prevalence of penicillin- and macrolide-resistant *S. pneumoniae* ranged from 18% to 22% and from 24% to 31%, respectively.[6,7] Given this information, it is important to consider natural treatments in cases resistant to antibiotics or as an adjunctive treatment to strengthen the immune response and increase the therapeutic effect.

Clinical Summary for Pneumococcal Pneumonia

- Pneumonia is usually preceded by upper respiratory tract infection.
- There is a sudden onset of shaking, chills, fever, and chest pain.
- Sputum is pinkish or blood-specked at first, then becomes rusty at the height of the infection, and finally becoming yellow and mucopurulent during resolution.
- Gram-positive diplococci are present in the sputum smear.
- A rapid urine test (Binax NOW) for *S. pneumoniae* antigens is positive.
- Initially chest excursion is diminished on the involved side, breath sounds are suppressed, and fine inspiratory rales are heard.
- Later, classic signs of consolidation appear (bronchial breathing, crepitant rales, dullness).

- Leukocytosis is present.
- Radiograph shows lobar or segmental consolidation.

THERAPEUTIC CONSIDERATIONS

Regardless of the form of bronchitis or pneumonia, the basic approach is to use an expectorant, mucolytic, and immune supportive nutrients to help resolve it. Although antibiotics are of limited value in acute bronchitis, they definitely have their place in treating pneumonia.

Expectorants

Botanical expectorants have a long history of use in bronchitis and pneumonia. Because impaired cough reflexes have been thought to play a role in recurrent bronchitis and pneumonia,[8] it seems reasonable that these botanicals would be useful in helping relieve this condition and preventing recurrences. Botanical expectorants act to increase the quantity, decrease the viscosity, and promote expulsion of the secretions of the respiratory mucous membranes. Many also have antibacterial and antiviral activity. Some expectorants are also antitussives; however, *Lobelia inflata,* a commonly used expectorant, actually helps promote the cough reflex.[9] Therefore *Lobelia* may be more effective at clearing the lungs than other expectorants when the cough is productive. Other commonly used expectorants include *Glycyrrhiza glabra* (licorice), *Pelargonium sidoides* (South African geranium), *Hedera helix* (ivy), and wild cherry bark.

Pelargonium sidoides (South African Geranium)

P. sidoides is a medicinal plant in the geranium family that is native to South Africa. *Umckaloaba,* its common name, is a close approximation of the word in the Zulu language that means "severe cough" and is a testimony to its effect in bronchitis. The plant has an intricate grouping of thick dark-red rhizomes and tubers underground that allows it to withstand the frequent grass fires in its habitat. Extracts from the rhizomes and tubers have been shown to exert a number of effects beneficial in upper respiratory tract infections, particularly bronchitis. Almost all of the research has been conducted using an ethanolic extract known as EPs 7630 (also marketed as Umcka) and it is an approved drug for the treatment of acute bronchitis in Germany. It is produced using 11% ethanol to produce a drug/extract ratio of 1:8 to 10. The primary active ingredients include highly oxygenated coumarins (e.g., umckalin) and polyphenolic compounds.[10]

Research with EPs 7630 shows that it exerts a three-pronged approach in acute bronchitis: (1) it enhances immune function; (2) it has some antimicrobial effects, including antimycobacterial[11] and antiviral activity,[12] and it also appears to inhibit the attachment of bacteria, viruses, and perhaps other organisms to mucous membranes of the respiratory tract[10]; and (3) it also acts as an expectorant.[10] In regard to its antiviral effects, EPs 7630 at concentrations up to 100 mcg/mL interfered with the replication of seasonal influenza A virus strains (H1N1, H3N2), respiratory syncytial virus, human coronavirus, parainfluenza virus, and coxsackievirus but did not affect replication of highly pathogenic avian influenza A virus (H5N1), adenovirus, or rhinovirus.[12]

A 2008 meta-analysis of four randomized clinical trials of EPs 7630 comprising 1647 patients with acute bronchitis support its safety and efficacy in acute bronchitis.[13] Inclusion criteria required patients to have been diagnosed with acute bronchitis within 48 hours and that they should not have received antibiotic therapy and had no obvious contraindications to therapy. The primary outcome or review of efficacy for most of the trials are changes in the Bronchitis Severity Score (BSS), which includes the symptoms of coughing, expectoration, chest pain, dyspnea, and wheezing from baseline versus after 7 days of treatment. Included in this review was a double-blind placebo-controlled study in 468 adults with recent onset of acute bronchitis who were given either placebo or EPs 7630 for 1 week. The results showed a significantly greater improvement in symptoms in the treatment group as compared with the placebo group. On average, participants who received the real treatment were able to return to work 2 days earlier than those given placebo. In another included study, 742 children with acute bronchitis showed a drop of at least 80% in the severity of component symptoms of the BSS within 2 weeks of therapy, and over 88% of the treating physicians rated the performance as "successful."

Since the 2008 meta-analysis there have been additional studies that show additional evidence of the safety and efficacy of EPs 7630 in acute bronchitis as well as further insight on dosage. In the most recent of these, 406 patients with acute bronchitis were randomly assigned to one of four parallel treatment groups—10-mg EPs 7630 tablets three times a day (30-mg group), 20-mg EPs 7630 tablets three times a day (60-mg group), 30-mg EPs 7630 tablets three times a day (90-mg group), or placebo three times a day (control group)—for a treatment period of 7 days.[14] The primary endpoint was the change in the total BSS score from baseline to day 7. Between day 0 and day 7, the mean BSS score decreased by 2.7 (control group), 4.3 (30-mg group), 6.1 (60-mg group), and 6.3 (90-mg group), respectively. These results indicated that the 20-mg tablets of EPs 7630 taken three times daily constitute the optimal dose. Similar results were seen in a study of 400 children with acute bronchitis using the same dosage assessment.[15]

In another study, 200 children with acute bronchitis were randomized to receive either EPs 7630 in liquid form or placebo for 7 consecutive days.[16] Dosage was based on age: from ages 1 to 6 years, 10 drops three times daily; from ages 6 to 12 years, 20 drops three times daily; and from ages 12 to 18 years, 30 drops three times daily. From baseline to day 7, the mean BSS score improved significantly more for EPs 7630 compared with placebo (3.4 vs. 1.2 points). On day 7, secondary measures of treatment outcome were significantly better, satisfaction with treatment more pronounced, onset of effect faster, and time of bed rest shorter as compared with placebo.

In clinical studies with umcka in over 2500 adults and children, adverse events occurred on par with a placebo and mainly consisted of mild gastrointestinal complaints and skin rashes. There were no known drug interactions.[10]

Hedera helix (Ivy)

In Europe, herbal preparations containing extracts from the leaves of ivy enjoy great popularity for the relief of cough as well as asthma. In 2007, more than 80% of herbal expectorants prescribed in Germany comprised ivy extract and amounted to nearly 2 million prescriptions nationwide. Ivy leaf contains saponins that show expectorant, mucolytic, spasmolytic, bronchodilatory, and antibacterial effects. The mucolytic and expectorant action of ivy is based on indirect β_2-adrenergic effects, and this action is due to the saponins α-hederin and hederacoside C, the latter of which is metabolized to α-hederin when ingested. The indirect effect is that α-hederin inhibits the intracellular uptake of β2receptors and leads to an increased β2-adrenergic response of the cell.[17]

Ivy is often used as a monopreparation with very good safety, compliance, and efficacy ratings from postmarketing surveillance studies

in both acute and chronic bronchitis.[18,19] One double-blind study in acute bronchitis used a combination of ivy and thyme (*Thymus vulgaris*).[20] The 361 patients with acute bronchitis and 10 or more coughing fits during the day, onset of bronchial mucus production with impaired ability to cough up at a maximum of 2 days prior to recruitment, and a BSS score of greater than or equal to 5 points were randomly assigned to an 11-day treatment (5.4 mL three times daily) with either thyme-ivy combination syrup or placebo syrup. The mean reduction in coughing fits on days 7 to 9 relative to baseline was 68.7% under the thyme-ivy combination compared with 47.6% under the placebo. In the thyme-ivy combination group, a 50% reduction in coughing fits from baseline was reached 2 days earlier compared with the placebo group. The symptoms of acute bronchitis (BSS) improved rapidly in both groups, but regression of symptoms was faster and the responder rates compared with placebo were higher at visit 2 (83.0% vs. 53.9%) and visit 3 (96.2% vs. 74.7%) under the treatment of the thyme-ivy combination. Treatment was well tolerated with no difference in the frequency or severity of side effects between the thyme-ivy combination and placebo groups.

Mucolytics

A mucolytic agent should be used to improve the quality of the mucous secretions so as to promote expectoration. Guaifenesin (also known as glycerol guiacolate) is a derivative of a compound originally isolated from beech wood. Guaifenesin is an approved over-the-counter expectorant and mucolytic. Alternatives include N-acetylcysteine and bromelain.

N-Acetylcysteine

N-acetylcysteine (NAC) has an extensive history of use as a mucolytic in the treatment of acute and chronic lung conditions. It directly splits the sulfur linkages of mucoproteins, thereby reducing the viscosity of bronchial and lung secretions. As a result, it improves bronchial and lung function, reduces cough, and improves oxygen saturation in the blood.

NAC is helpful in all lung and respiratory tract disorders, especially chronic bronchitis and chronic obstructive pulmonary disease. In detailed analyses of 39 trials, it has been concluded that oral NAC reduces the risk of exacerbations (severe worsening) and improves symptoms in patients with chronic bronchitis compared with placebo.

In addition to its effects as a mucolytic, NAC can increase the manufacture of glutathione, a major antioxidant for the entire respiratory tract and lungs. The typical dosage for NAC is 200 mg three times daily.

Bromelain

Bromelain is a useful adjunctive therapy for bronchitis and pneumonia owing to its fibrinolytic, antiinflammatory, and mucolytic actions and enhancement of antibiotic absorption.[21] Bromelain's mucolytic activity is responsible for its particular effectiveness in respiratory tract diseases, including pneumonia, bronchitis, and sinusitis.[22]

Vitamin C

In the early part of the twentieth century, before the advent of effective antibiotics, many controlled and uncontrolled studies demonstrated the efficacy of large doses of vitamin C in bronchitis and pneumonia but only when they were started on the first or second day of infection.[23] If administered later, vitamin C tended only to lessen the severity of the disease. Researchers also demonstrated that in pneumonia, white blood cells take up large amounts of vitamin C.

The value of vitamin C supplementation in elderly patients with pneumonia was demonstrated clearly in a double-blind study of 57 elderly patients hospitalized for severe acute bronchitis and pneumonia.[24] The patients were given either 200 mg/day of vitamin C or a placebo. Patients were assessed by clinical and laboratory methods (vitamin C levels in the plasma, white blood cells, and platelets; sedimentation rates; and white blood cell counts and differential). Patients receiving this modest dosage of vitamin C demonstrated substantially increased vitamin C levels in all tissues even in the presence of an acute respiratory infection. Using a clinical scoring system based on major symptoms of respiratory infections, results indicated that the patients receiving the vitamin C fared significantly better than those on placebo. The benefit of vitamin C was most obvious in patients with the most severe illness, many of whom had low plasma and white blood cell levels of vitamin C on admission.

Vitamin A

Vitamin A supplementation appears to be of value, especially in children with measles. This may be because of the increased rate of excretion of vitamin A found during severe infections such as pneumonia. One study evaluated 29 patients with pneumonia and sepsis and found that their mean excretion rate of vitamin A was 0.78 mmol/day. Subjects with fever excreted significantly more retinol than did those without fever. A remarkable 34% of the patients excreted more than 1.75 mmol/day of retinol, which is equivalent to 50% of the U.S. recommended daily allowance.[25]

This may be particularly important for children. A randomized, double-blind trial of 189 children with measles (average age 10 months) in South Africa evaluated the efficacy of vitamin A in reducing complications. Providing 400,000 IU (120 mg of retinyl palmitate), one half on admission and one half a day later, reduced the death rate by more than 50% and the duration of pneumonia, diarrhea, and hospital stay by 33%.[26]

However, another study did not show any benefit from vitamin A supplementation. The difference may be due to the lower dose (100,000 IU) used in the second study or to the fact that it was not limited to children with pneumonia as a complication of measles, a condition known to also decrease vitamin A levels.[27]

Evidence also indicates there are positive results from the use of vitamin A and concomitant zinc supplementation. One study of 2482 children aged 6 months to 3 years revealed that those children given initial high doses of vitamin A followed by 4 months of elemental zinc (10 mg/day for infants and 20 mg/day for children older than 1 year) brought about a reduced incidence of pneumonia, which was not seen in the group given only vitamin A.[28]

Vitamin E

Patients with influenza complicated by pneumonia experience a sharp rise in lipid peroxidation (LPO) products, especially those who are seriously ill. Administration of α-tocopherol promotes a significant decrease in the levels of lipid peroxidation products and more benign clinical course.[29]

Garlic

Allium sativum (garlic) has exhibited a broad spectrum of antibiotic activity against both gram-positive and gram-negative bacteria.[30] In vitro studies have demonstrated garlic to be an effective antibacterial agent against *S. pneumoniae*[31]; therefore, its use should be considered in cases of antibiotic resistance or as an adjunct to antibiotic therapy. Alternatively, berberine-containing plants like *Hydrastis canadensis* (goldenseal) may be helpful.

Bottle Blowing and Salt Pipes

A Swedish study was carried out with 145 adults hospitalized for community-acquired pneumonia.[32] These patients were divided into three groups. Group A was given early mobilization with no breathing-associated exercises, group B was instructed to sit up and take 20 deep breaths 10 times daily, and group C was instructed to sit up and blow bubbles in a bottle containing 10 mL water through a plastic tube 20 times on 10 occasions daily. In this study, length of hospitalization was significantly modified in groups B and C: group A patients were hospitalized for a mean of 5.3 days, group B for 4.6 days, and group C for only 3.9 days. The number of days with fever were least in the bottle-blowing group. It should be noted that early mobilization itself is known to significantly decrease hospital stays in pneumonia patients.[33] Despite the positive clinical results, C-reactive protein levels, peak expiratory flow, and vital capacity were not significantly affected.

Although it is not completely understood why the patients who performed bottle blowing had shorter hospital stays, it seems that the changes in respiratory pressure associated with this exercise may be involved in providing an environment for more efficient bacterial clearance. Another study also found decreased impairment of pulmonary function and an increase in total lung capacity in patients who had undergone coronary artery bypass.[34] This modality or another similar activity, like playing a wind instrument, may well prove useful as a means of decreasing the frequency and duration of respiratory events in patients who are vulnerable to respiratory infections like pneumonia.

An alternative to bubble blowing is the use of a salt pipe. These pipes are inhaler-type devices containing tiny salt particles said to ease breathing. The practice originated in central Europe, where individuals with respiratory complaints would spend time in salt caves or mines to help relieve their breathing problems.

THERAPEUTIC APPROACH

As stated above, the basic approach is to use an expectorant, mucolytic, and immune-supportive nutrients to help resolve the condition. Some general physical modalities and measures that may be helpful should be employed, including the following:

- Diathermy to chest and back: 30 min/day
- Mustard poultice: once/day
- Lymphatic massage: three times a day
- Postural drainage: three times a day
- Bottle-blowing therapy: blowing bubbles in a bottle containing 10 mL water through a plastic tube 20 times on 10 occasions a day
- Getting plenty of rest
- Drinking enough liquids
- Using a humidifier

Expectorants

Choose one or more of the following:

Lobelia inflata

- Dried herb: 0.2 to 0.6 g three times a day
- Tincture: 15 to 30 drops three times a day
- Fluid extract: 8 to 10 drops three times a day

Glycyrrhiza glabra

- Powdered root: 1 to 2 g
- Fluid extract (1:1): 2 to 4 mL (0.5 to 1 tsp)
- Solid (dry-powdered) extract (4:1): 250 to 500 mg

Pelargonium sidoides

Dosage recommendations for EPs 7630 or equivalent preparation are as follows:

Adults: 1.5 mL three times a day or 20-mg tablets three times a day for up to 14 days.

Children: age 7 to 12 years, 20 drops (1 mL) three times a day; age 6 years or less, 10 drops (0.5 mL) three times a day.

Hedera helix

Ivy leaf is available primarily in tincture and fluid extract forms and the dry powdered extract in capsules and tablets. Based upon clinical studies, the daily dosages are to deliver the following equivalent to dried herbal substance: 1 to 5 years: 150 mg; 6 to 12 years: 210 mg; above 12 years: 420 mg. Therefore the typical dosage for adults and children over 12 years of age for a 4:1 dried powdered extract is 100 mg daily.

Mucolytics

Choose one or more of the following:

Guaifenesin

Adults and children 12 years of age and older: 200 to 400 mg every 4 hours. It is inadvisable to take more than 2400 mg in a 24-hour period.

The dosage for children age 6 to 11 years is 100 to 200 mg every 4 hours and no more than 1200 mg in a 24-hour period. For children age 2 to 5 years, 50 to 100 mg every 4 hours and no more than 600 mg in 24 hours. Guaifenesin is not recommended for children under 2 years of age.

N-Acetylcysteine: 200 mg three times a day

Bromelain (1200 to 1800 milk clotting units [MCU]): 500 to 750 mg three times a day between meals

Supplements

- Vitamin A: 50,000 IU/day for 1 week *or* beta-carotene 200,000 IU/day (Note: Vitamin A should not be used in menstruating women owing to possible teratogenic effects.)
- Vitamin C: 500 mg every 2 hours
- Vitamin E: 200 IU/day
- Choose one of the following:
 Bioflavonoids (mixed citrus): 1,000 mg/day
 Grape seed (Vitis vinifera) extract (95% procyanidolic oligomers) 150 to 300 mg/day
 Pine bark extract (Pinus pinaster) 150 to 300 mg/day
- Zinc: 30 mg/day

Additional Recommendations for Pneumococcal Pneumonia

Choose one or both of the following:

Garlic

A commercial garlic product should provide a daily dose equal to at least 4000 mg of fresh garlic, which translates to at least 10 mg alliin or a total allicin potential of 4000 mcg (see Chapter 63, "*Allium sativum*").

Hydrastis canadensis

Given berberine's broad-spectrum antimicrobial activity and immune-enhancing effects, berberine-containing plants are an important consideration. The dosage should be based on berberine

content. Because of the wide range of quality in goldenseal preparations, standardized extracts are recommended. The following dosages are intended to be given three times daily:

- Dried root or as infusion (tea): 2 to 4 g
- Tincture (1:5): 6 to 12 mL (1.5 to 3 tsp)
- Fluid extract (1:1): 2 to 4 mL (0.5 to 1 tsp)
- Solid (powdered dry) extract (4:1 or 8% to 12% alkaloid content): 250 to 500 mg

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CHAPTER 154

Carpal Tunnel Syndrome

Robert M. Martinez, DC, ND

DIAGNOSTIC SUMMARY

- Insidious onset of numbness and tingling, primarily in the first three fingers, often bilaterally
- Pain over the palmar surface of the wrist, which may extend proximally up to the forearm or shoulder
- Pain often worse at night that may wake the patient
- Positive Tinel's and Phalen's signs
- Neurodiagnostic testing showing altered nerve conduction of the median nerve at the carpal tunnel

GENERAL CONSIDERATIONS

Carpal tunnel syndrome (CTS) involves compression of the median nerve in the carpal tunnel. Sensory impairment occurs in the first three digits and the lateral one half of the fourth digit of the hand. Pain may be felt in the palm, anterior wrist, forearm, and proximally to the shoulder. Loss of fine motor skills and strength in abduction and opposition of the thumb may develop. Atrophy of the opponens pollicis muscle may occur.[1]

Anatomy of the Carpal Tunnel

The floor and sides of the carpal tunnel are formed by the carpal bones; the roof by the flexor retinaculum. The median nerve lies between the flexor retinaculum and the finger flexors and pollicus longus tendons and their tenosynovium. The flexor retinaculum acts to prevent bowstringing of the flexor tendons. When the flexors contract, especially with the wrist in flexion, the tendons in the carpal tunnel compress the median nerve between the tenosynovium and the flexor retinaculum.

Etiology

Most cases of CTS are considered idiopathic. Nonspecific flexor tenosynovitis has been reported as the most common cause of CTS. The most common histologic findings in CTS are noninflammatory synovial fibrosis [2] and vascular proliferation. Conceptually, it helps to think of factors that cause the canal to get smaller or factors that cause the contents to swell.

Causes of CTS include the following[3]:

- Increased volume of canal contents/edema (nonspecific flexor tenosynovitis, obesity, pregnancy, oral contraceptives)
- Trauma (fracture, repetitive wrist flexion)
- Aberrant anatomy (cysts, lipomas, arthritic spurs)
- Infections (septic arthritis, Lyme disease)
- Metabolic conditions (diabetes, hypothyroidism)
- Inflammatory conditions (rheumatoid arthritis, gout, connective tissue disease)

Risk Factors and Frequency of Occurrence

CTS most often occurs after age 30 and women are affected three times as often as men.[4] Repetitive strain injury (RSI) from light duty work as a cause of CTS

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is not well supported by the current literature.[5] However, a study of 501 participants, 156 of whom were diagnosed with CTS, showed the following risk factors: repetitive activities with a flexed or extended wrist, hysterectomy without oophorectomy, and menopausal women who had their last menstrual period 6 to 12 months earlier.[6] Others report increased the incidence of CTS due to pregnancy, hypothyroidism, diabetes, and recent menopause.[7]

DIAGNOSTIC CONSIDERATIONS

There is no single reference standard for diagnosis of the syndrome; a combination of symptoms, signs, and tests should be used to characterize the disorder.[1]

History

CTS typically has an insidious onset of intermittent tingling or numbness, often bilaterally, of the first three fingers and the lateral one half of the fourth digit. Symptoms are frequently worse at night, often waking the patient. As the condition progresses, loss of fine motor skills and loss of grip strength with "things slipping from my fingers" are commonly reported. Relief is gained from shaking the affected hand or hands. Katz and Stirrat[8] developed a self-administered hand diagram test that has an 80% sensitivity and a 90% specificity for CTS. Loss of finger dexterity and atrophy are late complaints.

Physical Examination

Examination may show decreased sensation over the distribution of the median nerve to sharp, light touch and vibration (128-Hz tuning fork). Surprisingly, many patients are not able to localize the symptoms to the median distribution and feel that the whole hand is involved, which may be due to autonomic nerve involvement. Tingling in the distribution of the median nerve produced by tapping on the wrist crease (positive Tinel's sign), tingling in the distribution of the median nerve produced by holding the wrist in forced flexion for 60 to 90 seconds (Phalen's test), or tingling produced by forcibly extending the wrist and applying pressure over the median nerve (reverse Phalen's test) are signs of CTS. Early on, the perceived loss of strength may be due to loss of sensory feedback, not loss of strength. Manual muscle tests may elicit weakness of the LOAF muscles (muscles innervated by the median nerve in the hand; Lubricals first and second, Opponens pollicus, Abductor pollicus, Flexor pollicis brevis). As CTS advances, atrophy of the thenar eminence and weakness of the thumb abductor muscle may develop.

Other Diagnostic Tests

The carpal compression test, when the examiner exerts direct compression with the thumbs over the patient's carpal tunnel for 30 seconds and reproduces the symptoms, was reported as having 89% sensitivity and 96% specificity when performed with the Durkan guage.[9] Other studies have not reproduced these findings but have reported "Tinel's, Phalen's, Reverse Phalen's, and carpal tunnel compression tests are more sensitive, as well as being specific tests for the diagnosis of tenosynovitis of the flexor muscles of the hand, rather than being specific tests for CTS."[34,35] Weakness of the thumb abductor muscle is a strong indication to order neurophysiologic testing (nerve conduction studies [NCS] and/or electromyography). In CTS, NCS may show motor and sensory latencies across the wrist.

Magnetic resonance imaging (MRI) and high-definition ultrasound imaging can measure the dimensions of the carpal tunnel and size of the median nerve, but these tests are expensive and not needed in uncomplicated CTS.

DIFFERENTIAL DIAGNOSIS

When the clinical picture is not clear, other sources of paresthesia should be considered, such as compression of the brachial plexus in the thoracic outlet, impingement of the median nerve under the pronator teres muscle, entrapment of either the radial or ulnar nerves. The initial presentation of complex regional pain syndrome (reflex sympathetic dystrophy) may appear to be CTS.

THERAPEUTIC CONSIDERATIONS

Many patients report spontaneous recovery from CTS. CTS from pregnancy most often is self-resolving. The waxing and waning symptoms of CTS can give a false sense of success from conservative treatment. The cost of conservative care in persistent CTS may be greater than a carpal tunnel release when performed as an office procedure.[11] In cases of progressive neurologic deficit and pain, an open release procedure may be the best choice of treatment.[36] In The Netherlands, only open procedures are compensated by the state plan owing to their high rate of success and low rate of complications. Unless the surgeon has good skills, the more expensive endoscopic procedures have poorer outcomes.[10]

Physical Medicine

Splinting

Initially, the most recommended treatment is 4 weeks in a neutral wrist splint worn full time, which provides better results than night-only splinting, but night-only splinting has higher compliance. Splinting is most effective when it is started within 3 months of onset of CTS. Specialized splints have not been proved more effective than a good-quality well-fitted off-the-shelf splint.[12,13] Splinting should not be done after carpal tunnel release.[14]

Therapeutic Ultrasound

Ultrasound (US) therapy for 2 weeks is generally not beneficial, but one trial showed significant symptom improvement from US (1 MHz, 1.0 W/cm^2, pulse 1:4, 15 minutes per session) after 20 sessions over 7 weeks that was maintained at 6 months.[15] The cost of 15 to 20 sessions of US treatment may be prohibitive.

Yoga and Stretching

One small preliminary study described 10 yoga poses held for 30 seconds, each followed by 10 to 15 minutes of relaxation, that resulted in significantly reduced pain and increase grip strength persisting for more than 8 weeks.[16]

Tests recording carpal tunnel pressure showed a significant rise in pressure with wrist flexion, wrist extension, making a fist, holding objects, and isolated isometric flexion of a finger against resistance. But after 1 minute of specific stretching-loading exercises, intratunnel pressures dropped to normal levels, and remained normal for more than 15 minutes.[17]

Manual Manipulation

Studies of manipulation show benefits from soft tissue and joint mobilization of the forearm, wrist, and hand, but not from spinal manipulation alone.

A case report of manipulative treatment to the cervical spine, right elbow, and right wrist performed three times per week for 4 weeks reported improved grip strength; both Tinel's and Phalen's tests became negative and NCS studies improved.[18]

In 1993, Sucher[19] described the treatment of four patients with myofascial release and self-stretching techniques performed three to five times daily. Post-treatment comparison magnetic resonance imaging demonstrated increased dimensions in the carpal tunnel, and nerve conduction studies showed reduction in distal latencies or increase in motor response amplitudes. Nerve and tendon gliding exercise produced no changes in Phalen's test, Tinel's test, or NCS but reduced the number of reported surgeries.[20]

Low-Level Laser Therapy

One small (N=11) randomized double-blind placebo-controlled crossover trial of low-level laser therapy (LLLT) combined with microcurrent transcutaneous electrical nerve stimulation.[21] Eleven patients with mild to moderate symptoms of CTS who had failed to improve with standard medical or surgical treatment were treated with real or sham local applications of LLLT and microcurrent for 3 to 4 weeks. Following treatment there was significant improvement in scores on the McGill Pain Questionnaire; sensory and motor latency scores with EMG; and Tinel's and Phalen's tests but not after sham treatment.

Hydrotherapy

An anecdotal naturopathic treatment to relieve CTS pain is immersing the wrist and hand in hot water for 3 minutes, then immersing in cold water for 30 seconds, repeated three to five times once or twice a day. It is important to ensure that the hot water immersion is deeper than the cold.

Acupuncture

A randomized controlled study comparing prednisolone (20 mg for 2 weeks, then 10 mg for 2 weeks) to eight sessions of acupuncture over 4 weeks showed acupuncture to be effective in symptom control, but acupuncture decreased distal motor latency and prednisolone did not.[22]

One acupuncture study with puncture of PC-7 and PC-6 on the affected side demonstrated a positive response in 35 of 36 patients (14 of whom were previously treated unsuccessfully with surgery).[23]

Erognomics

There is insufficient epidemiologic evidence that computer work causes CTS.[4] Other studies have not demonstrated that work practices (other than high-force work, like that done by meat packers) has a direct influence on CTS.[24]

Nutrition

Vitamin B Supplementation

The increased incidence of CTS since its initial description by Phalen in 1950 parallels the increased presence of pyridoxine antimetabolites (hydrazine dyes, isoniazid, hydralazine, dopamine, penicillamine, and oral contraceptives) in the environment as well as the intake of excessive protein.

Ellis and coworkers[25-27] demonstrated the efficacy of vitamin B_6 supplementation for CTS with 50 mg initially and increased to 200 to 300 mg. Even greater effect was seen when vitamins B_6 and B_2 were given together, possibly owing to riboflavin-dependent enzymes, which convert pyridoxine to pyridoxal 5'-phosphate. Two randomized controlled trials suggest that vitamin B_6 is no better than placebo; however, given its safety profile, vitamin B_6 can be considered in the treatment of CTS.[28,29] Failure of vitamin B_6 supplementation to relieve CTS could be due to a lack of riboflavin or a genetic defect that does not allow sufficient levels of vitamin B_6 to be converted to the active P5P form.

Medications

Steroid injection proximal to the carpal tunnel provides relief for up to 8 weeks, but 50% of those receiving the steroid injection require surgery within a year. Oral prednisolone (20 mg for 2 weeks, then 10 mg for 2 weeks) provides short-term relief over 8 weeks. Nonsteroidal antiinflammatory drugs and diuretics provided no reduction in symptoms and should *not* be used owing to their potential side effects.[30]

No studies were found evaluating the use of the "natural" antiinflammatory medications (bromelain, curcumin, *Boswellia*, various oils). Remedies that address noninflammatory synovial fibrosis[2] and vascular proliferation would theoretically be beneficial.

Surgery

Surgery for CTS should not be considered before 6 months of more conservative treatment, but "In general, the management is surgery for persistent (not resolving after 1 year) or deteriorating (worsening clinically plus or minus deterioration on nerve conduction studies) CTS." Surgery should not be delayed beyond 3 years. Open carpal tunnel release surgery is one of the most commonly performed outpatient surgeries and is less expensive than endoscopic procedures. The abstract in the review in the Cochrane Library[31] reports no difference in long-term results between the procedures, but pain is reduced during the first 2 weeks following the endoscopic surgery compared with open procedures. Surgery with early mobilization,[14] surgery with oral homeopathic *Arnica* and topical *Arnica* ointment,[32] and surgery with controlled cold therapy[33] all showed benefits over surgery alone.

THERAPEUTIC APPROACH FOR MILD/MODERATE IDIOPATHIC CARPAL TUNNEL SYNDROME

Approximately 50% of patients will improve spontaneously. Identify and reduce causes of strain and vibration, and prevent repeated trauma.

Physical Medicine

Regular wrist stretching, yoga, and exercises. The key to these exercises is performing them several times daily and "breaking up" activities that are strenuous and repetitive. Nerve/tendon gliding may be helpful.

Splint. For moderate persistent CTS, full-time splinting in neutral is recommended. Splinting is less effective if it is not started within 3 months of onset or if the splints are only worn at night.

Acupuncture. PC-7 and PC-6 on the affected side should be needled. Laser acupuncture can be considered.

Manipulation/deep tissue mobilization. Manipulation of fixated carpals or separation distal radius and ulna may relieve pressure in the carpal tunnel.

Contrast hydrotherapy. Immerse for 3 minutes in hot water followed by a 30-second immersion in cold water three to five times daily. Heat alone is contraindicated.

Diet

All sources of hydrazines should be avoided.

All foods containing yellow dyes should be avoided.

Daily protein intake should be limited to a maximum of 0.75 g/kg body weight.

Supplements

- Pyridoxine: 50 to 200 mg/day: administer in divided dosages of 25 to 50 mg two to four times a day

If no response to pyridoxine, try pyridoxal 5'-phosphate: 10 mg two to four times a day.

- Riboflavin: 5 to 10 mg/day

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CHAPTER 155

Celiac Disease

Michael T. Murray, ND

DIAGNOSTIC SUMMARY

- A chronic intestinal malabsorption disorder caused by an intolerance to gluten
- Bulky, pale, frothy, foul-smelling, greasy stools with increased fecal fat
- Weight loss and signs of multiple vitamin and mineral deficiencies
- Increased levels of serum antiendomysium and/or transglutaminase antibodies
- Diagnosis confirmed by jejunal biopsy

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GENERAL CONSIDERATIONS

Celiac disease, also known as nontropical sprue, gluten-sensitive enteropathy, or celiac sprue, is characterized by malabsorption and an abnormal small intestinal structure that reverts to normal on removal of dietary gluten. The protein gluten and its polypeptide derivative gliadin are found primarily in wheat, barley, and rye grains. Symptoms most commonly appear during the first 3 years of life, after cereals are introduced into the diet. A second peak incidence occurs during the third decade, and although celiac disease is often thought of as a disease diagnosed early in life, more diagnoses are made in adulthood than in childhood.[1]

That the prevalence of celiac disease has increased dramatically, is undeniable and this is not solely because of increased detection. Until a few decades ago, celiac disease was believed to be relatively rare (approximately 1 case in 5000 within the United States). Now, however, celiac disease is thought to affect approximately 1% of most populations, but it remains largely undiagnosed.[1-3] Undetected celiac disease carries with it an increased mortality, indicating that widespread screening may be economically justified.

Chemistry of Grain Proteins

Gluten, a major component of the wheat endosperm, is composed of gliadins and glutenins. Only the gliadin portion has been demonstrated to activate celiac disease. In rye, barley, and oats, the proteins that appear to activate the disease are termed secalins, hordeins, and avenins, respectively, and prolamines collectively. Cereal grains belong to the family Gramineae. The closer a grain's taxonomic relationship to wheat, the greater its ability to activate celiac disease. Rice and corn, two grains that do not appear to activate celiac disease, are further removed taxonomically from wheat. The taxonomic relationship of the grains is shown in Figure 155-1.

Gliadins are single polypeptide chains that range in molecular weight from 30,000 to 75,000, with a high glutamine and proline content. Gliadins have been divided into four major electrophoretic fractions: alpha-, beta-, gamma-, and omega-gliadin. Alpha-gliadin is believed to be the fraction most capable of activating celiac disease, although beta- and gamma-gliadin are also capable of doing so. Omega-gliadin does not appear to activate the disease, although it has the highest content of glutamine and proline. Gliadin that has been subjected to complete hydrolysis does not activate celiac disease in susceptible individuals.[4]

Pathogenesis

Celiac disease appears to have a genetic etiology, since it is associated with specific HLA molecules—HLA-DQ2 in 95% of patients and DQ8 in the remainder. These

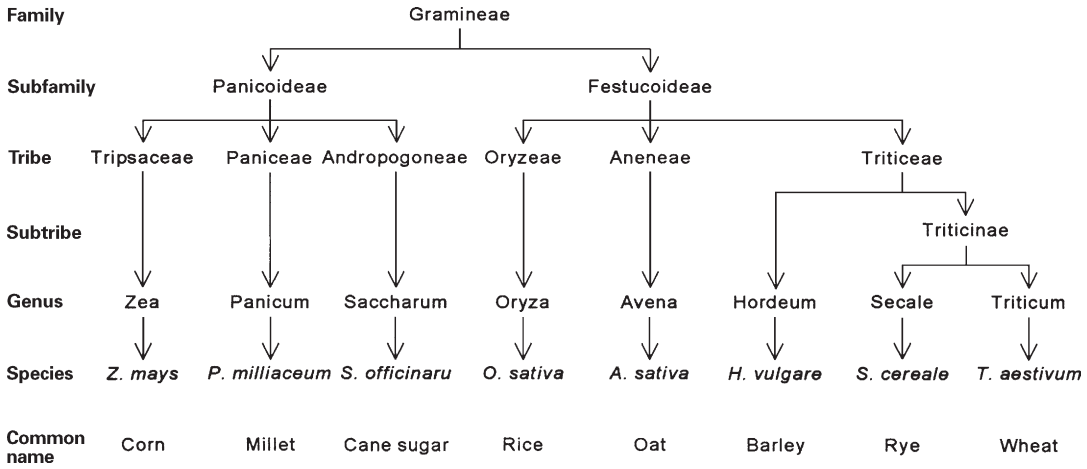


FIGURE 155-1 Taxonomic relationship of major cereal grains.

gene loci are believed to be linked to the immunologic recognition of antigens and specific T-cell–regulated immune responses.

Various hypotheses have been proposed to explain the pathogenesis of celiac disease. Currently, the most likely relates to abnormalities in the immune response rather than some "toxic" property of gliadin. Sensitization to gliadin occurs both in humoral and cell-mediated immunity, and it appears that T-cell dysfunction is the main factor responsible for the enteropathy.[4] A number of circulating antibodies that are specific for celiac disease, particularly antiendomysial antibody (AEA), have been identified. These serologic markers have been used successfully to screen patients and to estimate the true prevalence of celiac disease in the general population. The discovery that tissue transglutaminase (tTG) is the autoantigen for AEA led to the development of an improved enzyme-linked assay using recombinant tTG, which has been shown to be highly sensitive and specific for celiac disease. Tissue transglutaminase is a ubiquitous, predominantly cytoplasmic enzyme that can be released extracellularly, particularly in response to tissue wounding and stress. The observation that anti-tTG antibody titers fall and can become undetectable during a gluten-free diet suggests that tTG-gliadin complexes stimulate gluten-specific T cells to induce anti-tTG antibody production. T and B cells likely recognize different parts of this antigen complex, with T cells reacting to the smaller gliadin peptides and B cells responding to the larger tTG enzyme.[4]

Interestingly, breastfeeding appears to have a prophylactic effect, and breastfed babies have a decreased risk of developing celiac disease.[5,6] The reduced risk of celiac disease was even more pronounced in infants who continued to be breastfed after dietary gluten was introduced. Not surprisingly, the risk of celiac disease was greater when gluten was introduced in the diet in large amounts than when introduced in small or medium amounts. The early introduction of cow's milk is also believed to be a major etiologic factor.[7] Research in the past few years has clearly indicated that breastfeeding, along with delayed administration of cow's milk and cereal grains, are primary preventive steps that can greatly reduce the risk of developing celiac disease.

CLINICAL ASPECTS

The histologic lesions of celiac disease are often indistinguishable from changes caused by tropical sprue, food allergy, diffuse intestinal lymphoma, and viral gastroenteritis. Furthermore, celiac disease often leads to the development of multiple food allergies; disaccharidase deficiency, causing lactose intolerance; and increased intestinal permeability.[8] Improving nutritional status, even something as simple as taking a multiple B vitamin, appears to produce significant improvement in quality of life in patients with celiac disease. In one double-blind study, 65 patients with celiac disease who were on a strict gluten-free diet for several years were randomized to a daily dose of 0.8 mg folic acid, 0.5 mg cyanocobalamin, and 3 mg pyridoxine or placebo for 6 months.[9] Following vitamin supplementation, homocysteine levels dropped a median of 34%, accompanied by significant improvement in well-being, notably anxiety and depressed mood.

Associated Conditions

Perhaps the most significant condition associated with celiac disease is an early death. A landmark study looked at almost 30,000 patients between 1969 and 2008 and examined deaths in four groups: those with full-blown celiac disease, those with inflammation of the intestine but not full-blown celiac disease, those with latent celiac disease or gluten sensitivity (elevated gluten antibodies but negative intestinal biopsy), and a control group with no evidence of celiac disease or gluten sensitivity.[10] The findings were significant: as compared with the control group, there was a 39% increased risk of death in those with celiac disease, 72% increased risk in those with gut inflammation related to gluten, and 35% increased risk in those with gluten sensitivity but no celiac disease.

A review article lists 55 health conditions linked to celiac disease and gluten sensitivity, including irritable bowel disease, inflammatory bowel disease, anemia, migraines, epilepsy, fatigue, canker sores, osteoporosis, rheumatoid arthritis, lupus, multiple sclerosis, and almost all other autoimmune diseases.[11] Thyroid abnormalities, insulin-dependent diabetes mellitus, psychiatric disturbances (including schizophrenia), dermatitis herpetiformis, and urticaria have also been linked to gluten intolerance.[1] A more ominous association is the increased risk for malignant neoplasms seen in celiac patients, especially for non-Hodgkin's lymphoma.[12] The hypothesis that gluten is a contributing factor in some cases of schizophrenia is substantiated by epidemiologic, clinical, and experimental studies.[13-16] Pepsin hydrolysates of wheat gluten have demonstrated opioid activity. This activity is believed to be the factor responsible for the association between wheat consumption and schizophrenia. Gluten sensitivity has also been weakly linked to mood scores, cognitive impairment, and autism.[17-19]

DIAGNOSIS

Before the introduction of highly sensitive and specific serologic markers, endoscopy with jejunal biopsy was the definitive diagnostic procedure. Of these new markers, the test for human antitissue transglutaminase antibodies (Ig A anti-tTG) is emerging as the most widely used, primarily owing to a lower cost compared with antiendomysium (IgA EMA) and a greater sensitivity compared with antigliadin antibodies (AGAs). IgA EMA can detect celiac disease with a sensitivity and specificity of 90% and 99, respectively. Anti-tTG also has a high sensitivity (99%) and specificity (>90%) for identifying celiac disease. An equivocal result on tTG testing should be followed by IgA EMA. With IgA EMA testing, it is recommended that a total serum IgA level be checked in parallel, because celiac patients with IgA deficiency may be unable to produce the antibodies on which these tests depend, leading to a "false negative" result.

Endoscopy/gastroscopy and biopsy should still be performed if clinically warranted.

THERAPEUTIC CONSIDERATIONS

Diet

Once the diagnosis has been established, a gluten-free diet is indicated. This diet should not contain any wheat, rye, barley, triticale, or oats. Buckwheat and millet are often excluded as well. Although buckwheat is not in the grass family and millet appears to be more closely related to rice and corn, buckwheat and millet contain prolamines with similar antigenic activity to the alpha-gliadin of wheat.

In addition, other foods should be rotated, and milk and milk products should be eliminated until the patient's intestinal structure and function return to normal.

Patient Response

Usually, clinical improvement will be apparent within a few days or weeks (30% respond within 3 days, another 50% within 1 month, and 10% within another month). However, 10% of patients respond only after 24 to 36 months of gluten avoidance.[1]

If the patient does not appear to respond, the following should be considered:

- The diagnosis is incorrect.
- The patient is not adhering to the diet or being exposed to hidden sources of gliadin.
- There is an associated disease or complication, such as zinc deficiency.

The last of these points highlights the importance of multivitamin/multimineral supplementation in these patients. In addition to treating any underlying deficiency, supplementation provides the necessary cofactors for growth and repair. Celiac disease is refractive to dietary therapy if an underlying zinc deficiency is present.[20]

SUPPLEMENTS

Pancreatic Enzymes

The effect of pancreatic enzyme substitution therapy in the 2 months following the initial diagnosis of celiac disease (gluten enteropathy) was investigated in one double-blind study. The study sought to clarify the benefit of pancreatic enzyme therapy because previous studies had shown pancreatic insufficiency in 8% to 30% of celiac patients. In this study, patients followed a gluten-free diet, the standard treatment for celiac disease, and received either two capsules of pancreatic enzymes with each meal (6 to 10 capsules a day with each capsule containing lipase 5000 IU, amylase 2900 IU, and protease 330 IU) or two placebo capsules with meals. Complete nutritional and anthropomorphic evaluations were conducted at days 0, 30, and 60. Results indicated that pancreatic enzyme supplementation enhances the clinical benefit of a gluten-free diet during the first 30 days but does not provide any greater benefit than the placebo after 60 days. These results support the use of pancreatic enzyme preparations in the first 30 days after a diagnosis of celiac disease[21] (see Chapter 111 for a complete discussion).

Alternatively, a better choice than pancreatic enzymes might be enzyme preparations containing dipeptidyl peptidase IV (DPP-IV) from fungal sources. This enzyme targets both gliadin and casein (milk protein) and is resistant to breakdown by other digestive enzymes. DPP-IV is thought to be one of the key enzymes responsible for the digestion of these proteins and is known to be found in lower amounts in the intestinal mucosa of individuals with celiac disease and also to have an inverse correlation with the level of mucosal damage among those with as well as without celiac disease. The lower the DPP-IV, the more significant the damage to the intestinal lining. Preparations containing DPP-IV are often recommended in order to safeguard against any hidden sources of gluten.

THERAPEUTIC APPROACH

The therapeutic approach is straightforward: eliminate all sources of gliadin (see Appendix 5), eliminate dairy products initially, correct underlying nutritional deficiencies, treat any associated conditions, and determine and eliminate all food allergens. If the patient does not begin to respond within 1 month, reconsider the diagnosis and search for hidden sources of gliadin.

Maintenance of a strict gluten-free diet is difficult in the United States owing to the ubiquitous distribution of gliadin and other activators of celiac disease in processed foods. Patients must be encouraged to read labels carefully in order to avoid hidden sources of gliadin, as is found in some brands of soy sauce, modified food starch, ice cream, soup, beer, wine, vodka, whiskey, and malt. Patients should also be encouraged to consult resources for patient education and information on gluten-free recipes.

RESOURCES FOR PATIENTS

Gluten Intolerance Group
31214 124th Ave. SE
Auburn, WA 98092
Website: http://www.gluten.net

Celiac Sprue Association
P.O. Box 31700
Omaha, NE 68131-0700
Website: www.csaceliacs.org

Celiac Disease Foundation
13251 Ventura Blvd., Suite 1
Studio City, CA 91604
Website: http://celiac.org

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CHAPTER 156

Cervical Dysplasia

Tori Hudson, ND, and Michael T. Murray, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- Abnormal Pap smears (atypical cells of undetermined significance [ASC-US]; low-grade squamous intraepithelial lesions [LGSILs]; high-grade squamous intraepithelial lesions [HGSILs])
- Human papillomavirus (HPV) testing for the presence of high-risk strains
- Colposcopy, endocervical curettage, cervical biopsies

Since the Bethesda System of reporting was first established in 1988, it has been revised several times. The current U.S. cervical disease management guidelines were last updated in 2009 and include algorithms for managing high-risk HPV strains, ASC-US, atypical cells for which high-grade lesions cannot be ruled out (ASC-H), LGSILs, and HGSILs have changed and continue to evolve. Recommendations for HPV testing and cytology testing and the combination of the two, colposcopy and biopsies, follow-up cytology testing, and colposcopy based on abnormal results are complex and often change. Guidelines differ depending on the patient's age, history of previous abnormal cytology testing, pregnancy status, previous exposure to diethylstilbestrol, immunosupression status (ex/kidney transplants), human immunodeficiency virus (HIV) status, and hysterectomy for benign indications and prior history of cervical intraepithelial neoplasia (CIN). We recommend that the clinician consult the latest available guidelines for screening and evaluation with colposcopy, biopsy, and follow-up testing from the American College of Obstetricians and Gynecologists, the American Cancer Society, and/or the U.S. Preventive Services Task Force.

GENERAL CONSIDERATIONS

Cervical dysplasia is generally regarded as a precancerous lesion with risk factors similar to those of cervical cancer.[1] Therefore, this discussion focuses on the following lifestyle and nutritional factors that appear to be cofactors in the development and progression of cervical dysplasias and ultimately cervical cancer:

- Early age of first intercourse
- Multiple sex partners (in heterosexual women without barrier contraception)
- Other infectious agents (*Chlamydia,* herpesvirus)
- History of genital warts
- Immunosuppression (HIV, transplant patient)
- Smoking
- Oral contraceptive use
- Pregnancy
- Many nutritional factors[1,2]

Human Papillomavirus

Epidemiology and Natural History

Almost all cervical cancer is associated with long-term persistent HPV infection, which is easily transmitted by genital-to-genital contact. The time from exposure to the appearance of a lesion or an abnormal Pap smear can range from a few weeks to decades. The incidence of medical visits for HPV disease has increased more than 500% in the past 30 years and HPV infection is considered epidemic by many. It is now so common that up to 80% of the adult population may be infected. HPV DNA tests have documented the presence of HPV DNA in at least 60% of young

women; however, less than 10% develop cervical lesions. This suggests that the host immunity is able to defend against the development of clinical disease, and that HPV infections are often transient and result in minor manifestations such as ASC-US. For other individuals, especially women, HPV results in a clinical expression to which the host immune response has not been able to respond effectively. The result is clinical disease that can include flat or raised genital warts; cervical, vaginal, vulvar, or perianal dysplasias; or progression to invasive cancers of the same site. The first step in the development of dysplasias or invasive cancers is viral entry. A complex interaction of host immunity, viral load, viral type, and host susceptibility determines the natural course of the disease. HPV is implicated as the etiology of cervical cancer in virtually all (99.8%) of the 320,000 cases of cervical cancer that occur annually in women throughout the world. In addition, HPV is detected in approximately 50% to 80% of vaginal, 50% of vulvar, and nearly all penile and anal cancers.

Of nearly 120 HPV types, approximately 20% to 30% are unclassified types that have been only partially sequenced. About 30 HPV types primarily infect the squamous epithelium of the lower anogenital tracts of both men and women, resulting in both flat and raised warts or intraepithelial lesions of the vulva, vagina, cervix, and perianal regions. Disease caused by HPV types 6, 11, 42, 43, or 44 most commonly manifest as classic genital warts with a cauliflower appearance, but they may also manifest as flat lesions. Types 16, 18, 31, 33, 35, 45, 51, 52, and 56 are considered high-risk types because they have been found in cancers of the lower genital tract. They are also found in intraepithelial lesions. Lesions that are caused by low- and high-risk HPV types can regress to normal even without treatment, but currently it is not possible to predict which lesions will regress and which will persist or progress.

Approximately 80% of cervical cancers are associated with types 16, 18, 31, and 45; 15% are associated with types 31, 33, 35, 51, and 52. LGSILs can be caused by both low- and high-risk HPV types. In fact, high-risk types have been detected in 75% to 85% of low-grade lesions with mixed low- and high-risk types in approximately 15% and low-risk types exclusively in only 2% to 25%.

Histologic Considerations

The principal reservoir of HPV is the moist mucosa and the cutaneous epithelial tissue in adjacent areas. Ninety-five percent of cervical dysplasias and cancers originate in the squamocolumnar junction of the cervical os.[1] In adolescence, glandular epithelium covers much of the exocervix; but as adolescence progresses, the columnar epithelium is gradually replaced by squamous cells. This actively growing area seems to be more susceptible to multiple insults and the HPV, probably because of the metaplastic nature of the conversion process and the inflammatory process of metaplasia.

Development and Progression of the Disease

In heterosexual women, exposure to HPV is common in the teens and twenties, soon after unprotected intercourse. Detectable disease is uncommon, yet up to 60% in this age group test positive for HPV DNA by polymerase chain reaction (PCR) testing. As stated earlier, the nature of the HPV infection is transient and the immune system responds to HPV in most individuals. One of three things can happen following infection with HPV: (1) The infection remains permanently latent or produces only transient cytologic changes; (2) individuals develop HPV-associated cytologic changes diagnostic of HPV—infections in approximately 60% of women with atypia or LGSIL spontaneously regress and 20% to 30% persist; and (3) 10% develop HGSIL.

PCR testing has shown that up to 70% of women clear the virus within the first year of infection. Low-grade lesions can regress on their own, persist, or progress. Progression to high-grade lesions tends to peak between the ages of 25 and 29, an average of 4 to 7 years after peak incidence of mild cervical dysplasia. Most low-grade lesions, although the majority are due to high-risk HPV types, do not progress to invasive cancer even if allowed to follow the natural history of the disease with no treatment interventions. Even women infected with HPV type 16, the type detected in more than 60% of cervical cancers, tend to regress spontaneously over time. In the United States, the incidence of invasive cervical cancer reaches a plateau in white women approximately 15 years after the peak incidence of CIN III, usually between the ages of 40 and 45.

TABLE 156-1 **Risk Factors in Cervical Dysplasia/Cancer***

RISK FACTOR	RELATIVE RISK
Smoking (10+ cigarettes/day)	3.06
Multiple sex partners (2-5)	3.46
First intercourse before age 18	2.76
Deficient dietary β-carotene (<5000 IU/day)	2.813
Deficient dietary vitamin C (<30 mg/day)	6.716

*The actual values for the absolute risk of the various risk factors are as yet somewhat controversial. The numbers listed here represent the author's summarization of the literature. These risks are not linearly additive because they are usually closely related; more extensive multivariant analysis will be necessary to determine the actual relative risk of each.

Risk Factors (Table 156-1)

Sexual Transmission

Early age at first intercourse, multiple sexual contacts without use of condoms, or both are associated with an increased risk of cervical dysplasia/carcinoma.[1,2] From this and other evidence, it has been suggested that cervical cancer is a sexually transmitted disease in the sense that the implicated infectious agent, HPV, is easily transmitted by genital-to-genital contact. Because the time from exposure to the appearance of a lesion can range from weeks to decades, it is almost impossible to identify individuals who transmit the virus.

Genital-to-oral transmission is suggested to be possible owing to detection of HPV types 6, 11, and 16 in some oropharyngeal cancers, but oral HPV lesions are in fact rare. Nonsexual exposure to the virus may occur from examination tables, doorknobs, tanning beds, and other inanimate objects, but it is difficult to document and prove.

Other infectious agents such as herpes simplex, *Chlamydia,* and HIV may serve as cofactors for HPV. These agents may alter cervical immunity, contribute to inflammation, facilitate entry of HPV into the basal cells, accelerate replication of HPV in the host cell nucleus, and coexist with HPV infection.

Smoking

A significant risk factor for cervical cancer and cervical dysplasia is cigarette smoking: smokers have an approximately threefold increased incidence compared with nonsmokers (one study[3] showed the increase to be as high as seventeenfold in women ages 20 to 29).[3-6] Several hypotheses have been proposed to explain this association:

- Smoking may depress immune function, allowing a sexually transmitted agent to promote abnormal cellular development, leading to the onset of cervical dysplasia.
- Smoking induces vitamin C deficiency, since vitamin C levels are significantly depressed in smokers.[7]
- Cervical cells may concentrate nicotine.
- There may be unrecognized associations between smoking and sexual behavior.[3-6]

Oral Contraceptives

Earlier studies suggested that the use of oral contraceptives (OCs) increased the risk of cervical neoplasia, both the invasive and precancerous types. More recent studies controlled for sexual history have not confirmed this association. Three large, well-controlled studies looked at invasive cervical cancer and OC use and did not find statistically significant associations compared with women who never used OCs.[8-10] There was no overall change in risk of invasive cervical cancer; however, one of the three studies[8] found a modestly increased risk in long-term users of OCs. The other two studies failed to find a significantly increased risk of invasive cervical cancer even with long-term OC use. Two other studies assessed OC use and the risk of cervical dysplasia, and neither found any statistically significant associations.[11,12]

A more disturbing aspect is that OC use has been associated with an increased incidence of adenocarcinoma, a rare cancer of the cervix. This is a less common variant of squamous cervical cancer. It appears that the incidence of this disease has increased over the past several decades, while the incidence of invasive squamous cervical cancer has decreased since the pill was introduced. Two studies found a modest but statistically significant increased risk of invasive cervical adenocarcinoma in women who had used OCs for more than 12 years.[13,14]

OCs are known to potentiate the adverse effects of cigarette smoking and to decrease the levels of numerous nutrients, including vitamins C, B_6, and B_{12} as well as folic acid, riboflavin, and zinc.[15]

THERAPEUTIC CONSIDERATIONS

A follow-up Pap test is used to determine what course of action is needed. Many cases of mild cervical dysplasia (ASC-US, LSILs) will go away spontaneously. The median time required for progression from cervical dysplasia to carcinoma in situ ranges from 86 months for LSIL to 12 months for HSIL. In LSIL, the natural approaches provided in this chapter can be followed with a follow-up Pap smear and colposcopy at 3 months. If colposcopy finds abnormal tissue, endocervical curettage may be appropriate. Prescribing a patient diagnosed with HSIL a colposcopy with endocervical curettage is recommended.

Dietary Factors

Numerous nutritional factors have been implicated as cofactors in the development of cervical dysplasia. Although many single nutrients may play a significant role (particularly beta-carotene and retinoids, folic acid, pyridoxine, and vitamin C), it is important to recognize that a large proportion (67%) of patients with cervical cancer have multiple nutrient deficiencies or abnormal anthropometric measurements. Significant abnormalities have been found in height-to-weight ratios, triceps skin fold thickness, midarm muscle circumference, serum albumin levels, total iron-binding capacity, hemoglobin levels, creatinine height index, prothrombin time, and lymphocyte count. Many other patients have marginal but "normal" nutritional status as determined by these cursory evaluations,[16] suggesting that multiple nutrient deficiencies are probably the rule rather than the exception.

Vitamin assessment by biochemical evaluation (plasma and red cell folate; serum beta-carotene; vitamins A, B_{12}, and C; erythrocyte transketolase for thiamine determination; erythrocyte glutathione reductase for riboflavin determination; and erythrocyte aspartate transaminase for pyridoxine determination) in patients with untreated cervical cancer shows that at least one abnormal vitamin level was present in 67% of patients, whereas 38% displayed multiple abnormal parameters.[17]

General dietary factors are also important. A high fat intake has been associated with an increased risk for cervical cancer, whereas a diet rich in fruits and vegetables is believed to offer significant protection against carcinogenesis, probably owing to the higher intake of fiber, beta-carotenes, and vitamin C.[5] Total serum carotene and tocopherol levels and their association with dietary intakes and the risk of newly diagnosed CIN and invasive cervical cancer were evaluated in a case-control study in Brazil.[18] Increasing concentrations of serum lycopene were negatively associated with CIN 1, CIN 3, and cervical cancer. Increasing concentrations of serum alpha and gamma tocopherols and higher dietary intakes of dark green and deep yellow vegetables/fruits were associated with nearly 50% decreased risk of CIN 3. In another case-control study, 239 women with squamous cell carcinoma of the cervix from the tumor registry in Buffalo, New York, completed a questionnaire, whereby researchers investigated the relationships between intakes of selected dietary nutrients and food groups and risk of cervical cancer.[19] Significant reductions in risk of cervical cancer of approximately 40% to 60% were observed for women in the highest versus the lowest tertiles of dietary fiber, vitamin C, vitamin E, vitamin A, α-carotene, beta-carotene, lutein, and folate.

Nutritional Botanical Supplements

Several key individual supplements are discussed later, but a combination of products may work best. One study showed multiple vitamins and mineral formulas, vitamins A and E, and calcium were significantly associated with a lower risk of cervical cancer and a lower HPV viral load.[20] The study enrolled 1096 women between the ages of 18 and 65 and included 328-HPV positive women, 166 controls, 90 women with CIN I, and 72 women with CIN 2 or 3. Multiple vitamins and minerals, vitamins A and E, and calcium were significantly associated with a lower risk of CIN 2 or 3. The patients who took the multiple vitamins and minerals had a lower HPV viral load and a significantly decreased frequency of CIN 1.

Vitamin A and Beta-Carotene

A minor association appears to exist between dietary retinoids and the risk of cervical cancer or dysplasia as well as a strong inverse correlation between beta-carotene intake and the risk of cervical cancer or dysplasia.[21-23] Although only 6% of patients with untreated cervical cancer have below-normal serum vitamin A levels, 38% have stage-related abnormal levels of beta-carotene.[17] Low serum beta-carotene levels are associated with a threefold greater risk for severe dysplasia,[23] and serum vitamin A and beta-carotene levels were found to be significantly lower in patients with cervical dysplasia than in a control group (54 vs 104 mg/dL for vitamin A and 21.3 vs. 13.9 mcg/dL for beta-carotene).[24,25]

Unfortunately response rates to intervention with carotenoids have been inconsistent. In a double-blind randomized placebo-controlled trial comprised of over 100 women who used either 30 mg/day of beta-carotene or placebo,[25a] cervical biopsies were performed before treatment and after 6 and 24 months. Persistence of

CIN 3 resulted in the patient's removal from the study. Of the 124 women included, 21 were not randomized because they moved, became pregnant, or voluntarily withdrew or the pathologic review of their initial cervical biopsies did not confirm CIN 2 or 3. Of the remaining 103 women, 33 experienced lesion regression, 45 had persistent or progressive disease, and 25 women did not complete the study and were considered nonresponders.

The overall regression rate (32%) was similar between beta-carotene and placebo arms and when stratified for CIN grade. HPV typing of 99 women showed that 77% were HPV-positive and 23% HPV-negative at enrollment. HPV-positive lesions were subdivided into indeterminate, low-, and high-risk categories. The response rate was highest for women with no HPV detected (61%), lower for those ranked at indeterminate or low risk (30%), and lowest for those classified at high risk (18%). In conclusion, beta-carotene did not enhance the regression of high-grade CIN, especially in HPV-positive subjects.[26]

Other intervention studies also faired poorly for beta-carotene:

- No difference in regression of CIN 1 lesions after 12 months with 30 mg of beta-carotene daily versus placebo[27]
- No regression of CIN lesions with 10 mg/day of beta-carotene versus placebo[28]
- After 9 months, lower regression rates of CIN 1 to 3 with 30 mg/day beta-carotene versus placebo[29]
- Slightly increased progression of ASCUS and CIN 1 with 30 mg/day of beta-carotene versus no treatment[30]

That said, mixed natural carotenoids have been a mainstay of comprehensive naturopathic treatment plans. Carotenoids and retinols offer several types of protection. They improve the integrity and function of the epithelial tissues, provide antioxidant properties, and enhance immune system function (see Chapter 56). As with other diseases, it appears that supplementation with beta-carotene is more advantageous than that with retinoids, possibly owing to their greater antioxidant properties, immune-enhancing effects, and tendency to be concentrated in epithelial tissues.

Topical vitamin A was used in a study of 301 women who received either four consecutive 24-hour applications (using a collagen sponge in a cervical cap) of retinoid or placebo followed by two more applications at 3 and 6 months. Retinoic acid increased the complete regression rate of moderate dysplasia from 27% in the placebo group to 43% in the treatment group. The women with severe cervical dysplasia did not improve.[31] In a University of Arizona study, vitamin A was delivered to 20 women via a cervical cap. In 10 of 20 women, cervical dysplasia completely disappeared. Of the 10 patients with a complete response, 5 had mild dysplasia and 5 had moderate dysplasia.[32] There were too few patients with severe dysplasia to be evaluated.

Vitamin A suppositories have also been used as part of a multifactorial treatment plan using oral folic acid, vitamin C, and carotenes with topical vitamin A suppositories and herbal vitamin suppositories. Other patients with more severe disease were treated with a topical "escharotic treatment." This study of atypia, mild, moderate, and severe dysplasia and carcinoma in situ comprised 43 women.[33,34] Of these, 38 returned to a normal disease-free state, 3 had partial improvements, 2 stayed the same, and none progressed to a more severe state of dysplasia during the course of the natural treatment protocol.

Vitamin C

A significant decrease in vitamin C intake and plasma levels occurs in patients with cervical dysplasia, and it has been documented that inadequate vitamin C intake is an independent risk factor for the development of premalignant cervical disease and carcinoma in situ.[35,36] Vitamin C is known to do the following[15]:

- Act as an antioxidant
- Strengthen and maintain normal epithelial integrity
- Improve wound healing
- Enhance immune function
- Inhibit carcinogen formation

Folic Acid

Low folic acid levels are implicated in many cases of cervical dysplasia, although this link is less now with widespread folic acid fortification of the food supply. When cervical cells lack folic acid, they become "macrocytic" in the same way as red blood cells (RBCs). Cervical cytologic abnormalities related to folic acid deficiency precede hematologic abnormalities by many weeks.[37,38] Prior to fortification of the food supply with folic acid it was the most common vitamin deficiency in the world and was especially common in women who were pregnant or taking oral contraceptives (OCs).[38,39] it is possible that many abnormal cytologic smears in the past reflected folate deficiency rather than "true" dysplasia.[38,30,31]

Even with food fortification, folic acid is still a factor in many cases of cervical dysplasia. This observation is particularly applicable to patients taking OCs. It has been hypothesized that OCs induce a localized interference with folate metabolism and, although serum levels may be increased, tissue levels at end-organ targets, such as the cervix, may be deficient.[40,41] This is consistent with the observation that tissue status as measured by erythrocyte folate is typically decreased (especially in those with cervical dysplasia), whereas serum levels may be normal or even increased.[42] OCs are believed to induce the synthesis of a macromolecule that inhibits folate uptake by cells. In controlled clinical studies in women with cervical dysplasia taking OCs, folic acid supplementation (10 mg/day) has resulted in the improvement or normalization of Pap smears.[40,43,44] Regression rates for patients with untreated cervical dysplasia are typically 1.3% for mild and 0% for moderate dysplasia. When patients were treated with folic acid, the regression-to-normal rate, as determined by colposcopy/biopsy examination, was observed to be 20% in one study,[44] 63.7% in another,[43] and 100% in another.[40] Furthermore, the progression rate of cervical dysplasia in untreated patients is typically 16% at 4 months, a figure matched in the placebo group in one study, while the folate-supplemented group had a 0% progression rate.[41] These figures were achieved despite the fact that the women remained on OCs.

Lower folic acid status has been shown to enhance the effect of the other risk factors for cervical dysplasia. For example, low RBC folate appears to be a major risk factor for HPV infection of the cervix.[43-45] In particular, higher circulating concentrations of folate are independently associated with a lower likelihood of becoming positive for high-risk human papillomaviruses (HR-HPVs) and of having a persistent HR-HPV infection and a greater risk for HSIL.

Vitamin B_{12} supplementation should always accompany folate supplementation to rule out the possibility that the latter may be masking an underlying vitamin B_{12} deficiency. In addition, women with higher concentrations of plasma folate who also had sufficient plasma vitamin B_{12} had 70% lower odds of being diagnosed with cervical dysplasia.[46]

Pyridoxine

Vitamin B_6 status, as determined by erythrocyte transaminase, is decreased in one third of patients with cervical cancer.[47] Decreased

pyridoxine status would have a significant effect on the metabolism of estrogens and tryptophan while also impairing the immune response.

Selenium

Low selenium levels in the diet and blood have been reported to be significantly lower in patients with cervical dysplasia. In one study, significantly lower selenium and zinc levels were found in both HSIL and cervical cancer patients compared with the control group. The activity of the selenium containing antioxidant enzyme glutathione peroxidase was significantly lower in the patients with HSIL or cancer than with the control group, and total antioxidant ability decreased from the control group to those with CIN to those with cancer. Increased glutathione peroxidase activity resulting from increased selenium intake is believed to be the factor responsible for selenium's anticarcinogenic effect, although other factors may be of equal significance.[48]

Copper:Zinc Ratio, Zinc, and Retinol

An increase in the serum copper:zinc ratio is a nonspecific reaction to inflammation or malignancy. In a study involving gynecologic cancer, it was suggested that the serum copper:zinc ratio "is clinically of utmost importance, since it constitutes a tool with which to establish the extent of the cancer."[49] A ratio above 1.95 indicated malignancy in 90% of the patients in that study. Elevated ratios are also seen in various conditions, including the following:

- OC use
- Pregnancy
- Acute and chronic infections
- Chronic liver disease
- Inflammatory conditions

Therefore, the serum copper:zinc ratio should not be used to predict malignancy in patients with these conditions. A decrease in available zinc may explain why retinol-binding protein was either absent or undetectable in 80% of dysplastic tissue samples as compared with 23.5% in normal tissue. A large study of 206 women found an inverse relationship between serum levels of both retinol and zinc and the incidence of cervical dysplasia.[50]

Indole-3-Carbinol/Diindolymethane

Indole-3-carbinol (I3C) is a phytochemical found in cabbage family vegetables. It is converted in the stomach to several compounds including diindolymethane (DIM). I3C and DIM are antioxidants and potent stimulators of natural detoxifying enzymes in the body. Studies have shown that increasing the intake of cabbage family vegetables or taking I3C or DIM as a dietary supplement significantly increases the conversion of estrogen from cancer-producing forms to non-toxic breakdown products.[51,52] The body breaks down estrogen in several ways. It can be converted into a substance called 16-α-hydroxyestrone, a compound that promotes estrogen-dependent cancer. Another method of breakdown produces 2-hydroxyestrone, which does not stimulate cancer cells. Women with HSIL have altered estrogen metabolism with a higher level of 16-α hydroxyestrone and fewer 2-hydroxyestrogen metabolites than normal.[53]

Given the ability of I3C or DIM to improve estrogen metabolism and possibly exert anti-HPV activity, these agents are very good candidates in the treatment of cervical dysplasia.[52] Preliminary studies are very encouraging. In one double-blind placebo-controlled study of 30 women with HSIL (biopsy-proved CIN 2 or 3), the women were given either 200 or 400 mg of I3C or a placebo for 12 weeks.[53] In 4 of 8 patients in the group who took 200 mg per day of I3C and 4 of 9 in the 400-mg group there was complete regression of their severe dysplasia, compared with none of the placebo group. HPV was detected in 7 of 10 placebo patients, in 7 of 8 in the 200 mg/day group, and in 8 of 9 in the 400 mg/day group.

DIM was used in another study of 64 patients with HSIL (biopsy-proved CIN 2 or 3) who were scheduled for loop electrosurgical excision procedure (LEEP). The patients were randomized 2:1 to receive DIM at approximately 2 mg/kg/day for 12 weeks or placebo. Although there was no statistically significant difference in any outcome between the DIM and placebo group overall the results with DIM showed an improved Pap smear in 49% (22 out of 45) with either a less severe abnormality or normal result. Colposcopy also improved in twenty-five subjects in the DIM group (56%).[54]

Green Tea

Constituents of green tea, namely polyphenol E and epigallocatechin-3-gallate (EGCG), have been effective against HPV-infected cervical cells and lesions in both laboratory and clinical studies. Green tea appears to induce apoptosis of HPV-infected cervical cells and also to arrest cell cycles, modify gene expression, and inhibit tumor formation.[55,56]

A clinical study confirmed these findings in patients through the use of either topical application via a green tea polyphenol ointment and/or oral ingestion of a green tea polyphenol capsule or an EGCG capsule. All treatment groups improved more than the placebo group (50% to 75% vs. 10%), but those given the topical treatment improved most significantly.[56]

Miscellaneous Considerations

Vaginal Depletion Pack

The vaginal depletion pack (or "vag pack") has a long history of effective use by naturopathic and eclectic physicians in the treatment of cervical dysplasia. Although its mechanism of action has not yet been elucidated, it is thought to work by promoting the sloughing of the superficial cervical cells, particularly those that are abnormal. It is effective as part of a multifactorial nutritional and topical treatment approach.[33,34] (See Appendix 12 for a complete description of this technique.)

Escharotic Treatment

The escharotic treatment is a topical herbal cryotherapy treatment of the cervix used to remove abnormal cells. It involves the use of zinc chloride mixed with *Sanguinaria canadensis*, a botanical. A full description of this protocol is given in Appendix 2. The escharotic treatment is especially indicated for CIN 2 and CIN 3, both HGSIL, but only when a satisfactory colposcopy has been performed by a clinician. In addition, the use of the escharotic treatment, rather than a LEEP or conization, must fall within the guidelines outlined under "Therapeutic Approach." The escharotic treatment is best implemented twice a week with 2 full days between treatments. The zinc chloride solution must be made by a compounding pharmacy as a prescription item.

THERAPEUTIC APPROACH

Treatment of cervical dysplasia requires proper monitoring and coordination of care if one practitioner is doing the workup with colposcopy/biopsies and another is proceeding with natural or integrated treatment approaches. The basic approach is to eliminate all factors known to be associated with cervical dysplasia and to optimize the patient's nutritional status. In particular, smoking and OC use are eliminated and the patient follows the supplementation program listed here.

The guidelines provide further insight on what is appropriate medical care of cervical dysplasia.

A. Criteria for Naturopathic Protocol
 1. ASC-US.
 2. ASC-US with documented HPV.
 3. ASC-H: endocervical curettage is negative or positive with a satisfactory colposcopy.
 4. Low-grade squamous intraepithelial neoplasia: endocervical curettage is negative with a satisfactory colposcopy.
 5. High-grade squamous intraepithelial neoplasia: endocervical curettage is negative with a satisfactory colposcopy.
 6. ASC-H: endocervical curettage is positive with a satisfactory colposcopy but either the patient is at low risk for more serious disease, has a low-risk type of HPV, or even if they do not have low risk HPV, the natural treatment protocol may be recommended at the discretion of the practitioner.
 7. Low-grade squamous intraepithelial neoplasia: endocervical curettage is positive with a satisfactory colposcopy, but either the patient is at low risk for more serious disease or has a low-risk type of HPV or the practitioner may recommend the natural treatment protocol at their discretion.
 8. High-grade squamous intraepithelial neoplasia: endocervical curettage is positive, with a satisfactory colposcopy, but the patient is at low risk or even if not, the natural treatment protocol may be recommended at the discretion of the practitioner and considered carefully after colposcopy, biopsies, and careful evaluation.
 9. It is possible to treat carcinoma in situ in select cases, but this is definitely a judgment call and should be considered very carefully after colposcopy, biopsies, and careful follow-up.

B. Referrals for Colposcopy with Biopsies
 1. ASC-US if HPV DNA testing is positive for high-risk HPV; if no HPV testing is done, then the Pap test should be repeated twice at 4- to 6-month intervals. If HPV typing is negative for high risk types, then the Pap test should be repeated in 12 months.
 2. ASC-H.
 3. Low-grade squamous intraepithelial lesions.
 4. High-grade squamous intraepithelial lesions.
 5. Atypical glandular cells of undetermined significance (AGUS); endometrial biopsy is needed as well.
 6. Adenocarcinoma in situ (AIS): endometrial biopsy is needed as well.
 7. Pap smear diagnosis of microinvasion or frank invasion.
 8. Endometrial cells present in a postmenopausal woman; also calls for an endometrial biopsy even if the cells are benign.
 9. A patient who may not follow through with the recommended follow-up Pap smear after an abnormal Pap result.
 10. Visible unknown cervical lesion regardless of the Pap smear test result.
 11. Initial examination of a DES daughter.
 12. Unexplained or persistent cervical bleeding.
 13. Vulvar condyloma with abnormal Pap test result.
 14. To be used for follow-up after treatment plan is completed, especially in high-grade squamous intraepithelial lesions.

C. Referrals for Conization or Loop Electrosurgical Excision Procedure (LEEP)
 1. Pap test results show more than one grade of dysplasia different than that seen on colposcopy or reported on in the biopsy.
 2. Biopsy shows squamous intraepithelial lesions with three to four quadrants involved.
 3. Unsatisfactory colposcopy with any degree of squamous intraepithelial lesions on biopsy.
 4. The patient may not be a good candidate for ongoing treatment and the closer follow-up required by alternative treatments.
 5. No improvement in pathology with the initial naturopathic plan or repeated alternate plan.
 6. If AGUS is found on the Pap test and no disease is detected on colposcopy, biopsies and endocervical curettage are indicated.
 7. If AIS is found on the Pap test and no disease is detected on colposcopy, biopsies and endocervical curretage are indicated.

D. At the Discretion of the Practitioner and Patient
 1. Positive endocervical curettage with any degree of squamous intraepithelial lesions. A more assertive approach is recommended.
 2. High-risk patients: The last Pap test more than 1 year previous, a history of genital warts, a history of cervical dysplasia, smokers, multiple sex partners with lack of safe sex practices. In these cases, a more proactive and assertive approach is recommended.

E. Referral for Probable Hysterectomy
 1. Microinvasive cervical cancer.
 2. Frank invasive cervical cancer.
 3. Adenocarcinoma.

Diet

Increase fruits and vegetables, especially those yellow and orange in color. A general immune supportive diet is considered prudent—high in fiber, vegetables, fruits, nuts, and seeds; low in fat and saturated fat.

Nutritional Supplements

- High potency multiple vitamin and mineral formula
- Folic acid: 10 mg/day for 3 months, then 2.5 mg/day for one year
- Vitamin B_{12} (methylcobalamin): 1 mg/day
- Beta-carotene: 150,000 IU/day for 3 months, then decrease to 25,000 IU/day for one year
- Vitamin C: 1 to 3 g/day for 3 to 12 months
- Vitamin E: 200 IU/day for 3 to 12 months
- Selenium: 200-400 mcg/day for 3 to 12 months
- Zinc: 20-30 mg/day for 3 to 12 months

Choose one of the following:

- I3C: 200 to 400 mg/day for 3 months
- DIM: 2.2 mg per kg body weight/day

Botanical Medicine

- Green tea extract (>90% total polyphenol content): 150 to 300 mg/day for 3-12 months

Sample Treatment Protocols

Atypical Cells of Undetermined Significance

- Topical

 Week 1: Insert vitamin A suppository every night for 6 nights.
 Week 2: Insert herbal vaginal suppository every night for 6 nights.
 Week 3: Repeat vitamin A.
 Week 4: Repeat herbal.
 Weeks 5 to 12: Insert green tea suppository two nights a week.
- Supplementation as previously noted for a minimum of 3 months

Low-Grade Squamous Intraepithelial Lesions

- Topical
 Week 1: Insert vitamin A suppository every night for 6 nights.
 Insert vag pack suppository on night 7.
 Week 2: Insert herbal suppository every night for 6 nights.
 Insert vag pack suppository on night 7.
 Week 3: Repeat vitamin A.
 Insert vag pack suppository on night 7.
 Week 4: Repeat herbal suppository.
 Insert vag pack suppository on night 7.
 Weeks 5 to 12: insert green tea suppository twice a week.
- Supplementation as previously noted for a minimum of 3 months

High-Grade Squamous Intraepithelial Lesions

- Topical
 Escharotic treatment twice a week for 5 weeks
 The last treatment is followed by 1 month of suppository routine as in LGSIL, then a green tea suppository twice a week for weeks 5 through 12
- Supplementation as previously noted for a minimum of 3 months

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CHAPTER 157

Chronic Fatigue Syndrome

Mark Dreher, PhD, and Michael T. Murray, ND

DIAGNOSTIC SUMMARY

- Mild fever
- Recurrent sore throat
- Painful lymph nodes
- Muscle weakness
- Muscle pain
- Prolonged fatigue after exercise
- Recurrent headache
- Migratory joint pain
- Depression
- Sleep disturbance (hypersomnia or insomnia)

INTRODUCTION

Chronic fatigue syndrome (CFS) describes varying combinations of symptoms including recurrent fatigue, sore throat, low-grade fever, swollen lymph nodes, headache, muscle and joint pain, intestinal discomfort, emotional distress, depression, and loss of concentration. Although newly defined and currently popular, CFS is not a new disease. References to a similar condition in the medical literature go back as far as the 1860s. In the past, CFS has been known by various names including the following:

- Chronic mononucleosis-like syndrome or chronic Epstein-Barr virus (EBV) syndrome
- Yuppie flu
- Post-viral fatigue syndrome
- Post-infectious neuromyasthenia
- Chronic fatigue and immune dysfunction syndrome (CFIDS)
- Iceland disease
- Royal Free Hospital disease

In addition, symptoms of CFS mirror symptoms of neurasthenia, a condition first described in 1869.

Definition

In response to the growing interest, CFS was formally defined in 1988 by a consensus panel convened by the Centers for Disease Control and Prevention (CDC) in an attempt to establish a guide for evaluating patients with chronic fatigue of unknown cause by clinical physicians and researchers.[1]

The CDC established a formal (and controversial) set of diagnostic criteria (Box 157-1). These are controversial for many reasons, including the fact that psychological symptoms are both a minor criterion and potential grounds for exclusion. One of the major complaints from physicians about the CDC definition is that it appears better suited for research than for clinical purposes. A major problem with the CDC criteria is that they ignore many of the common symptoms reported by patients with CFS (Table 157-1).

The British and Australian criteria for the diagnosis of CFS are less strict than those of the CDC.[2] In particular, the minor diagnostic criteria are not required and the major diagnostic criteria are not as strict. For example, in the Australian definition, the major criterion is simply fatigue at a level that causes disruption of daily activities in the absence of other medical conditions associated with fatigue.

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BOX 157-1 Centers for Disease Control and Prevention Diagnostic Criteria for Chronic Fatigue Syndrome

Major Criteria
- New onset of fatigue causing 50% reduction in activity for at least 6 months
- Exclusion of other illnesses that can cause fatigue

Minor Criteria
- Presence of 8 of the 11 symptoms listed, or 6 of the 11 symptoms and 2 of the 3 signs

Symptoms
1. Mild fever
2. Recurrent sore throat
3. Painful lymph nodes
4. Muscle weakness
5. Muscle pain
6. Prolonged fatigue after exercise
7. Recurrent headache
8. Migratory joint pain
9. Neurologic or psychological complaints
 - Sensitivity to bright light
 - Forgetfulness
 - Confusion
 - Inability to concentrate
 - Excessive irritability
 - Depression
10. Sleep disturbance (hypersomnia or insomnia)
11. Sudden onset of symptom complex

Signs
1. Low-grade fever
2. Nonexudative pharyngitis
3. Palpable or tender lymph nodes

Using the CDC criteria, the prevalence of CFS in individuals suffering from chronic fatigue in the United States is thought to be about 11.5%. Using the British criteria, it is about 15%, and using the Australian criteria, it is about 38%.[2]

ETIOLOGY

Infectious Agents

Owing in part to the similarity of CFS to acute or chronic infection, it was initially thought to be caused by a virus (i.e., EBV mononucleosis).[3] It now seems clear that CFS is not caused by any single recognized infectious disease agent. The CDC's four-city surveillance study found no association between CFS and infection by a wide variety of human pathogens, including EBV, human retroviruses, herpesvirus, rubella, *Candida albicans,* and others. No one pathogen appears to be causing CFS. However, the possibility remains that CFS may have multiple causes leading to a common endpoint, in which case, some viruses or other infectious agents may play a contributing role.

Immune System Abnormalities

There is little argument that a disturbed immune system plays a central role in CFS. A variety of such abnormalities have been reported in CFS patients (Box 157-2). Although no specific immunologic dysfunction pattern has been recognized, the most consistent abnormality is a decreased number or activity of natural killer (NK) cells.[4-7] NK cells received their name because of their ability to destroy cells that have become cancerous or infected by viruses. In fact, for a time, CFS was also referred to as *low natural killer cell syndrome (LNKS).*

Other consistent findings include a reduced ability of lymphocytes, key in the battle against viruses, to respond to stimuli.[7] One reason for this lack of response may be reduced activity or decreased production of interferon. Although both low and high levels of interferon have been reported in CFS, levels are depressed in most cases. When interferon levels are low, reactivation of latent viral infection is likely. Conversely, when interferon (as well as other chemical mediators like interleukin-1) levels are high, many of the symptoms may be related to the physiologic effects of interferon. When interferon is used as a therapy in

TABLE 157-1 **Frequency of Symptoms in Chronic Fatigue Syndrome**

SYMPTOM/SIGN	FREQUENCY (%)
Fatigue	100
Low-grade fever	60-95
Muscle pain	20-95
Sleep disorder	15-90
Impaired mental function	50-85
Depression	70-85
Headache	35-85
Allergies	55-80
Sore throat	50-75
Anxiety	50-70
Muscle weakness	40-70
Post-exercise fatigue	50-60
Premenstrual syndrome (women)	50-60
Stiffness	50-60
Visual blurring	50-60
Nausea	50-60
Dizziness	30-50
Joint pain	40-50
Dry eyes and mouth	30-40
Diarrhea	30-40
Cough	30-40
Decreased appetite	30-40
Night sweats	30-40
Painful lymph nodes	30-40

BOX 157-2 Immunologic Abnormalities Reported for Chronic Fatigue Syndrome

- Elevated levels of antibodies to viral proteins
- Decreased natural killer cell activity
- Low or elevated antibody levels
- Increased or decreased levels of circulating immune complexes
- Increased cytokine (e.g., interleukin-2) levels
- Increased or decreased interferon levels
- Altered ratio of T-helper cells to T-suppressor cells

BOX 157-3 Diagnostic Criteria for Fibromyalgia*

Major Criteria
- Generalized aches or stiffness of at least three anatomic sites for at least 3 months
- Six or more typical reproducible tender points
- Exclusion of other disorders that can cause similar symptoms

Minor Criteria
- Generalized fatigue
- Chronic headache
- Sleep disturbance
- Neurologic and psychological complaints
- Joint swelling
- Numbness or tingling sensations
- Irritable bowel syndrome
- Variation of symptoms in relation to activity, stress, and weather changes

*Fulfillment of all three major criteria and four or more minor criteria required.
Data from Murphree R: Treating and beating fibromyalgia. http://drrodgermurphree.com/fibromyalgia/.

BOX 157-4 Causes of Chronic Fatigue

- Preexisting physical condition
 - Diabetes
 - Heart disease
 - Lung disease
 - Rheumatoid arthritis
 - Chronic inflammation
 - Chronic pain
 - Cancer
 - Liver disease
 - Multiple sclerosis
- Prescription drugs
 - Antihypertensives
 - Antiinflammatory agents
 - Birth control pills
 - Antihistamines
 - Corticosteroids
 - Tranquilizers and sedatives
- Depression
- Stress and/or low adrenal function
- Impaired liver function, environmental illness, or both
- Impaired immune function
 - Chronic *Candida* infection
 - Other chronic infections
- Food allergies
- Hypothyroidism
- Hypoglycemia
- Anemia and nutritional deficiencies
- Sleep disturbances
- Cause unknown

cancer and viral hepatitis, the side effects produced are similar to the symptoms of CFS.

Chronic Fatigue Syndrome, Fibromyalgia, and Multiple Chemical Sensitivities

Fibromyalgia (FM) and multiple chemical sensitivities (MCS), like CFS, are recently recognized disorders with a substantial overlap of symptomatology.[4,5,8,9] The only difference in the diagnostic criteria for FM and CFS is the requirement of musculoskeletal pain in fibromyalgia and fatigue in CFS. The likelihood of being diagnosed as having fibromyalgia or CFS depends on the type of physician consulted. Specifically, if a rheumatologist or orthopedic specialist is consulted, the patient is much more likely to be diagnosed with fibromyalgia. (Box 157-3 presents the diagnostic criteria for fibromyalgia.)

One group of researchers carefully compared the symptomatology of 90 patients who had been diagnosed as having CFS, MCS, or FM (30 in each category).[9] Using the same questionnaire for all 90 patients, 70% of the patients diagnosed with FM and 30% of those with MCS met the CDC criteria for CFS. Particularly significant was the observation that 80% of both the FM and MCS patients met the CFS criteria of fatigue lasting more than 6 months with a 50% reduction in activity. More than 50% of the CFS and FM patients reported adverse reactions to various chemicals.

Other Causes of Chronic Fatigue

Chronic fatigue can be caused by various physical and psychological factors. Box 157-4 lists the major causes of chronic fatigue in an order of importance that represents how common the cause is among sufferers of chronic fatigue in the general population. The list is based on the findings of several large studies as well as the author's clinical experience (CFS is listed under a broader category of impaired immune function).

DIAGNOSIS

A great number of factors must be considered when evaluating a patient with chronic fatigue. Women tend to be at higher risk than men.[10] A detailed medical history and review of body systems goes a long way toward identifying important factors. The goal is to identify as many factors as possible that may be contributing to the patient's feeling of fatigue. For example, if a patient has heart disease, diabetes, or some other health condition and the condition or the drug he or she is taking is clearly responsible for the fatigue, the treatment of the fatigue becomes secondary to the treatment of his or her underlying health condition.

In many cases of chronic fatigue, further evaluation is necessary. The next steps can include a complete physical examination and laboratory studies. In the physical examination, it is important to look for clues that may point to the cause for chronic fatigue. For example, swollen lymph nodes may indicate a chronic infection, and the presence of a diagonal crease on both earlobes usually indicates impaired blood flow to the brain, a significant cause of fatigue in the elderly.

Plasma neuropeptide Y (PNY) has been reported as a potential biomarker for symptom severity in CFS.[11] Clinical research has demonstrated a significant correlation of PNY with stress, negative mood, general health, depression, and impaired cognitive function. However, expensive laboratory tests are best not ordered unless they are absolutely necessary. For example, if it is quite obvious that the patient has impaired immunity, it does not make much sense to perform elaborate and expensive blood tests on immune function because the results of these tests are not likely to influence the method of treatment.

Of particular value are assessments of liver detoxification function, bowel dysbiosis, and gastrointestinal permeability (see Chapters 10, 20, 27 and 53).

THERAPEUTIC CONSIDERATIONS

Because chronic fatigue and CFS are generally multifactorial conditions, the therapeutic approach typically involves multiple therapies that address different facets of the clinical picture.

A person's energy level, as well as his or her emotional state, is determined by an interplay between two primary factors—internal focus and physiology. Many people with chronic fatigue focus on how tired they are. They repeatedly reaffirm their fatigue to themselves and to anyone who will listen. Their physiology includes not only the chemicals and hormones circulating in the body but also the way they hold their bodies (usually slouched) and the way

they breathe (shallow). In most patients with chronic fatigue, both the mind and the body must be addressed. The most effective treatment is a comprehensive program designed to help people use their minds, attitudes, and physiologies to fuel higher energy levels.

Underlying Health Problems

Depression

The first factor to address is any underlying depression. Depression is one of the major causes of chronic fatigue, and it is a common feature of CFS. In the absence of a preexisting physical condition, depression is generally regarded as the most common cause of chronic fatigue. However, it is often difficult to determine whether the depression preceded the fatigue or vice versa. Depression is fully discussed in Chapter 142.

Stress

Stress is another factor to consider in the patient with chronic fatigue or CFS. Stress can be the underlying factor in the patient with depression, low immune function, or another cause of chronic fatigue (see Chapter 60 for guidelines on assessing the role of stress in chronic fatigue and CFS).

One of the tools we recommend to rate stress levels is the Social Readjustment Rating Scale developed by Holmes and Rahe.[12] The scale was originally designed to predict the likelihood of a person getting a serious disease due to stress. Various life-changing events are numerically rated according to their potential for causing disease. Even events commonly viewed as positive, such as an outstanding personal achievement, carry stress with them.

Impaired Liver Function, Environmental Illness, or Both

Exposure to food additives, solvents (e.g., cleaning materials, formaldehyde, toluene, benzene), pesticides, herbicides, heavy metals (e.g., lead, mercury, cadmium, arsenic, nickel, aluminum), and other toxins can greatly stress the liver and detoxification processes.[13,14] This exposure can lead to a condition labeled by many naturopathic and nutrition-oriented physicians as the "congested liver," "sluggish liver," or the more recently coined "impaired hepatic detoxification." These terms signify a reduced ability of the liver to detoxify. The congested or sluggish liver is characterized by a diminished bile flow, a condition known in medical terms as cholestasis or steatohepatitis, whereas the term *impaired hepatic detoxification* refers to decreased phase I or II enzyme activity, or both. Phase I detoxification rates in excess of phase II activity also cause toxicity problems owing to excessive accumulation of activated intermediates. In addition to exposure to toxic chemicals, various other agents and conditions, as listed in Box 157-5, can cause impairment of bile flow within the liver.

Although many of the conditions listed in Box 157-5 are typically associated with alterations in laboratory tests of liver function (e.g., serum bilirubin, aspartate aminotransferase, alanine transaminase, lactate dehydrogenase, γ-glutamyl transpeptidase), these tests alone may not be adequate to evaluate liver function because they are elevated only when the liver has been significantly damaged, and many of these conditions in the initial or "subclinical" stages of chronic fatigue may yield normal laboratory values.

Although there are more sensitive tests to determine the functional activity of the liver, such as the serum bile acid assay and various clearance tests (see Chapter 53), clinical judgment based on medical history remains the major diagnostic tool for the "sluggish liver" or impaired hepatic detoxification enzymes, the presence of chronic fatigue being the hallmark symptom.

BOX 157-5 Causes of Cholestasis

- Dietary factors
 - Saturated fat
 - Refined sugar
 - Low fiber intake
 - Obesity
- Diabetes
- Presence of gallstones
- Alcohol
- Endotoxins and other gut-derived bacterial toxins
- Hereditary disorders such as Gilbert's syndrome
- Pregnancy
- Natural and synthetic steroid hormones
- Anabolic steroids
- Estrogens
- Oral contraceptives
- Certain chemicals or drugs
- Cleaning solvents
- Pesticides
- Antibiotics
- Diuretics
- Nonsteroidal antiinflammatory drugs
- Thyroid hormone
- Viral hepatitis

People with a sluggish liver may also complain of the following:

- Depression
- General malaise
- Headaches
- Digestive disturbances
- Allergies and chemical sensitivities
- Premenstrual syndrome
- Constipation

Not surprisingly, people exposed to toxic chemicals often complain of the same symptoms. Many toxic chemicals (especially solvents) and heavy metals have an affinity for nervous tissue, giving rise to various psychological and neurologic symptoms[14,15]:

- Depression
- Headaches
- Mental confusion
- Mental illness
- Tingling in the extremities
- Abnormal nerve reflexes
- Other signs of impaired nervous system function

A hair mineral analysis is a possible screening test for heavy metal toxicity. Refer to Chapter 23 (Metal Toxicity: Assessment of Exposure and Retention) for further discussion.

A multi-clinic research study of chronically ill patients, many of whom were diagnosed as suffering from CFIDS, evaluated the efficacy of a comprehensive detoxification program. Patients were placed on a hypoallergenic diet and given a dietary food supplement rich in nutrients that assist in liver detoxification. These patients reported a 52% reduction in symptoms after 10 weeks, and symptom improvement was mirrored by normalization of hepatic phase I and phase II detoxification.[15]

Gastrointestinal Permeability

Excessive gastrointestinal permeability, as measured by the lactulose-mannitol absorption test (see Chapter 20), is a common finding in CFS.[16]

Hepatic Detoxification Functions

A treatment program using hypoallergenic rice protein food replacement formula to support hepatic phases I and II detoxification, was provided to patients who fulfilled the classic criteria of

BOX 157-6 Questionnaire for the Recognition of Impaired Immune Function

- Do you get more than two colds per year?
- When you catch a cold, does it take more than 5 to 7 days to get rid of the symptoms?
- Have you ever had infectious mononucleosis?
- Do you have herpes?
- Do you suffer from chronic infections of any kind?

the CDC and National Institutes of Health for CFS. The treatment resulted in symptom reduction, with clinical improvement being paralleled by improved hepatic detoxification function.[17]

Impaired Immune Function, Chronic Infection, or Both

When the immune system is impaired, infections can linger and fatigue can persist. There is a good reason for this: fatigue is the body's response mechanism to infection because the immune system works best when the body is at rest.

In order to determine the role that the immune system is playing in patients with chronic fatigue, the series of questions listed in Box 157-6 can be used during the patient interview to indicate an impaired immune system. Chapter 19 describes in substantial detail the laboratory methodologies for assessing immune function.

Chronic Candidal Infection

One of the most common findings in individuals with impaired immune function is gastrointestinal overgrowth of *Candida albicans*. Candidal overgrowth is now becoming recognized as a complex medical syndrome also known as "the yeast syndrome" and "chronic candidiasis." This overgrowth is believed to cause a wide variety of symptoms in virtually every system of the body, with the gastrointestinal, genitourinary, endocrine, nervous, and immune systems being the most susceptible. Box 157-7 lists the typical chronic candidiasis patient profile (see Chapter 51 for a comprehensive discussion).

The diagnosis of chronic candidiasis is often difficult because there is no specific diagnostic test. Stool cultures and elevated antibody levels to *Candida* are useful diagnostic aids, but they should not be relied on for diagnosis. The best method for diagnosing chronic candidiasis in most cases is a detailed medical history and patient questionnaire (see Appendix 1). Box 157-8 lists the factors that typically predispose a patient to candidal overgrowth.

Food Allergies

As far back as 1930, chronic fatigue was recognized as a key feature of food allergies.[18] Originally, Rowe and Rowe[19] used the term *allergic toxemia* to describe a syndrome that included the symptoms of fatigue, muscle and joint aches, drowsiness, difficulty in concentration, nervousness, and depression. Around the 1950s, this syndrome began to be referred to as the "allergic tension-fatigue syndrome."[19] With the popularity of CFS, many physicians and others are forgetting that food allergies can lead to chronic fatigue. Furthermore, between 55% and 85% of individuals with CFS have allergies. For more information on food allergies, see Chapter 15.

Hypothyroidism

Hypothyroidism is a common cause of chronic fatigue. However, the condition is often overlooked. The reason for this may be the reliance on standard blood measurements of thyroid hormone levels as the method of diagnosis.[20-22] Undiagnosed hypothyroidism is a serious concern, because failure to treat such a critical and underlying problem reduces the effectiveness of every other measure designed to increase energy levels. For more information, see Chapter 177.

BOX 157-7 Typical Chronic Candidiasis Patient Profile

- Gender: female
- Age: 15 to 50 years

General Symptoms
- Chronic fatigue
- Loss of energy
- General malaise
- Decreased libido

Gastrointestinal Symptoms
- Thrush
- Bloating, gas
- Intestinal cramps
- Rectal itching
- Altered bowel function

Genitourinary System Complaints
- Vaginal yeast infection
- Frequent bladder infections
- Primarily menstrual complaints

Nervous System Complaints
- Depression
- Irritability
- Inability to concentrate

Immune System Complaints
- Allergies
- Chemical sensitivities
- Low immune function

Past History
- Chronic vaginal yeast infections
- Chronic antibiotic use for infections or acne
- Oral birth control use
- Oral steroid hormone use

Associated Conditions
- Premenstrual syndrome
- Sensitivity to foods, chemicals, and other allergens
- Endocrine disturbances
- Psoriasis
- Irritable bowel syndrome

BOX 157-8 Factors Predisposing to Candidal Overgrowth

- Impaired immune function
- Antiulcer drugs
- Broad-spectrum antibiotics
- Cellular immunodeficiency
- Corticosteroids
- Diabetes mellitus
- Excessive sugar in the diet
- Intravascular catheters
- Intravenous drug use
- Lack of digestive secretions
- Oral contraceptive agents

Hypoglycemia

The association between hypoglycemia and fatigue is well known. What is not as well known is the role of hypoglycemia as a contributor to depression. Numerous studies have shown that depressed individuals suffer from hypoglycemia.[23-26] Because depression is the most common cause of chronic fatigue, hypoglycemia must always be ruled out (see Chapter 176).

Hypoadrenalism

Adrenal exhaustion was first proposed as a cause of chronic fatigue more than 50 years ago by Tintera.[27] A small but growing, body of evidence now supports the role of a disruption of the hypothalamic-pituitary-adrenal (HPA) axis in CFS.[28] Salivary tests of chronic fatigue patients show lower cortisol levels on wakening.[29] Other research suggests that there is no specific change to the HPA axis in CFS and that the observed changes are of multifactorial etiology, with some factors occurring as a consequence of the

illness. This second school of thought suggests that the HPA axis might play a role in exacerbating or perpetuating symptoms late in the course of the illness but not as a primary etiology.[30]

Either way, one of the major symptoms of glucocorticoid deficiency is debilitating fatigue. Glucocorticoid insufficiency is also characterized by a stressing event followed by feverishness, arthralgias, myalgias, adenopathy, postexertional fatigue, exacerbation of allergic responses, and disturbances of mood and sleep (i.e., the typical presentation of CFS). These symptoms are seen in partial or subclinical adrenal insufficiency, which may be detected only by the adrenocorticotropic hormone (ACTH) stimulation test or other endocrine testing. Glucocorticoids have a profound endogenous immunosuppressive effect. In subclinical adrenal insufficiency, this may allow for the symptoms of chronic fatigue, including exacerbation of allergic responses, enhanced antibody titers to various viral antigens, and elevations in cytokine levels. A group of CFS researchers believe that these patients form a heterogeneous group with various infectious and noninfectious antecedents.[28] They feel that CFS does not represent a discrete disease with a singular cause but rather a clinical condition. CFS is analogous to a number of complex medical conditions such as hypertension, in which various direct and indirect factors lead to the development of the clinical syndrome.

The researchers hypothesize that in CFS, specific pathophysiologic antecedents such as acute infection, stress, and preexisting or concurrent psychiatric illness may ultimately converge in a final common biological pathway, resulting in the clinical syndrome of CFS. They believe that their data and those of others suggest that a reduction in adrenocortical secretion is an important pathophysiologic component in the development of many biological and behavioral features of the syndrome.

For example, in one of their studies, 30 patients with classically defined CFS were compared with 72 normal volunteers and patients.[31] The CFS patients were found to have significantly reduced evening cortisol levels and low 24-hour urinary-free cortisol excretion. The CFS patients also had elevated basal ACTH concentrations and increased adrenocortical sensitivity to ACTH but a reduced maximal response, and they showed an attenuated net integrated ACTH response to corticotrophin-releasing hormone. These results are most compatible with a mild central adrenal insufficiency secondary to either a deficiency of corticotrophin-releasing hormone (CRH) or some other central stimulus to the pituitary-adrenal axis. The authors feel that the hyper-responsiveness of the adrenal cortex to ACTH in patients with CFS may reflect a secondary adrenal insufficiency in which adrenal ACTH receptors have become hypersensitive owing to inadequate exposure to ACTH. The reduction in response to large doses of ACTH might suggest overall adrenal atrophy. The evidence suggests that the mild hypocortisolism in these patients reflects a defect at or above the level of the hypothalamus, resulting in deficiency in the release of CRH or other secretagogues, or both, that serve to activate the pituitary-adrenal axis.

Mind and Attitude

The mind and attitude play a critical role in determining the status of the immune system and energy levels. Many patients with chronic fatigue (including CFS) are either depressed or just seem to have lost a real enthusiasm for life. Of course it is not easy to have much enthusiasm when you do not have much energy. But the two usually go hand in hand. Related to these psychological difficulties, it has been shown that there is a lack of social support for CFS patients.[32] It is a question of whether the lack of energy affects the CFS patient's ability to maintain a relationship or vice versa, or possibly both.

Cognitive behavioral therapy has shown some effective results in clinical use.[33,34] The first step is to convey to CFS patients that they can get better. Many patients with CFS are told that this is "something they will have to live with" and that "there is no cure." Achieving or maintaining a positive mental attitude is critical to good health and high energy levels, especially in patients with CFS. In order to achieve a positive mind set, a person must exercise or condition the attitude, much as one would condition the body. In order to help patients, physicians can prescribe mental exercises such as visualizations, goal setting, affirmations, and empowering questions, as detailed in Chapter 142.

Diet

Energy level appears to be directly related to the quality of foods routinely ingested. Patients should be encouraged to adhere to the dietary guidelines given in Chapter 44. It is especially important to eliminate or restrict caffeine and refined sugar.

Although acute caffeine consumption provides stimulation, regular caffeine intake may actually lead to chronic fatigue. Although mice fed one dose of caffeine demonstrated significant increases in their swimming capacity, when the dose of caffeine was given repeatedly for 6 weeks, a significant decrease in the mice's swimming capacity was observed.[35]

Several studies have found caffeine intake to be extremely high in individuals with psychiatric disorders. Another interesting finding is that the degree of fatigue experienced is often related to the quantity of caffeine ingested. In one survey of hospitalized psychiatric patients, 61% of those ingesting at least 750 mg/day (at least five cups of coffee) complained of fatigue, compared with 54% of those ingesting 250 to 749 mg/day and only 24% of those ingesting less than 250 mg/day.[36]

In patients who routinely drink coffee, abrupt cessation of coffee drinking will probably result in symptoms of caffeine withdrawal, including fatigue, headache, and an intense desire for coffee.[37,38] Fortunately this withdrawal period does not last more than a few days.

Nutritional Supplements

Nutritional supplementation is essential in the treatment of chronic fatigue. A deficiency of virtually any nutrient can produce the symptoms of fatigue as well as render the body more susceptible to infection. Individuals with chronic fatigue require, at the bare minimum, a high-potency multivitamin-multimineral formula along with extra vitamin C (3000 mg/day in divided doses) and magnesium (500 to 1200 mg/day in divided doses).

Magnesium

An underlying magnesium deficiency, even if subclinical, can result in chronic fatigue and symptoms similar to those of CFS. In addition, low red blood cell magnesium levels, a more accurate measure of magnesium status than routine blood analysis, have been found in many patients with chronic fatigue and CFS. The literature demonstrates that magnesium deficiency is not necessarily due to low dietary intake,[39] and several studies have shown good results with supplementation with improvements in magnesium stores.

For example, in one double-blind placebo-controlled trial, 32 CFS patients received an intramuscular injection of either magnesium sulfate (1 g in 2 mL of injectable water) or a placebo

(2 mL of injectable water) for 6 weeks. At the end of the study, 12 of the 15 patients receiving magnesium reported, on the basis of strict criteria, significantly improved energy levels, improved emotional state, and less pain. In contrast, only 3 of the 17 placebo patients reported that they felt better and only 1 reported improved energy levels.[40]

This study seems to confirm some impressive results obtained in clinical trials during the 1960s on patients suffering from chronic fatigue.[41-44] These studies used oral magnesium and potassium aspartate (1 g each) rather than injectable magnesium. Between 75% and 91% of the nearly 3000 patients studied experienced relief of fatigue during treatment with the magnesium and potassium aspartate. In contrast, the number of patients responding to a placebo was between 9% and 26%. The beneficial effect was usually noted after only 4 to 5 days, but sometimes it took as long as 10 days to achieve results. Patients usually continued treatment for 4 to 6 weeks; afterward, fatigue frequently did not return.

Injectable magnesium is not necessary to restore magnesium status.[45] Absorption studies indicate that magnesium is easily absorbed orally when it is bound to aspartate or citrate. In addition, both of these compounds may also help to fight fatigue. Aspartate feeds into the Krebs cycle, the final common pathway for the conversion of glucose, fatty acids, and amino acids to chemical energy (adenosine triphosphate [ATP]), while citrate is itself a component of the Krebs cycle. Krebs cycle components including aspartate, citrate, fumarate, malate, and succinate usually provide a better mineral chelate, as evidence suggests that minerals chelated to the Krebs cycle intermediates are better absorbed, used, and tolerated compared with inorganic or relatively insoluble mineral salts including magnesium chloride, oxide, or carbonate.[45,46]

Essential Fatty Acids

In one study, essential fatty acid supplementation was shown to improve the clinical picture and red blood cell phospholipid membrane profile of patients with post-viral fatigue. The preparation given contained linoleic, gamma-linolenic, eicosapentaenoic, and docosahexaenoic acids and was given as eight 500-mg capsules per day over a 3-month period.[47] In another study, an essential fatty acid supplement rich in eicosapentaenoic acid (EPA) was given daily to a female patient with a 6-year history of unremitting symptoms of chronic fatigue syndrome.

Within 6 to 8 weeks, the EPA-rich essential fatty acid supplementation led to a marked clinical improvement in the symptoms of CFS.[48] Previous research suggest that CFS is associated with pathophysiologic brain changes such as an enlargement in cerebral ventricular volume.[49] More clinical research is needed.

Nicotinamide Adenine Dinucleotide

Nicotinamide adenine dinucleotide (NADH), the active coenzyme form of vitamin B_3, has been shown to be effective in countering the negative effects of jet lag on cognition and wakefulness.[50] It is also known to encourage energy production through increased ATP generation. One small trial of NADH found a beneficial effect and improvement in quality of life in CFS patients. This study supplemented the stabilized oral absorbable form in a 26-subject randomized double-blind placebo-controlled crossover study. Subjects were randomly assigned to receive either 10 mg of NADH or placebo for 1 month. Following a 1-month washout period without supplement, subjects were then crossed to the alternate regimen for a final 1-month period. Within this cohort of 26 patients, 8 of 26 (31%) responded favorably to NADH, in contrast to 2 of 26 (8%) to placebo. No severe adverse effects were observed related to NADH,[51] nor have studies in animals shown any toxicity, even at megadoses.[52] More clinical research is necessary to fully elucidate the possible beneficial effects of NADH in CFS patients.

L-Carnitine

Carnitine is an essential nutrient for the transport of long-chain fatty acids into the mitochondrial matrix. One randomized controlled crossover study compared the efficacy of L-carnitine to amantidine, a drug known to relieve fatigue in patients with multiple sclerosis. Each intervention was given for 2 months, with a 2-week washout period between medicines. In 30 CFS patients, L-carnitine or amantadine was given as the first medicine. Amantadine was poorly tolerated by the CFS patients, of whom only 15 were able to complete the 8 weeks of treatment. In those individuals who completed 8 weeks of treatment, there was no statistically significant difference in any of the clinical parameters. With L-carnitine, there was a statistically significant clinical improvement in 12 of the 18 studied parameters after 8 weeks of treatment, with none of the clinical parameters showing any deterioration. The greatest improvement took place between weeks 4 and 8 of L-carnitine treatment. Only one patient, owing to diarrhea, was unable to complete the 8 treatment course.[53] L-Carnitine is extremely safe, with no significant side effects having been reported in any of the human clinical studies.

Coenzyme Q10 (CoQ10)

CoQ10 plays a role as a mitichondrial nutrient that acts as an essential cofactor for the production of ATP in the mitochondria.[54] Plasma CoQ10 has been found to be significantly lower ($P = 0.00001$) in CFS patients than in controls. Symptoms such as fatigue and neurocognitive impairment may be related to CoQ10 depletion.

Other Therapies

Breathing, Posture, and Bodywork

Proper care of the body is critical to the achievement of high levels of energy. Breathing with the diaphragm, good posture, and bodywork (e.g., massage, spinal manipulation) are all important in helping to relieve the stress that is a common contributor to fatigue.

Exercise

Exercise alone has been demonstrated to have a tremendous impact on mood and the ability to handle stressful life situations.[55] Regular exercise has also been shown to lead to improved immune status. For CFS patients, regular exercise has been shown to lead to a significant increase (up to 100%) in NK cell activity.[56,57] Although more strenuous exercise is required to benefit the cardiovascular system, light to moderate exercise may be best for the immune system. One study found that immune function was significantly increased by the practice of t'ai chi exercises.[58] Tai chi is a martial art technique that features movement from one posture to the next in a flowing motion that resembles dance.

The research thus far suggests that light to moderate exercise stimulates the immune system, whereas intense exercise (e.g., training for the Olympics) can have the opposite effect.[35,59] Graded exercise therapies, in which the patient begins with gradual walking and weight exercises and increases duration and intensity as are comfortable over time, may be the best approach.[60] Although there is concern for overtraining, one study has shown this method to be superior to relaxation and flexibility exercises.[61]

Botanical Medicines

Several botanical medicines support adrenal function and may offer significant benefits in CFS. Most notable are adaptogens like Chinese ginseng *(Panax ginseng)*, Siberian ginseng *(Eleutherococcus senticosus)*, rhodiola (Rhodiola rosacea), and ashwaganda (Withania somnifera). The effects of these herbs as "adaptagen" are discussed in Chapter 60, Stress Management. Of these herbal adaptogens, both Siberian ginseng and rhodiola have shown effects specific to CFS.

Siberian Ginseng (E. senticosus)

In addition to supporting adrenal function and acting as a nonspecific adaptogen, Siberian ginseng has been shown to exert a number of beneficial effects on immune function that may be useful in the treatment of CFS. In one double-blind study, 36 healthy subjects received either 10 mL of a fluid extract of ginseng or placebo daily for 4 weeks.[62] The group receiving the ginseng demonstrated significant improvements in various immune system parameters. Most notable were a significant increase in T-helper cells and an increase in NK cell activity—both of which are of value in the treatment of CFS.

Rhodiola rosea

Rhodiola rosea (artic root), a popular plant in traditional medical systems in Eastern Europe and Asia, where it has traditionally been recommended to help combat fatigue and restore energy. In one randomized, placebo-controlled trial of 60 patients with stress-related fatigue, Rhodiola was found to have an anti fatigue effect that increased mental performance, particularly the ability to concentrate, as well as decreased the cortisol response to awakening stress.[63]

Licorice Root (Glycyrrhiza glabra)

Considering the possible roles of viral infection and hypoadrenalism in CFS, licorice root with its antiviral and glucocorticoid-potentiating properties (see Chapter 96 for documentation of these properties) would seem to be an ideal botanical for this condition.[64] Unfortunately, this has not been rigorously evaluated, although an excellent response in a single patient has been reported.[65]The whole root must be used to assure glucocorticoid-potentiating glycyrrhizic and glycyrrhetinic acid activity.

THERAPEUTIC APPROACH

Successful treatment of CFS requires a comprehensive diagnostic and therapeutic approach. Especially important is identifying underlying factors that may be affecting the patient's energy levels or immune system. The strong correlation between CFS, FM, and MCS suggests that all may respond to hepatic detoxification, food allergy control, and a gut-restoration diet. Special attention should be paid to the advice on immune support in Chapter 56.

Diet

Food allergies should be identified and controlled. Water consumption should increase while consumption of caffeine-containing drinks and alcohol should stop. A diet of whole organically grown foods should be encouraged. Hypoglycemia should be controlled through the elimination of sugar and other refined foods and the regular consumption of small meals and snacks.

Lifestyle

The patient should be taught diaphragmatic breathing and proper posture. A regular exercise program should be prescribed; low-intensity activities may produce the greatest benefits.

Supplementation

- High-potency multivitamin and mineral formula according to guidelines given in Chapter 44
- Vitamin C: 500 to 1000 mg three times a day
- Vitamin E: 100 to 200 IU/day
- Magnesium bound to citrate or Krebs cycle intermediates: 200 to 300 mg three times a day
- Pantothenic acid: 250 mg/day
- NADH: 10 mg/day on an empty stomach
- L-carnitine: 1500 to 2000 mg/day in divided doses
- Fish oil: 5 g/day for at least 3 to 4 months
- Coenzyme Q10: 200 to 300 mg/day

Botanical Medicines

- Siberian ginseng *(E. senticosus)*
 - Dried root: 2 to 4 g
 - Tincture (1:5): 10 to 20 mL
 - Fluid extract (1:1): 2 to 4 mL
 - Solid (dry powdered) extract (20:1 or standardized to contain >1% eleutheroside E): 100 to 200 mg
- *Rhodiola rosea*
 - The therapeutic dose varies according to the rosavin content. The typical dosage is 200 to 300 mg/day of the extract standardized to contain 3% rosavins and 0.8% to 1% of salidroside.
- Licorice root *(G. glabra)*
 - Powdered root: 1 to 2 g
 - Fluid extract (1:1): 2 to 4 mL
 - Solid (dry powdered) extract (4:1): 250 to 500 mg

Counseling

The patient should either be counseled directly or referred to a professional counselor for cognitive behavioral therapy[66] and to establish a regular pattern of mental, emotional, and spiritual affirmations.

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CHAPTER 158

Congestive Heart Failure

Michael T. Murray, ND

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DIAGNOSTIC SUMMARY

- Left ventricular failure—exertional dyspnea, cough, fatigue, orthopnea, cardiac enlargement, rales, gallop rhythm, and pulmonary venous congestion
- Right ventricular failure—elevated venous pressure, hepatomegaly, dependent edema
- Both left and right ventricular failure
- Diagnosis confirmed by echocardiography

GENERAL CONSIDERATIONS

Congestive heart failure (CHF) refers to the inability of the heart to pump enough blood. The contractile function of the heart is governed by five primary factors:

- The contractile state of the myocardium
- The preload of the ventricle
- End-diastolic volume
- Impedance to left ventricular ejection
- Heart rate

Chronic CHF is most often due to the long-term effects of high blood pressure, previous myocardial infarction, disorder of a heart valve, cardiomyopathy, or chronic lung disease. These conditions produce CHF by affecting one or more of the primary determinants of myocardial contractile function. (Precipitating or exacerbating factors in CHF are presented in Box 158-1.)

One of the most serious consequences of reduced cardiac output is a reduction in renal blood flow and glomerular filtration rate, which in turn lead to sodium and fluid retention. Adding more stress is activation of the renin-angiotensin-aldosterone system, leading to an increase in peripheral vascular resistance; increased ventricular afterload, and increased levels of circulating vasopressin, which also serves as a vasoconstrictor and antidiuretic.

In an attempt to compensate for the reduced cardiac output, several compensatory mechanisms occur: tachycardia, increased activation of the sympathetic nervous system, ventricular dilation, and hypertrophy. These mechanisms are a bit of a mixed blessing. For example, while the increase in sympathetic activity increases cardiac output by increasing heart rate and force of contraction, it also leads to increased vascular resistance.

The signs and symptoms of CHF depend on which ventricle has failed. The clinical symptoms of left ventricular failure are dominated by symptoms of pulmonary congestion and edema, whereas right ventricular failure is characterized by signs of systemic venous congestion and peripheral edema. Weakness, fatigue, and shortness of breath are common to both right and left ventricular failure as well as biventricular failure.

DIAGNOSTIC CONSIDERATIONS

CHF is most effectively treated via natural measures in the early stages. Hence early diagnosis and prevention by addressing causative factors are imperative. The first symptom of CHF is usually shortness of breath. A chronic nonproductive cough may also be the first manifesting symptom. Patients suspected of having CHF should have an extensive cardiovascular evaluation including a complete physical examination to look for the characteristic signs of CHF (e.g., peripheral signs of heart failure, enlarged

BOX 158-1 Precipitating or Exacerbating Factors in Congestive Heart Failure

- Low levels of essential fatty acids
- Increased platelet aggregation
- Increased demand
 - Anemia
 - Fever
 - Infection
 - Fluid overload
 - Increased sodium intake
 - High environmental temperature
 - Renal failure
 - Hepatic failure
 - Thyrotoxicosis
 - Arteriovenous shunt
 - Respiratory insufficiency
 - Emotional stress
 - Pregnancy
 - Obesity
- Arrhythmias
- Pulmonary embolism
- Ethanol ingestion
- Nutrient deficiency
- Uncontrolled hypertension
 - Drugs
 - Beta-adrenergic blockers
 - Antiarrhythmic drugs
 - Sodium-retaining drugs
 - Corticosteroids
 - Nonsteroidal antiinflammatory drugs

and sustained left ventricular impulse, diminished first heart sound, gallop rhythm), electrocardiography, and echocardiography.



THERAPEUTIC CONSIDERATIONS

In the initial stages of CHF, natural measures designed to address the underlying cause (e.g., hypertension) or improve the metabolic functions of the myocardium (described later, as well as measures described in Chapter 145) are often effective. In later stages, however, medical treatment involving the use of diuretics and angiotensin-converting enzyme (ACE) inhibitors, digitalis glycosides, or both, is indicated in most cases. The measures described here can be used as adjunctive therapy in these more severe cases. The New York Heart Association (NYHA) staging system for CHF can be used in an effort to better identify likely respondents to natural therapy alone (Table 158-1). In general, excellent clinical results can be expected in stages I and II with the use of the natural measures described below.

Nutritional Supplements

The natural approach focuses on improving myocardial energy production, as CHF is always characterized by a state of energy depletion. This impaired energy production is often the result of nutrient or coenzyme deficiency (e.g., magnesium, thiamine, coenzyme Q_{10} [CoQ_{10}], carnitine). The dietary recommendations given in Chapter 174 are appropriate for most patients with CHF, especially if the CHF is due to long-term hypertension. Of particular importance is a diet low in sodium and high in potassium. A high intake of sodium greatly exacerbates the hemodynamic aspects of CHF. Sodium intake should be restricted to below 1.8 g daily. Furthermore, the dietary intake of several nutrients is usually well below recommended levels in patients with CHF.[1] Most notably low are magnesium, calcium, zinc, copper, manganese, thiamine, riboflavin, and folic acid. A high-potency multivitamin/multimineral formula is critical in these patients, especially if they are taking a diuretic.

TABLE 158-1 **Stages of Congestive Heart Failure as Defined by the New York Heart Association**

STAGE	SYMPTOMS
Stage I	Patient is symptom-free at rest and with treatment.
Stage II	Patient experiences impaired heart function with moderate physical effort. Shortness of breath with exertion is common. There are no symptoms at rest.
Stage III	Even minor physical exertion results in shortness of breath and fatigue. There are no symptoms at rest.
Stage IV	Symptoms such as shortness of breath and signs such as lower extremity edema are present when the patient is at rest.

Magnesium

Low magnesium levels (particularly white blood cell magnesium) are commonly found in patients with CHF. This association is extremely significant, since magnesium levels have been shown to correlate directly with survival rates. In one study, CHF patients with normal levels of magnesium had 1- and 2-year survival rates of 71% and 61%, respectively, compared with rates of 45% and 42%, respectively, in patients with lower magnesium levels.[2] These results are not surprising considering that magnesium deficiency is associated with cardiac arrhythmias, reduced cardiovascular prognosis, worsened ischemia, and increased mortality in acute myocardial infarction.

The magnesium deficiency probably stems from a combination of inadequate intake and increased wasting due to overactivation of the renin-angiotensin-aldosterone system, as is commonly seen in patients with heart failure. It can also be the effect of diuretics like furosemide.

In addition to providing benefits of its own in CHF, magnesium supplementation prevents the magnesium depletion caused by the conventional drug therapy for CHF (i.e., digitalis, diuretics, and vasodilators such as beta blockers and calcium channel blockers). Magnesium supplementation has even been shown to produce positive effects in CHF patients receiving conventional drug therapy even if serum magnesium levels are normal.[3] However, magnesium supplementation is not indicated in patients with renal failure, as this condition predisposes them to hypermagnesemia—a significant risk factor for mortality.[4] ACE inhibitors appear to produce a magnesium-sparing effect in patients on furosemide.[5] Typical dosages are 200 to 300 mg one to three times per day of magnesium in the citrate form. Oral magnesium can be effective in raising white blood cell magnesium and potassium levels.[6] It is highly important to monitor serum magnesium levels so as to prevent hypermagnesemia in patients with renal impairment as well as those on digoxin. Magnesium significantly reduces the frequency and complexity of ventricular arrhythmias in digoxin-treated patients with CHF even without the presence of digoxin toxicity, but too much magnesium may interfere with digoxin.[7]

Thiamine

Interest has recently risen regarding the potential role of thiamine deficiency in CHF. Thiamine was the first B vitamin discovered, hence its designation as vitamin B_1. It is well established that

thiamine deficiency can result in the cardiovascular manifestations of "wet beri beri," sodium retention, peripheral vasodilation, and heart failure. It is also well established that furosemide (Lasix), the most widely prescribed diuretic, has been shown to cause thiamine deficiency in animals and patients with CHF.

Although severe thiamine deficiency is relatively uncommon except in alcoholics, many Americans do not consume the recommended daily allowance of 1.5 mg, especially elderly patients in hospitals or nursing homes. In an attempt to gauge the prevalence of thiamine deficiency in the geriatric population, 30 unselected consecutive outpatients visiting a university outpatient clinic in Tampa, Florida, were tested for thiamine levels. Depending on the thiamine measurement, plasma versus red blood cell thiamine, low levels (defined as a level below the lowest reference range for younger age groups) were found in 57% and 33%, respectively.[8]

These results highlight the growing body of evidence that a significant percentage of the geriatric population is deficient in one or more of the B vitamins. Given the essential role of thiamine and other B vitamins in normal human physiology, especially cardiovascular and brain function, routine supplementation of B vitamins in this age group appears to be worthwhile.

The association between thiamine deficiency and long-term furosemide use was discovered in 1980, when it was shown that after only 4 weeks of furosemide use, thiamine concentrations and the activity of the thiamine-dependent enzyme transketolase were significantly reduced. The first study, looking at thiamine as a potential adjunct in the treatment of CHF, showed only modest benefits. However, several subsequent studies have shown that daily doses of 80 to 240 mg of thiamine daily improved the clinical picture, as indicated by a 13% to 22% increase of left ventricular ejection fraction.[9,10] This is quite significant, as an increase in ejection fraction is associated with a greater survival rate in patients with CHF. In one study, biochemical evidence of severe thiamine deficiency was found in 98% patients receiving at least 80 mg/day of furosemide and in 57% of patients taking 40 mg furosemide daily.[11]

Given the possible benefit, lack of risk, and low cost of thiamine supplementation, administration of 200 to 250 mg of thiamine daily appears to be warranted in patients with CHF, especially if they are on furosemide.

Carnitine

Normal heart function is critically dependent on adequate concentrations of carnitine and CoQ_{10} (discussed later). These compounds are essential in the transport of fatty acids into the myocardium and mitochondria for energy production. Although the normal heart stores more carnitine and CoQ_{10} than it needs, if the heart does not have a good supply of oxygen, carnitine and CoQ_{10} levels quickly decrease. Both of these agents have shown benefit in the treatment of CHF.

Several double-blind clinical studies have shown carnitine supplementation to improve cardiac function in patients with CHF.[12-14] In one double-blind study, only 1 month of treatment (500 mg three times daily) was necessary to cause significant improvement in heart function.[13] The longer carnitine was used, the more dramatic the improvement. After 6 months of use, the carnitine group demonstrated an increase in maximum exercise time of 25.9% and a 13.6% increase in ventricular ejection fraction. In another double-blind study in similar patients, at the end of 6 months of treatment, maximum exercise time on the treadmill increased by 16.4% and the ejection fraction increased by 12.1%.[14]

Even more obvious benefits were seen in a 3-year study of 80 patients with moderate to severe heart failure (NYHA classifications III to IV) caused by dilated cardiomyopathy. After a period of stable cardiac function up to 3 months, patients were randomly assigned to receive either carnitine (2 g/day orally) or placebo. After a mean of 33.7 months of follow-up (range, 10-54 months), 70 patients were in the study: 33 in the placebo group and 37 in the carnitine group. At the time of analysis, 63 patients were alive. Six deaths occurred in the placebo group and one death in the carnitine group. Survival analysis showed that patients' survival was statistically significant in favor of the carnitine group.[15]

Coenzyme Q_{10}

Numerous studies have also shown CoQ_{10} supplementation to be extremely effective in the treatment of CHF. Most of these studies used CoQ_{10} as an adjunct to conventional drug therapy. In one of the early studies, 17 patients with mild CHF received 30 mg/day of CoQ_{10}.[16] All patients improved, and 9 (53%) became asymptomatic after 4 weeks. In another early study, 20 patients with congestive heart failure due to either atherosclerosis or high blood pressure were treated with CoQ_{10} at a dosage of 30 mg/day for 1 to 2 months.[17] Of these patients, 55% reported subjective improvement; 50% showed a decrease in NYHA classification; and 30% showed a "remarkable" decrease in chest congestion as seen on chest radiography. Patients with mild disease tended to improve more often than those with more severe disease. Subjective improvements in these patients—including increased cardiac output, stroke volume, cardiac index, and ejection fraction— were confirmed by various objective tests. These results were consistent with CoQ_{10} producing an increased force of heart muscle contraction (a positive inotropic effect) similar to but less potent than the effect of digitalis.[18,19]

Three more studies have also shown CoQ_{10} to be effective in significantly improving heart function in patients with CHF. In a double-blind Scandinavian study of 80 patients, participants were given either CoQ_{10} (100 mg/day) or placebo for 3 months and then crossed. The improvements noted with CoQ_{10} were found to be actually more positive than those obtained from conventional drug therapy alone.[20] In another double-blind study, 641 patients with CHF received either CoQ_{10} (2 mg/kg) or a placebo for 1 year.[21] The number of patients requiring hospitalization or experiencing serious consequences due to CHF was significantly reduced in the CoQ_{10} group compared with the placebo group.

In the largest study to date, a total of 2664 patients in NYHA classes II and III were enrolled in an open study in Italy.[22] The daily dosage of CoQ_{10} was 50 to 150 mg orally for 90 days, with the majority of patients (78%) receiving 100 mg/day. After 3 months of CoQ_{10} treatment, the proportions of patients with improvement in clinical signs and symptoms were as follows:

- Cyanosis: 78.1%
- Edema (fluid retention): 78.6%
- Pulmonary edema: 77.8%
- Enlargement of liver area: 49.3%
- Venous congestion: 71.8%
- Shortness of breath: 52.7%
- Heart palpitations: 75.4%
- Sweating: 79.8%
- Subjective arrhythmia: 63.4%
- Insomnia: 66.2%
- Vertigo: 73.1%
- Nocturnal urination: 53.6%

Improvement of at least three symptoms occurred in 54% of patients, indicating a significantly improved quality of life (QoL) with CoQ_{10} supplementation. The results also showed a low incidence of side effects—only 36 patients (1.5%) reported mild side effects attributed to CoQ_{10}.

These positive results with CoQ_{10}, however, were not seen in one clinical trial. In this double-blind study, 55 patients with CHF NYHA classes III and IV, ejection fraction of less than 40%, and peak oxygen consumption less than 50% during standard therapy were randomly assigned to receive CoQ_{10} (200 mg) or placebo. Analysis indicated that there were no changes in ejection fraction, peak oxygen consumption, or exercise duration in either group. Possible explanations for failure to achieve a therapeutic benefit in this study may include the insufficient strength of CoQ_{10} to produce significant effects in more severe stages of CHF or the fact that blood levels of CoQ_{10} did not reach sufficient levels. Although the mean serum concentration of CoQ_{10} increased from 0.95 mcg/mL to 2.2 µg/mL in 19 of 22 patients on CoQ_{10}, blood levels were below the suggested threshold of 2.5 mcg/mL.[23]

Arginine

Another amino acid of value in CHF is arginine, although via totally different mechanisms from those of other nutrients. One of the experimental findings in patients with CHF is that they are less able to achieve peripheral vasodilation during exercise due to endothelial dysfunction. Since the endothelial cells make the natural vasodilator nitric acid from arginine, several researchers have evaluated the efficacy of arginine in improving CHF. The first study of orally administered arginine showed promising results. In a randomized double-blind placebo-controlled study of 5.6 to 12.6 g/day of oral L-arginine, peripheral blood flow was found to increase by 29%; in addition, 6-minute walking distance increased by 8% and arterial compliance by 19%.[24] Subsequent studies have shown arginine supplementation to improve endothelial cell and renal function (as shown by improvements in glomerular filtration rate, natriuresis, and plasma endothelin level) in patients with CHF.[25,26] Use of arginine is cautioned by a report in one study in survivors of myocardial infarction where supplementation with arginine (9 g/day for 6 months) was associated with an increase in mortality compared with the placebo group (8.6% vs. 0%).[27]

Botanical Medicines

Crataegus oxyacantha (Hawthorn)

Preparations of *Crataegus* sp. appear to be quite useful in CHF, especially in the early stages as a sole agent and in the latter stages in combination with digitalis cardioglycosides. The effectiveness of *Crataegus* in CHF has been repeatedly demonstrated in double-blind studies.[28-30] In one of the most recent of these, 30 patients with CHF (NYHA stage II) were assessed in a randomized double-blind study.[29] Treatment consisted of a *Crataegus* extract standardized to contain 15-mg procyanidin oligomers per 80-mg capsule. Treatment duration was 8 weeks, and the substance was administered at a dosage of one capsule taken twice daily. The group receiving the *Crataegus* extract showed a statistically significant advantage over placebo in terms of changes in heart function as determined by standard testing procedures. Systolic and diastolic blood pressures were also mildly reduced. As in all other studies with *Crataegus* extracts, no adverse reactions occurred.

In another study, 78 patients with CHF (NYHA stage II) were given either 600 mg of standardized *Crataegus* extract or placebo daily.[30] The parameter used to measure effectiveness was the patient's working capacity on a bicycle ergometer. After 56 days of treatment, the *Crataegus* group had a mean increase of 25 W compared with the placebo group's increase of only 5 W. In addition, the *Crataegus* group also experienced a mild but significant reduction in systolic blood pressure (171-164 mm Hg) and heart rate (115 to 110 beats per minute). There was no change in blood pressure or heart rate in the placebo group.

In patients with NYHA stage III CHF, *Crataegus* may not be sufficient to produce clinical effects. A randomized double-blind placebo-controlled trial comprised of 120 ambulatory patients with NYHA class II to III CHF. All patients received conventional medical therapy as tolerated and were randomized to either hawthorn 450 mg twice daily or placebo for 6 months. The primary outcome at 6 months was a change in the 6-minute walk distance. Secondary outcomes included QoL measures, peak oxygen consumption, and anaerobic threshold during maximal treadmill exercise testing, NYHA classification, left ventricular ejection fraction (LVEF), neurohormones, and measures of oxidative stress and inflammation. There were no significant differences between groups in the 6-minute walk distance or on measures of QoL, functional capacity, neurohormones, oxidative stress, or inflammation. However, a modest difference in LVEF favored hawthorn.[31]

Terminalia arjuna

A traditional Ayurvedic botanical for cardiac failure has recently been shown to be effective in a controlled clinical study. Twelve patients with severe refractory congestive heart failure (class IV NYHA) received an extract (500 mg every 8 hours) from the bark of *Terminalia arjuna* or placebo for 2 weeks. Those receiving the medicinal plant experienced, according to echocardiographic evaluation, statistically significant improvements in several parameters of cardiac function, such as end-systolic volume and left ventricular ejection fraction. A second uncontrolled phase of the study using a combination of *T. arjuna* with conventional medication found that after 2 years, 9 patients showed a remarkable improvement to NYHA class II, with the other 3 improving to class III.[32]

THERAPEUTIC APPROACH

Treatment with diet and the natural agents as described earlier is effective in the initial stages of CHF (i.e., NYHA stages I and II). In later stages, adjunctive drug therapy is usually necessary. Treatment is designed to address the underlying pathophysiology and to improve myocardial function through improved energy production.

Diet

Patients should be encouraged to achieve their ideal body weight, restrict sodium intake (below 1.8 g daily), increase the consumption of plant foods in the diet, reduce the intake of saturated fat, and follow the other dietary guidelines given for lowering blood pressure.

Nutritional Supplements

Magnesium: 200 to 400 mg three times a day
Thiamine: 200 to 250 mg a day
L-Carnitine: 500 to 1000 mg three times a day
CoQ_{10}: 100 to 300 mg a day
Arginine: 1000 to 2000 mg three times a day

Botanical Medicines

- *C. oxyacantha* (Hawthorn) extract (1.8% vitexin-4% rhamnoside or 10% procyanidin content): 200 to 300 mg three times a day
- *T. arjuna* extract: 500 mg three times a day

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CHAPTER 159

Cystitis and Interstitial Cystitis/Painful Bladder Syndrome

Geovanni Espinosa, ND, LAc, and Michael T. Murray, ND

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DIAGNOSTIC SUMMARY

- Burning pain on urination
- Increased urinary frequency, urgency, nocturia
- Turbid, foul-smelling, or dark urine
- Lower abdominal pain
- Urinalysis showing significant pyuria and bacteriuria with bacterial cystitis
- Pain in the pelvis (suprapubic) or between the vagina and anus in women or between the scrotum and anus in men (perineal)
- Chronic pelvic pain
- A persistent urgent need to urinate
- Pain during sexual intercourse

GENERAL CONSIDERATIONS

Bladder infections in women are surprisingly common: 10% to 20% of all women have urinary tract discomfort at least once a year, 37.5% of women with no history of urinary tract infection (UTI) will have such an infection within 10 years, and 2% to 4% of apparently healthy women have elevated levels of bacteria in their urine, indicative of an unrecognized UTI. Women with a history of recurrent UTI will typically have an episode at least once every year.[1] Recurrent bladder infections can be a significant problem because 55% will eventually involve the upper urinary tract (i.e., the kidneys). Recurrent kidney infections can cause abscess formation, disseminated intravascular coagulation, acute respiratory distress syndrome, sepsis, and chronic progressive renal damage, resulting in scarring and, for some, kidney failure.

Except in infants, UTIs are much less common in males than females and in general indicate an anatomic abnormality, a prostate infection, or rectal intercourse. Table 159-1 lists incidence by age and gender.

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic bladder disorder characterized by chronic pelvic pain (CPP) and irritative voiding symptoms. IC/PBS is not due to infection; it is characterized by symptoms similar to cystitis, and patients may also report otherwise undiagnosed CPP. The symptoms of IC/PBS can overlap with such conditions as endometriosis, recurrent UTI, CPP, overactive bladder, and vulvodynia. Studies have indicated that IC affects 52 to 67 per 100,000 people in the United States.[2] Some investigators believe these numbers are vastly underestimated owing to lack of proper diagnosis.

DIAGNOSIS

The diagnosis of bladder infection is imprecise because clinical symptoms and the presence of significant amounts of bacteria in the urine do not correlate well. As indicated in Table 159-2, only 60% of women with the typical symptoms of UTI actually have significant levels of bacteria in their urine. Equally important, however, is the fact that 20% have the more potentially serious involvement of the upper tract.

In general, the diagnosis is made according to signs and symptoms and urinary findings. A pelvic examination is indicated if there is a history consistent with vaginitis or cervicitis or if there is confusion regarding diagnosis. Microscopic examination of the infected urine shows high levels of white blood cells (WBCs)

TABLE 159-1 **Incidence of Urinary Tract Infection According to Age and Gender**

AGE GROUP	INCIDENCE	MALE:FEMALE RATIO
Neonatal	1	1.5:1
Preschool age	1.5-3	1:10
School age	1.2	1:30
Reproductive age	3-5	1:50
Geriatric	10-30	1:1.5

Modified from Rubin RH. Infections of the urinary tract. In Dale DC, Federman DD, eds. Scientific American Medicine. New York: Scientific American, 1997.

TABLE 159-2 **Results of Women Presenting with Typical Urinary Tract Infection Symptoms and No Fever, Vaginal Symptoms, or Toxicity**

DIAGNOSIS	PERCENTAGE OF SUBJECTS
Upper urinary tract infection	20
Bladder infection	40
Low levels of bacteria in urethra	16
Urethral *Chlamydia*	8
Unsuspected vaginitis	4
Other (e.g., herpes, gonorrhea, pelvic inflammatory disease)	12

Modified from Reilly BM. Practical strategies in outpatient medicine. Philadelphia: Saunders, 1984:277.

TABLE 159-3 **Bacteriologic Findings (percentage positive) in Outpatients and Inpatients with Urinary Tract Infections**

BACTERIAL SPECIES	OUTPATIENTS	INPATIENTS
Escherichia coli	89.2	52.7
Proteus mirabilis	3.2	12.7
Klebsiella pneumoniae	2.4	9.3
Enterococcus	2	7.3
Enterobacter aerogenes	0.8	4
Pseudomonas aeruginosa	0.4	6
Proteus spp.	0.4	3.3
Serratia marcescens	0	3.3
Staphylococcus epidermidis	1.6*	0.7
Staphylococcus aureus	0	0.7

Modified from Rubin RH. Infections of the urinary tract. In Dale DC, Federman DD, eds. Scientific American Medicine. New York: Scientific American, 1997.
*Recent evidence suggests that this may be more prevalent than is currently thought—in sexually active college-age women, it may account for as much as 20% of asymptomatic urinary tract infections.

and bacteria. Culturing the urine determines the quantity and type of bacteria involved. As shown in Table 159-3, *Escherichia coli* (from the colon) is by far the most common. The presence of fever, chills, and low back pain can indicate involvement of the kidneys. Those with recurrent infections should be examined by intravenous urogram to determine if a structural abnormality is present.[3]

IC/PBS can also be difficult to diagnose because the symptoms overlap with a variety of other disorders, including endometriosis, UTI, chronic CPP, overactive bladder (OAB), and vulvodynia.[4,5] Because there is no definitive diagnostic test, IC/PBS remains a diagnosis of exclusion. The presence of additional symptoms caused by other pain generators can confuse the diagnosis even further. Patients may not receive an accurate diagnosis for years. The median time between the development of IC/PBS symptoms and the diagnosis is approximately 5 years.[6]

CPP is pain lasting 6 months or longer that is severe enough to affect daily functioning or requires medical care.[4] The specific etiology of CPP is often unknown and may be multifactorial.[7] Gynecologic conditions that can cause CPP include endometriosis, adhesions, pelvic inflammatory disease (PID), cysts, and polyps.[7] However, a retrospective cohort analysis of a large primary care database in the United Kingdom found that only 20.2% of all cases of CPP had a gynecologic etiology.[8] Gastrointestinal diagnoses represented 37.7% of cases, with irritable bowel syndrome (IBS) accounting for 29.1%. Cystitis accounted for 30.8% of diagnoses in this population of women with noncyclic pain lasting for 6 months or longer. Up to one half of the women in primary care practices who have CPP may have more than one diagnosis for their pain. As described previously, it is common for a patient with CPP to have both endometriosis and IC/PBS.[7]

Physical examination is a critical component of diagnosing IC/PBS. In IC/PBS patients, this can be emotionally distressing because of pain, so it is important that the physician proceed slowly and carefully.[9] Because the bladder is a pain generator in IC/PBS, tenderness with single-digit examination of the trigonal area (bladder base or urethra) can help establish a diagnosis of IC/PBS, as can pain in the pelvic floor or levator ani.[4] Patients with IC/PBS tend to have urethral or bladder tenderness, whereas those with vestibulodynia have vestibular tenderness.[10] Tenderness on single-digit examination of the vaginal fornices can help distinguish endometriosis from IC/PBS.[9]

Urinalysis can rule out hematuria, and urine culture is required to identify bladder infection.[9] Cytology and computed tomography with double contrast when indicated (hematuria, history of smoking, 40 years of age and older) can help rule out urinary tract malignancies.[11] Patients with results suggesting a malignancy should be referred to a urologist. Several optional diagnostic tests can help diagnose IC/PBS. The presence of glomerulations seen on cystoscopy with hydrodistention may aid in the diagnosis of IC/PBS. A negative cystoscopic evaluation should never be used to rule out IC/PBS, because many patients with early IC/PBS will not have glomerulations.[12] The potassium sensitivity test (PST) may indicate a defective bladder lining. The PST involves intravesical instillation of a potassium solution, which triggers symptoms of pain and urgency in patients with abnormal permeability of the bladder surface.[13] Intravesical instillation of an anesthetic cocktail can be used as a diagnostic tool as well as a treatment. Known as the "anesthetic bladder challenge," this test can help localize pain to the bladder.[14,15]

Collection of Urine Specimen for Culture

The optimal clinical method for obtaining a urine sample is the voided midstream specimen. It involves cleaning of the urethral meatus or vaginal vestibule before the sample is collected. If vaginal epithelial cells are present, a new specimen should be collected. To avoid repeating the collection, a satisfactory technique for the female, called "the clean catch," consists of spreading the labia and cleaning the area with two gauze sponges moistened with an

antimicrobial solution and a dry gauze sponge. The washing is accomplished by making a single front-to-back motion with each of the two moist sponges and then the dry sponge. While the labia are still held apart, a small amount of urine is allowed to pass into the toilet (or bedpan); then a midstream specimen is collected in a sterile container and immediately closed.

Occasionally, the urine must be collected via catheterization. This is a more invasive procedure and carries with it a 1% to 2% chance of initiating a UTI via the introduction of microorganisms into the bladder. Suprapubic aspiration is the most accurate method of urine collection, but obviously it is also the most invasive one.

Examination of the Collected Urine

Several methods are routinely employed in the detection of bacteria in the urine. They range from the use of dipsticks to microscopic examination and culture. For most accurate determinations, the urine should be examined within 1 hour. If examination must be delayed, refrigeration at 58° C preserves the urine for most routine examinations. However, culturing requires that the urine not be refrigerated for more than 8 hours.

Dipstick Methods

The modern examination of urine specimens typically involves the use of reagent strips, which are dipped into the urine and removed. Parts of each dipstick are impregnated with chemicals that react with specific substances in the urine to produce various colors. Color standards, with which the color can be compared, are provided. Careful attention must be paid to match the dipstick to the color standard at the appropriate time. Instructions accompany commercially prepared dipsticks.

Dipsticks are invaluable for qualitative and rough quantitative analysis. Typically they provide information on pH, protein, glucose, ketones, bilirubin, hemoglobin, leukocyte esterase, nitrite, and urobilinogen. Some dipsticks also allow for the detection of WBCs and bacteria (including semiquantitative cultures).

Urinary infections typically increase the number of WBCs present. The leukocyte esterase test is used to detect WBCs in the urine. Because many common organisms contain enzymes that reduce nitrate in the urine to nitrite (Box 159-1), the measurement of urinary nitrite provides an inexpensive and rapid way to detect significant bacteriuria, but the findings should be confirmed by culture. Although both tests have a high specificity (approximately 95%), the leukocyte esterase test is approximately 80% to 90% sensitive, whereas the nitrite test is only approximately 50% sensitive compared with a quantitative culture as the gold standard. However, the combination of both tests improves the sensitivity up to the range of 85% to 90%.[16]

Microscopic Examination

Microscopic examination should be performed within the first hour after collection. A drop of fresh urine or a drop of resuspended sediment from centrifuged fresh urine is placed on a microscope slide, covered with a coverslip, and examined with the high-dry objective under reduced illumination. The presence of more than 10 bacteria per field in an unstained specimen suggests a bacterial count of more than 100,000/mL of urine. Smears may also be made using a Gram stain and examined under the oil immersion objective. The presence of WBCs further indicates an infectious process. The presence of large quantities of protein, WBC casts, or both in the micrographic examination may be indicative of renal involvement, most commonly pyelonephritis.

BOX 159-1 **Nitrates and Biological Organisms**

Organisms That Reduce Nitrates to Nitrites

Citrobacter spp.
Escherichia coli
Klebsiella pneumoniae
Proteus spp.
Pseudomonas spp.
Serratia marcescens
Shigella
Staphylococcus spp. (most)

Organisms That Do Not Reduce Nitrates to Nitrites

Neisseria gonorrhoeae
Streptococcus faecalis
Mycobacterium tuberculosis

Urine Culture

Typically, only quantitative cultures are used. After introduction of diluted urine to the suitable medium and incubation, the colonies are counted and multiplied by the dilution factor to yield the bacterial count per milliliter. Bacteriuria is considered significant if it is more than 100,000/mL, but even 1000/mL is considered clinically significant in the presence of symptoms characteristic of UTI. Most physicians are now employing semiquantitative tests[17] using dipsticks or glass slides coated with culture media. Colonies are counted and appearance is compared within 12 to 24 hours of incubation. For recurrent or chronic infection, sensitivity studies are often performed.

In more than 95% of UTIs, a single bacterial species is the problem. When mixed bacterial species are grown, the probability of contamination is high. Recurrence of UTI after the initial bacterial infection is resolved is common.

Staphylococcus epidermidis, diphtheroids, and lactobacilli are commonly found in the distal urethra but rarely cause UTI. Symptoms of recurrent UTI include urgency, frequency, nocturia, and pelvic pain. Diagnosis is established by a positive urine culture.[18]

COEXISTING CONDITIONS AND DIFFERENTIAL DIAGNOSIS

Although bacterial cystitis usually appears acutely and by itself, IC/PBS typically manifests with comorbities that include endometriosis, IBS, vulvodynia, and OAB.

A detailed medical history and physical examination are the basis for diagnosing the cause of CPP. The use of questionnaires, such as the Pelvic Pain, Urgency Frequency Questionnaire (PUF), or O'Leary Sant Questionnaire (OLS) indices, may elicit information about urinary symptoms. Tenderness of the bladder base on pelvic examination is a characteristic feature of IC/PBS that may help to distinguish it from other causes of CPP.[9] Optional tests, including laparoscopy and diagnostic imaging, may also be helpful.[6] Additional useful information may be gained from the PST or intravesical anesthetic challenge.

Endometriosis is characterized by the presence of endometrial-like glands and stroma outside the uterine cavity. Symptoms include pain in the lower abdomen, dysmenorrhea, and dyspareunia and can also include such voiding symptoms as dysuria and frequency.[20] Endometriosis and IC/PBS frequently coexist in the same patient. In one study of women with CPP and bladder tenderness on examination, more than 70% had both endometriosis and IC/PBS.[21]

OAB is characterized by urgency with or without urge incontinence and usually includes frequency and nocturia. The key symptom is urgency.[22] OAB and IC/PBS can coexist in the same patient. Urgency can be caused by detrusor overactivity, which usually can be demonstrated through urodynamic testing. Urgency is a common symptom of both OAB and IC/PBS, although the cause differs. In patients with OAB, urgency results in a strong desire to avoid leakage, whereas in patients with IC/PBS, urgency results in a strong need to void to relieve pain caused by bladder fullness.[23]

Vulvodynia is characterized by vulvar discomfort, often reported as burning pain. Pain can occur during intercourse, during vigorous activity, after intercourse, or even at rest. The etiology of vulvodynia is unknown, and the diagnosis is one of exclusion. Symptoms of vulvodynia that overlap those of IC/PBS include pain and dyspareunia but not frequency or nocturia; this can help to distinguish vulvodynia from IC/PBS. It is also possible for a patient to have both IC/PBS and vulvodynia. The history and physical examination are important in diagnosing vulvodynia. A history of chronic pain at the vestibule lasting more than 3 months can suggest vulvodynia. Infectious causes may include viral, bacterial, or fungal organisms; therefore, these must be ruled out as causes of vulvar pain. Vulvar dermatoses may also account for vulvar symptoms.[24] Tenderness to pressure with a cotton swab at the vestibule is a hallmark of vulvodynia,[25] whereas tenderness at the bladder base is typical of IC/PBS.

TREATMENT

The primary goal in the natural approach to treating infectious cystitis is enhancing normal host protective measures against UTI. Specifically, this means enhancing the flow of urine by achieving and maintaining proper hydration, promoting a pH that inhibits the growth of the organisms, preventing bacterial adherence to the endothelial cells of the bladder, and enhancing the immune system. In addition, several botanical medicines with antimicrobial activity can be employed.

Increasing Urine Flow

Increased urine flow can easily be achieved by increasing the quantity of liquids consumed. Ideally, these liquids should be in the forms of pure water and herbal teas. Fresh fruit and vegetable juices should be diluted with at least twice the amount of water. The patient should be encouraged to drink at least 2 L of liquid, with at least half being simply pure water. The patient should also be advised to avoid such liquids as soft drinks, concentrated fruit drinks, coffee, and alcoholic beverages.

Chronic Interstitial Cystitis

In addition to the general measures given later for cystitis, the focus for interstitial cystitis is on enhancing the integrity of the interstitium along with the lining of the bladder wall. The "leaky bladder urothelium" theory postulates that there is a problem with the glycosaminoglycan layer of the bladder epithelium, which results in making the bladder wall more permeable to potassium, causing inflammation and pain. The elimination of food allergies to reduce inflammation appears to be a valid goal even though the association between food allergies and cystitis is not well established. Food allergies have been shown to produce cystitis in some patients. Repeated ingestion of a food allergen could easily explain the chronic nature of interstitial cystitis. For a complete discussion of food allergies, see Chapter 15.

Education of patients with IC/PBS helps empower them to control their symptoms and to be active participants in their own therapy. Patients should be counseled to avoid triggers that lead to increased IC/PBS symptoms. They should also be encouraged to reduce stress and use support groups to deal with the impact IC/PBS has on their daily lives. Dietary changes can provide relief of symptoms.[26]

Herati et al[27] established the prevalence and characteristics of food sensitivities in patients with IC/PBS and Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS). Validated questionnaires containing a list of 175 comestibles as well as pain questions were mailed to 325 patients with IC/PBS and 286 with CP/CPPS. The researchers found that although patients with IC/PBS were more likely to be food sensitive than patients with CP/CPPS, these questionnaires showed that the symptoms of patients with both IC/PBS and CP/CPPS were aggravated by similar comestibles, such as grapefruit juice, spicy foods, alcohol, and caffeinated coffee. The findings also revealed that the symptoms of both groups of patients were improved by certain comestibles, namely water and an antacid containing calcium glycerophosphate (Prelief).[27] In 2007, a study done at Long Island University reported that over 90% of patients with interstitial cystitis experience an increase in symptoms when they consume certain foods and beverages, especially coffee, tea, soda, alcoholic beverages, citrus fruits and juices, artificial sweeteners, and hot pepper.[28]

Food restrictions have not been conclusively proved to help slow the progression of the disease or to improve its course. Usually food restriction should be weighed against the decrease in the patient's quality of life. After 2 weeks, patients are usually asked to start adding one food item back into their diets every 3 days to identify any specific alimentary sensitivity.

Medical treatments include tricyclic antidepressants (amitriptyline being the most popular),[29] anticholinergics to reduce symptoms of urinary urgency, and antihistamines for their efficacy in decreasing mast cell activation and reducing inflammation.[30,31]

Mast cells, once thought to be responsible for allergic reactions, have in some studies been shown to be critically important in interstitial cystitis. Current evidence from clinical and laboratory studies confirms that they play a central role in IC/PBS.[32] Histamine causes pain, swelling, and scarring and prevents the lining of the bladder from healing.

Pentosan polysulfate sodium (Elmiron), is an FDA-approved oral treatment heparinoid compound that is thought to replenish the defective bladder lining. According to one placebo-controlled randomized clinical trial, when it is taken orally, only 1% to 3% of the active drug reaches the bladder. Based on levels of improvement and side effects, treatment can be continued for 3 months and then extended as needed.[33]

Second-line therapies include immunosuppressive agents like prednisone, which was used to treat severe IC/PBS in one small clinical trial.[34] Thirty patients with the Hunner's ulcer subtype of IC/PBS showed considerable improvement following endoscopic submucosal injection of triamcinolone.[35] Cyclosporine has been shown in clinical trials to relieve the symptoms of severe IC/PBS.[36] Symptoms generally recur after treatment is discontinued.

Intravesical therapy can be used for flare management. Dimethylsulfoxide (DMSO) is the only FDA-approved intravesical IC/PBS treatment.[37] Intravesical instillation of anesthetic can bring immediate relief. A study of patients with IC/PBS receiving intravesical instillation of heparin and alkalinized lidocaine showed that this treatment provided immediate and sustained relief of pain and urgency.[38]

Various intravesical cocktails use combinations of heparin, lidocaine, sodium bicarbonate, gentamicin, and glucocorticoids for the treatment of patients with IC/PBS.[39]

Muscle relaxants, used to treat increased muscle spasticity of the pelvic floor associated with CPP, appear to have a beneficial effect. Cyclobenzaprine is an agent closely related to the tricyclic antidepressants. It is used at starting doses of 10 mg daily, which can be prescribed up to three times daily. Tizanidine is a centrally acting alpha$_2$ agonist shown to be superior to placebo in treating spasticity in several conditions. In addition, clonazepam has been useful in treating neuropathic pain.[40]

Alternative Treatments

Biofeedback is another aspect of physical therapy that can provide beneficial results for pelvic pain. Through biofeedback, the patient can learn to control the musculature of the pelvic floor by visualizing the activity of the muscle on a computer and using the visual feedback to achieve conscious control over muscular contractions, thus breaking the cycle of spasm. Ger et al studied 60 patients with intractable rectal pain, 70% of whom were diagnosed with levator spasm. Biofeedback was performed on 14 of the 60 patients for 30- to 60-minute sessions a week for 6 weeks. In 6 of the 14 patients (43%), pain relief was rated as good or excellent at the 15-month follow-up.[41] A prospective trial using biofeedback and a rectal manometric balloon included 16 patients with levator ani syndrome. The median pain score before biofeedback therapy was 8 (on a 0-10 linear analog scale) and significantly improved to a median score of 2 after therapy. All patients reported nontender musculature after treatment.[42]

Herbs and Supplements

Katherine Whitmore, a urologist from Drexel University, found that the Chinese herbs *Cornus,* garden rhubarb, *Psoralea,* and *Rehmannia* decreased pain after 4 weeks in 61% of the subjects studied (n = 25). In 3 months, an additional 22% of the subjects had a significant response.[43] The most consistent research evidence was found for *Centella asiatica* (gotu kola) and horsetail *(Equisetum arvense).*[43] *Centella* appears to address some other pathologic features of chronic interstitial cystitis. Specifically, *Centella* extracts have been shown to improve the integrity of the connective tissue composing the interstitium as well as to heal ulcerations of the bladder.[45] Horsetail *(Equisetum arvense)* has astringent properties.[46]

Aloe vera, also known as the "burn plant," has been used extensively to heal and relieve the pain of burns. In a small open-label double-blind crossover study using a freeze-dried whole-leaf *Aloe vera* concentrate, three 600-mg capsules were given twice daily for 3 months, followed or preceded by placebo. Of 12 patients with interstitial cystitis, 8 completed the study and 7 had significant symptom relief.[47]

L-Arginine

L-arginine is an essential amino acid that increases the production of nitric oxide (NO), which is dependent on the enzyme nitric oxide synthetase (NOS). NO and NOS have antibacterial, smooth muscle relaxant, hormone releasing, and immune-modulating (by increasing T-cell counts) properties. In a randomized double-blind trial of oral L-arginine in the treatment of interstitial cystitis, NOS production was found to be decreased in patients with interstitial cystitis and increased in patients with UTI when compared with controls. L-arginine (1.5 g/day) was given to 10 patients with interstitial cystitis for 6 months. The urinary NOS was then measured and found to have increased, and clinical symptoms of frequency and nocturia improved in 8 of the 10 patients.[48] The same authors performed a randomized, double-blind trial using 1.5 g of L-arginine per day for 3 months. At the end of this period, 6 (29%) of the 21 patients in the L-arginine group and 2 (8%) of the 25 patients in the placebo group were clinically improved. When an intent-to-treat analysis was done, no significant difference was found between the L-arginine and placebo groups, although Likert scales showed a significant difference in pain intensity and global scores favoring those taking L-arginine.[49] Another randomized controlled trial with L-arginine found no improvement in symptoms scores of interstitial cystitis when compared with controls.[50] The efficacy of L-arginine, NO, and NOS in the treatment of interstitial cystitis remains controversial.

Quercetin

Quercetin is a naturally occurring flavonoid that inhibits histamine release from mast cells and has antiinflammatory and antioxidant properties. It is rich in onions, seeds, citrus fruits, olive oil, tea, and red wine. A quercetin-containing compound was studied in 22 interstitial cystitis patients given 500 mg twice a day for 4 weeks. Two patients dropped out of the study. Of the remaining 20 patients, 57% had a significant decrease in the O'Leary Sant Symptom and Problem indices and a decreased global assessment of pain (Likert scale; range 0-10).[49] A randomized placebo-controlled trial is needed to determine the efficacy of quercetin.

Cranberry Juice (Vaccinium macrocarpon)

Cranberries and cranberry juice have been used for the treatment and prevention of UTI for several hundred years. Several clinical studies of benefit in patients with UTI have shown mixed results. In one study, 0.5 L/day of cranberry juice produced beneficial effects in 73% of the subjects (44 females and 16 males) with active UTI.[52] Furthermore, withdrawal of cranberry juice in the people who benefited resulted in recurrent bladder infection in 61%.

In vitro experiments have demonstrated that cranberry reduces adherence of *Escherichia coli* to uroepithelial cells. *E. coli* accounts for up to 80% of UTI acquired in the community. The effect of cranberry on *E. coli* adherence is dose-dependent; exposure to cranberry also can displace preattached *E. coli*.[53] In order for bacteria to infect, they must first adhere to the mucosa. By interfering with adherence, cranberry juice greatly reduces the likelihood of infection and helps the body fight it off. This is the most likely explanation of cranberry juice's positive effects in bladder infections.

A large double-blind placebo-controlled study evaluated the efficacy of 300 mL of cranberry juice in 153 women (average age 78.5) with confirmed bacteriuria.[54] Even this small an amount dramatically decreased the level of bacteria in the women's urine and the frequency of recurrence of infection. Interestingly, the researchers used saccharin-sweetened juice. Because saccharin is a suspected carcinogen, we strongly recommend avoiding this artificial sweetener.

In one study of seven juices (cranberry, blueberry, grapefruit, guava, mango, orange, and pineapple), only cranberry and blueberry demonstrated inhibitory effects.[55] Blueberry juice *(Vaccinium augustifolium)* is a strong cousin of cranberry juice and a suitable alternative to cranberry juice in bladder infections.

It must be pointed out that most cranberry juices on the market contain one-third cranberry juice mixed with water and sugar. Because sugar has such a detrimental effect on the immune

system,[56-58] the use of sweetened cranberry juice cannot be recommended. Fresh cranberry (unsweetened) or blueberry juice is preferred to avoid the deleterious effects of sugar consumption.

Cranberry extracts are also available commercially in pill form. To compare the efficacy and cost of tablets with fresh juice for the prevention of UTI, 150 sexually active women between 21 and 72 years of age were studied in a randomized controlled trial for 1 year.[59] Tablets were taken twice daily, as well as juice at 250 mL three times daily. Both cranberry juice and cranberry tablets significantly decreased the number of patients experiencing at least 1 symptomatic infection per year (20% and 18%, respectively) compared with placebo (32%). The mean annual cost of cranberry tablets was $624, whereas the juice cost $1400. Furthermore, total consumption of antibiotics was less in both treatment groups compared with placebo. Although the cranberry tablets may be more cost-effective, it is important to remember that sufficient fluid intake is still important, so ample water should be ingested if tablets are used.

Of interest, in a large trial of cranberry juice compared with placebo juice conducted among 376 British inpatients 60 years of age and older, the incidence of symptomatic UTI was also lower than anticipated in the placebo group, but there was no significant difference between groups.[60] Both the active and placebo juices contained ascorbic acid.

Another randomized controlled trial of 305 individuals with neuropathic bladder following spinal cord injury found that the ingestion of cranberry tablets did not reduce rates of UTI relative to the standard regimen.[61]

The most recent study to date looked at 319 college women presenting with acute UTI. In this double-blind randomized trial, participants were followed up until a second UTI or for 6 months, whichever came first. The study concluded that an 8-oz dose of low-calorie cranberry juice twice daily gave no protection against the risk of recurrent UTI among college-aged women.[62] Research juice was formulated to be similar to the commercially available Ocean Spray and was sweetened with Splenda (sucralose), exactly as is the retail juice. Batches of the tested juice were standardized to 112 mg per day of proanthocyanidin content. The placebo juice was formulated by Ocean Spray to imitate the flavor (sugar and acidity) and color of the cranberry beverage but without any cranberry content. In addition to other food and pharmaceutical-grade substances, both juices contained ascorbic acid in their formulations.

Last, there is a theoretical concern regarding the use of cranberry juice and the formation of kidney stones. Because cranberries are considered an oxalate-containing food, it is thought that this may encourage oxalate-rich kidney stone formation. However, urinary oxalate excretion does not increase after drinking cranberry juice and none of the studies using cranberries has reported an increased incidence of kidney stones.[63]

Acidify or Alkalinize?

Although many practitioners believe that acidification of the urine is the best approach in addressing cystitis, several arguments can be made for alkalinizing the urine. First, it is often difficult to acidify the urine. Many popular methods of attempting to acidify the urine, such as ascorbic acid supplementation and the drinking of cranberry juice, have little effect on pH at commonly prescribed doses.

The best argument for alkalinizing the urine is that it appears to be more effective, especially in women without pathogenic bacteria in their urine. The best method for alkalinizing the urine appears to be the use of citrate salts (e.g., potassium citrate, sodium citrate). These salts are rapidly absorbed and metabolized without affecting gastric pH or producing a laxative effect. They are excreted partly as carbonate, thus raising the pH of the urine.

Potassium citrate, sodium citrate, or both have long been employed in the treatment of lower UTI. They are often used as a "holding exercise" until the results of a urine culture become available. Some clinical studies support this practice. For example, in one study, women presenting with symptoms of UTI were given 4 g of sodium citrate every 8 hours for 48 hours.[64] Of the 64 women evaluated, 80% had relief of symptoms, 12% had deterioration of symptoms, and 91.8% rated the treatment as acceptable. Of the 64 women, 19 were shown to have positive bacterial cultures. There was more variation in response to treatment in the group with proved bacterial infection, with those having symptoms of urethral pain (7 of 10) and dysuria (13 of 18) improving more than those with symptoms of frequency (9 of 17) and urgency (6 of 13). These results were similar to those of a previous study demonstrating significant symptomatic relief and abacteriuria in 80% of the 159 women studied.[65]

Because of these positive results, it has been suggested that urine culture could be restricted to those women who fail to respond to alkalinization therapy. Restricting urine cultures to nonresponders would also lower health care costs.

One more possible advantage to alkalizing rather than acidifying the urine exists. Many herbs used to treat UTI, such as *Hydrastis canadensis* and *Arctostaphylos uva ursi*, contain antibacterial components that work most effectively in an alkaline environment.

Acupuncture

Acupuncture is attracting the interest of patients with all kinds of urologic conditions. The use of acupuncture also gives urologists an opportunity to collaborate with other health care professionals, such as acupuncturists.[66]

Patients with IC/PBS can potentially gain benefit from 10 to 20 sessions of acupuncture.[43] Alraek has been able to show in a study with 61 women that a traditional Chinese medicine diagnosis can be useful in cystitis.[67]

In a study of 14 patients, Rapkin and Kames found that 6 to 8 weeks of acupuncture reduced the pain of interstitial cystitis.[68]

One reported a case study involves a 31-year-old woman whose symptoms of interstitial cystitis were reduced with acupuncture to the kidney and bladder meridians.[69]

In a Norwegian study, 67 adult women with a history of recurrent lower UTI were randomized into three groups: one receiving acupuncture treatment, one receiving sham acupuncture, and one given no treatment. A statistically significant 85% of patients in the acupuncture group were free of cystitis during the 6-month observational period, as compared with 58% in the sham group and only 36% in the control group.[70] Although more clinical studies are necessary to thoroughly elucidate the efficacy of acupuncture, this safe treatment method seems to be a reliable choice as a primary or adjunctive treatment option. Some practitioners also combine acupuncture with the Chinese herbal tradition, which can also be useful in the treatment of long-term chronic conditions.

Nutrient Supplementation

D-Mannose

D-Mannose is a simple sugar that acts similarly to cranberry juice in that it helps to prevent the pili of *E. coli* and other bacteria from adhering to the bladder wall. In fact, D-mannose is

TABLE 159-4 **Bacteriologic Susceptibility to Nutrients and Botanical Medicines**

BACTERIAL SPECIES	AGENT
Escherichia coli	*Allium sativum, Hydrastis canadensis, Arctostaphylos uva ursi*
Klebsiella pneumoniae	*Allium sativum, Hydrastis canadensis*
Proteus mirabilis	*Allium sativum, Hydrastis canadensis*
Pseudomonas aeruginosa	*Hydrastis canadensis*
Staphylococcus saprophyticus	*Allium sativum, Hydrastis canadensis*

contained in cranberry juice but in lower doses than are available through specific supplementation. Although there are no clinical trials available to support the use of D-mannose powder, a handful of research articles explaining its function strongly support its use.

One in vitro study evaluated the effect of D-mannose on 73 *E. coli* strains of epithelial vaginal and buccal cells from women who suffered recurrent UTI. Of the strains from urinary, vaginal, or anal isolates, 66 (90%) demonstrated adherence to vaginal epithelial cells. When applied, D-mannose completely inhibited the adherence of 25 strains (42%) to epithelial cells and inhibited an additional 11 strains (18%) by at least 50%. Similar results were obtained with buccal cells. The inhibitory effect of D-mannose was similar regardless of the origin of the strains.[71] Another study of Sprague Dawley rats given intravesicular injections of D-mannose found significant improvement in bacteruria in a dose-dependent manner in the animals given D-mannose.[72]

Jonathan Wright recommends an adult dose of 0.5 to 1 tsp three times daily mixed in a little water. It is sweet-tasting and has been used successfully in appropriately reduced doses for pediatric UTI as well. Admittedly more research is necessary to fully evaluate the usefulness and efficacy of this therapy.

Botanical Medicines

Many herbs have been used through the centuries in the treatment of UTIs (Table 159-4). The following are several whose use is supported by both folk medicine and scientific evidence.

Arctostaphylos uva ursi

Most research has focused on *Arctostaphylos uva ursis* (bearberry or upland cranberry) urinary antiseptic component, arbutin, which typically comprises 6.3% to 9.6% of the leaves.[73] Arbutin is hydrolyzed to hydroquinone and glucose in the body. Hydroquinone is most effective in an alkaline urine. However, crude plant extracts are more effective medicinally than isolated arbutin.[74] *A. uva ursi*, reported to be especially active against *E. coli*, also has diuretic properties.[75]

The prophylactic effect of a standardized *A. uva ursi* extract on recurrent cystitis was evaluated in a double-blind study in 57 women.[76] At the end of 1 year, 5 of 27 women in the placebo group had a recurrence, whereas none of the 30 women receiving *A. uva ursi* extract had a recurrence. No side effects were reported in either group. These impressive results indicate that regular use of *A. uva ursi*, like cranberry, may prevent bladder infections.

A. uva ursi has also been shown to be helpful in increasing susceptibility of antibiotic-resistant bacteria to antibiotics like beta-lactams. A Japanese group studied the effect of corilagin, a polyphenolic compound from *A. uva ursi*, used against methicillin-resistant *Staphylococcus aureus*. Corilagin reduced the minimal inhibitory concentration of oxacillin and other beta-lactam antibiotics by 100- to 2000-fold. The effect of corilagin and oxacillin was synergistic and bactericidal. Some other antibiotics studied were not enhanced by corilagin. The authors also mentioned that catechins, compound P, and epicatechin gallate from green tea, as well as baicalin from *Scutellaria amoena,* may also produce similar effects.[77]

Care must be taken to avoid excessive doses of *A. uva ursi*—as little as 15 g (0.5 oz) of the dried leaves have been shown to produce toxicity in susceptible individuals. Toxic signs include the following[74]:

- Ringing in the ears
- Nausea
- Vomiting
- Sense of suffocation
- Shortness of breath
- Convulsions
- Delirium
- Collapse

Allium sativum

Garlic has been shown to have antimicrobial activity against many disease-causing organisms including those associated with urinary tract infections, such as the following[79,80]:

- *E. coli*
- *Proteus* spp.
- *Klebsiella pneumoniae*
- *Staphylococcus* spp.
- *Streptococcus* spp.

Hydrastis canadensis

Goldenseal is among the most effective of the herbal antimicrobial agents. Its long history of use by herbalists and naturopathic physicians for the treatment of infection is well documented in the scientific literature. Of particular importance here is its efficacy against *E. coli*, *Proteus* species, *Klebsiella* species, *Staphylococcus* species, *Enterobacter aerogenes* (large dose required), and *Pseudomonas* species.[81,82] Berberine, like hydroquinone from *A. uva ursi*, works better in an alkaline urine (see Chapter 97 for a full discussion).

THERAPEUTIC APPROACH

Although most cases of cystitis are relatively benign, it is extremely important that the patient be properly diagnosed, treated, and monitored. Proper monitoring includes having the patient notify the physician of any change in his or her condition. If the original culture was positive, it is appropriate to follow up with another culture 7 to 14 days after treatment was started. Citrates can be used to ameliorate symptoms. Because of the possibility of a kidney infection, patients should notify their physician if there is fever, low back pain, nausea, or vomiting. Pyelonephritis requires immediate antibiotic therapy and sometimes hospitalization.

Although the occasional acute bladder infection is easily treated, treating women with chronic cystitis can be a significant challenge. Long-term success requires determining the underlying cause: structural abnormalities, excessive sugar consumption, food allergies, nutritional deficiencies, chronic vaginitis, local foci of infection (e.g., prostate, kidneys), and current or

childhood sexual abuse. All potential causes must be evaluated and resolved.

Although the causative agents of cystitis have not changed over time, bacterial resistance to antibiotics is fast becoming an issue; even one-time cases of simple acute cystitis have become recalcitrant.[83,84] Resistance to common antibiotics—including trimethoprim-sulfamethoxazole, beta-lactam drugs, and fluoroquinolone—is emerging at an alarming rate. In this milieu, it makes sense to use natural therapeutics that involve fluid intake to protect the urinary tract, immune support, plus nutrient and botanical medicines as first-line therapy in nonpyelonephritic cases and as adjunctive therapy to increase the efficacy of antibiotic treatment if necessary.

General Measures

Patients should be advised to drink large amounts of fluids (at least 2 L/day) including at least 0.5 L of unsweetened cranberry or 0.25 L of blueberry juice.

Patients should be taught to urinate after intercourse. Women who develop bladder infections after intercourse should wash the labia and urethra with a strong tea of *H. canadensis* (2 tsp/cup) both before and after. If this is inadequate, a dilute solution of povidone-iodine usually proves effective.

Diet

UTIs are mostly ascending infections caused by bacteria derived from stools. Because alterations in the bacterial composition of stools depend on the diet, it is reasonable that the risk for infection will change with dietary modifications. Patients should avoid all simple sugars, refined carbohydrates, full-strength fruit juice (diluted fruit juice is acceptable), and food allergens. Yogurt products with live probiotics are also recommended. Patients should restrict calories and eat liberal amounts of garlic and onions.

Patients with IC/PBS should exclude coffee, tea, soda, alcoholic beverages, citrus fruits and juices, artificial sweeteners, and hot pepper from their diets. Other foods such as gluten and dairy products may also be suspect. Although no scientific data exist to support or reject this hypothesis, the authors believe, on the basis of clinical experience, that patients benefit from the exclusion of these foods. An elimination/challenge diet may be worthwhile for this group of patients.

Nutritional Supplements for Bacterial Cystitis

- D-Mannose powder: 0.75 tsp three times a day
- Vitamin C: 500 mg every 2 hours
- Bioflavonoids: 1000 mg/day
- Vitamin A: 25,000 IU/day
- Beta-carotene: 200,000 IU/day
- Zinc: 30 mg/day
- Choline: 1000 mg/day

Nutritional Supplements for Nonbacterial Interstitial Cystitis/Painful Bladder Syndrome

- L-Arginine: 1500 mg in divided doses
- Quercetin: 500 mg twice a day

Botanical Medicines for Bacterial Cystitis

Dosages are three times a day quantities:

A. uva ursi

- Dried leaves or as a tea: 1.5 to 4 g (1 to 2 tsp)
- Freeze-dried leaves: 500 to 1000 mg
- Tincture (1:5): 4 to 6 mL (1 to 1.5 tsp)
- Fluid extract (1:1): 2 to 4 mL (0.5 to 1 tsp)
- Powdered solid extract (10% arbutin): 250 to 500 mg

H. canadensis

- Dried root (or as tea): 1 to 2 g
- Freeze-dried root: 500 to 1000 mg
- Tincture (1:5): 4 to 6 mL (1 to 1.5 tsp)
- Fluid extract (1:1): 2 to 4 mL (0.5 to 1 tsp)
- Powdered solid extract (8% alkaloid): 250 to 500 mg
- Sandalwood oil: 1 to 2 drops

Botanical Medicines for Nonbacterial Interstitial Cystitis/Painful Bladder

Centella asiatica

- Dried herb: a tea can be made of the dried leaf, to be taken three times a day
- Powdered herb (available in capsules): 1000 to 4000 mg, three times a day
- Tincture (1:2 w/v, 30% alcohol): 30 to 60 drops (equivalent to 1.5 to 3 mL; there are 5 mL in a teaspoon), three times a day
- Standardized extract: 50 to 250 mg two to three times a day. Standardized extracts should contain 40 % asiaticoside, 29% to 30 % asiatic acid, 29% to 30% madecassic acid, and 1% to 2% madecassoside.

Equisetum arvense

- Standardized dose: 300 mg three times a day, standardized to contain 10% to 15% silica
- Herbal infusion (tea): 2 to 3 tsp three times a day. Hot water is poured onto the herb, steeped for 5 to 10 minutes, and taken as directed.
- Tincture (1:5): 1 to 4 mL three times a day
- External (compresses): 10 g of herb per 1 L water a day

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CHAPTER 160

Dermatitis Herpetiformis

Michael Traub, ND, DHANP, FABNO, and Michael T. Murray, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- Pruritic papulovesicular eruption, usually on the extensor surfaces
- Most common in middle-aged white males but may be seen in individuals of any age
- IgA deposits in the dermal papillae; confirmed by immunofluorescence
- Asymptomatic celiac disease (gluten-sensitive enteropathy) in 75% to 90% of patients

GENERAL CONSIDERATIONS

Dermatitis herpetiformis (DH) is a cutaneous manifestation of gluten-sensitive enteropathy (celiac disease). Patients with DH demonstrate serum IgA antibodies against epidermal transglutaminase and tissue transglutaminase.[1] The putative autoantigen of DH is epidermal transglutaminase. DH has been referred to as "celiac disease of the skin."[2] Just as in celiac disease (CD), a gluten-free diet is most often all that is required to resolve the lesions. Absorption studies (see Chapter 20) can be used to assess the degree of enteropathy.

Most individuals with CD have celiac-associated antibodies and specific pairs of allelic variants in two HLA genes, HLA-DQA1 and HLA-DQB1.[3] Only 3% of individuals with one or both of these alleles develops CD, yet 30% of the general population has one of them. Therefore, their presence is not diagnostic of CD but their absence excludes a diagnosis of CD. Genetic testing is available for the assessment of CD.

The average age at onset of DH is 7.2 years; it has a predilection for the elbows, knees, and buttocks. Skin biopsy shows granular or fibrillar IgA deposits.[4] The characteristic skin lesions found in patients with DH are extremely itchy grouped vesicles most frequently located on extensor surfaces. Intense pruritus is the predominate symptom; however, DH is a clinical chameleon and can present with excoriations, eczematous lesions, or minimal patterns of discrete erythema or digital purpura.[5]

THERAPEUTIC CONSIDERATIONS

Gluten

The most important factor in the treatment of patients with DH is the elimination of all sources of gluten. Frazer's criteria for the diagnosis of gluten-sensitive enteropathy (improvement on a gluten-free diet and relapse after reintroduction) have been used in many studies and have shown conclusively that the rash and villous atrophy of DH are largely gluten dependent.[6-11] Gluten elimination results in improvement in virtually all patients, including elimination of the reticulin and gluten antibodies found in patients with DH.[2,12]

Further study of the wheat connection has shown that the gliadin polypeptide of gluten is most likely the key antigen. Indirect immunofluorescence shows antibodies to gliadin in the sera of 45% of patients with DH. The titer and correlation increase with increasing severity of the disease; 81% of patients with severe jejunal abnormalities show antibodies to gliadin.[13]

Despite the published benefits of a gluten-free diet in the treatment of DH for more than 30 years now, this treatment is still often omitted from conventional dermatology and medical textbooks. The advantage of a gluten-free diet over drugs

like dapsone (the most widely prescribed drug for DH) is obvious, as this drug is often associated with severe side effects. With the gluten-free diet, on the other hand:

- Most patients (more than 65%) experience complete resolution and the rest improve substantially.
- There is complete resolution of the enteropathy associated with DH.
- Harsh medications can be eliminated or substantially reduced.
- Most patients experience an improved sense of well-being.

Also of interest is the fact that those who used a gluten-free diet rather than drugs appear also to be protected against developing lipomas.[14]

Food Allergy

Although gluten control is critical in the treatment of patients with DH, some (about 35%) are not adequately helped. In particular, only one half the patients totally eliminate the cutaneous IgA deposits and develop normal jejunal tissue. This is probably because of the presence of other food allergies that, although probably not initiating, developed as a result of the increased leakage of macromolecules across the damaged gastrointestinal membranes. Milk, in particular, has been found to be significantly problematic in some patients.[15,16] Using a sensitive enzyme-linked immunoassay (ELISA), 75% of DH patients were shown to have serum antibodies reactive against gliadin, bovine milk, or ovalbumin.[17] These results suggest that other food sensitivities are implicated in DH. An elemental diet followed by careful food reintroduction usually produces better results than a simple gluten-free diet.[18]

Para-aminobenzoic Acid

Para-aminobenzoic acid (PABA) has been used successfully in the control of DH, even in those patients who are not controlling the gluten content of their diet.[19] However, because its use is recommended only for symptom control and it probably does not result in repair of the villous atrophy, it is not recommended as the treatment of choice but rather as an adjunct in unresponsive cases or to help in particularly severe cases.

Treatment of Nutritional Deficiencies

Deficiencies of iron, zinc, calcium, fat-soluble vitamins, and folic acid should be sought; also the possibility of osteopenia and osteoporosis should be assessed and treated if found.

THERAPEUTIC APPROACH

After all sources of gluten and gliadin have been eliminated (see Appendix for the gluten content of foods), a careful search should be made for other food allergies (for more detail, see Chapter 15) Once the allergens are under control, a therapeutic regimen similar to that for atopic dermatitis (see Chapter 149) should be used. Patience is necessary because a response may take several weeks to 6 months to be seen.

Diet

Use a normal, healthy diet free of processed foods, gluten-containing grains, and foods likely to promote allergy.

Supplement

PABA: 5 g/day until remission (maximum of 3 months)

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CHAPTER 161

Diabetes Mellitus

Michael T. Murray, ND

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DIAGNOSTIC SUMMARY

Elevated blood glucose is determined by the following:

- Fasting (overnight): venous plasma glucose concentration greater than or equal to 126 mg/dL on at least two separate occasions.
- Following ingestion of 75 g of glucose: venous plasma glucose concentration greater than or equal to 200 mg/dL at 2 hours postingestion and at least one other sample during the 2-hour test.
- A random blood glucose level of 200 mg/dL or more plus the presence of suggestive symptoms.
- Classic symptoms of polyuria, polydipsia, and polyphagia.
- Fatigue, blurred vision, poor wound healing, periodontal disease, and frequent infections are often manifesting symptoms as well in type 2 diabetes.

GENERAL CONSIDERATIONS

Diabetes is a chronic disorder of carbohydrate, fat, and protein metabolism characterized by fasting elevations of blood glucose levels and a greatly increased risk of cardiovascular disease, renal disease, and neuropathy. Diabetes is divided into two major categories: types 1 and 2. Type 1 diabetes (T1DM) occurs most often in children and adolescents. For this reason it is often referred to as juvenile-onset diabetes. About 5% to 10% of all diabetic patients have T1DM. (Box 161-1 lists the major complications of diabetes.)

T1DM is an autoimmune disease caused by destruction of the beta cells of the pancreas, which manufacture insulin. Positive antibodies against beta cells or insulin occur in 75% of patients with T1DM. Why the immune system is activated to attack the pancreas is not fully clear, but viral infection, food sensitivities, and chemical or free radical damage is likely, combined with genes that may predispose to T1DM. These individuals will require lifelong insulin for the control of blood glucose levels. The individual with T1DM must learn how to manage blood glucose levels on a day-by-day basis, modifying insulin types and dosages as necessary according to meals eaten, liver production of glucose, and the results of regular blood glucose testing.

Type 2 diabetes (T2DM) historically has had an onset after age 40 in overweight individuals but today it is seen even in pediatric patients because of the obesity epidemic, which affects all age groups in America. It is generally thought that up to 90% of all those with diabetes have T2DM. Initially, insulin levels are typically elevated in T2DM, indicating a loss of sensitivity to insulin by the body's cells. Obesity is a major contributing factor to this loss of insulin sensitivity. Approximately 90% of individuals categorized as having T2DM are obese. The achievement of an ideal body weight in these patients is often associated with the restoration of normal blood glucose levels. Even if T2DM has progressed to the point where insulin deficiency is present, weight loss nearly always results in significant improvements in blood glucose control and dramatic reductions in other health risks, such as cardiovascular disease (Table 161-1).

T2DM is a disease characterized by progressive worsening of glycemic control, which starts with mild alterations in postprandial glucose homeostasis followed by an increase in fasting plasma glucose and often ultimately a lack of production of insulin and the need for insulin therapy.

There are other types of diabetes, such a latent autoimmune diabetes of the adult, sometimes termed type 1.5. This is a slower-onset autoimmune type of diabetes

BOX 161-1 Major Complications of Diabetes

- Cardiovascular disease: Adults with diabetes have death rates from cardiovascular disease about two to four times higher than adults without diabetes.
- Hypertension: About 75% of adults with diabetes have high blood pressure.
- Retinopathy: Diabetes is the leading cause of blindness among adults.
- Renal disease: Diabetes is the leading reason for dialysis treatment, accounting for 43% of new cases.
- Neuropathy: About 60% to 70% of people with diabetes have mild to severe forms of nervous system damage. Severe forms of diabetic nerve disease are a major contributing cause of lower extremity amputations.
- Amputations: More than 60% of lower limb amputations in the United States occur among people with diabetes.
- Periodontal disease: Almost one third of people with diabetes have severe periodontal (gum) disease.
- Pain: Many people with diabetes fall victim to chronic pain due to conditions such as arthritis, neuropathy, circulatory insufficiency, or muscle pain (fibromyalgia).
- Depression: This is a common accompaniment of diabetes. Clinical depression can often begin to occur even years before diabetes is fully evident. It is difficult to treat in those with poorly controlled diabetes.
- Autoimmune disorders: Thyroid disease, inflammatory arthritis, and other diseases of the immune system commonly add to the suffering of people with diabetes.

TABLE 161-1 Differences Between Type 1 and Type 2 Diabetes

FEATURES	TYPE I	TYPE 2
Age at onset	Usually younger than 40 years	Usually older than 40 years
Proportion of all diabetics	<10%	>90%
Family history	Uncommon	Common
Appearance of symptoms	Rapid	Slow
Obesity at onset	Uncommon	Common
Insulin levels	Decreased	Normal to high initially, decreased after several years
Insulin resistance	Occasional	Often
Treatment with insulin	Always	Usually not required

that occurs later in life, often after people reach 35 years of age. Diabetes may also occur as a result of chronic pancreatitis and other insults to the pancreas. Gestational diabetes, another type, affects about 4% of all pregnant women, adding up to about 135,000 cases in the United States each year. This occurs in women who were not diabetic before they became pregnant but developed diabetes during pregnancy. Gestational diabetes occurs more frequently among African Americans, Hispanic/Latino Americans, and American Indians. It is also more common among obese women and women with a family history of diabetes. After pregnancy, 5% to 10% of women with gestational diabetes are found to have T2DM. Women who have had gestational diabetes have a 20% to 50% chance of developing diabetes in the following 5 to 10 years. The least common types of diabetes are genetic disorders, such as neonatal diabetes and mature-onset diabetes of youth, which are generally due to faulty genes causing impaired insulin function.

Prediabetes and Metabolic Syndrome

Prediabetes (also called "impaired glucose tolerance") is characterized by a fasting glucose between 100 and 125 mg/dL and/or a postprandial glucose of 140 to 199 mg/dL. It is the first step in insulin resistance and estimated to affect 57 million Americans. Many people with prediabetes will go on to develop full-blown T2DM despite the fact that prediabetes is usually reversible and, in most cases, diabetes can be completely avoided through dietary and lifestyle changes. Factors implicated in contributing to prediabetes, insulin resistance, and the progression to T2DM include a diet high in refined carbohydrates, particularly high-fructose corn syrup; an elevated intake of saturated fats; overeating due to increased portion sizes of food; increases in inflammatory markers; lack of exercise; industrial pollution; abdominal weight gain; hormonal imbalances; inadequate sleep; and nutritional deficiencies.

Research increasingly indicates that prediabetes is accompanied by serious health risks, especially an increased risk for cardiovascular disease. Individuals with prediabetes often meet the criteria for the metabolic syndrome (MetS). This is a cluster of factors that together carry a significantly greater risk for cardiovascular disease and the development of T2DM. They include:

- Greater waist-to-hip ratio
- Two of the following:
 - Triglycerides greater than 150 mg/dL
 - HDL-C less than 40 mg/dL for men, less than 50 mg/dL for women
 - Blood pressure equal to or greater than 130/85 mm Hg
 - Fasting plasma glucose equal to or greater than 100 mg/dL

By this definition and using data from the National Health and Nutrition Examination Survey (1999-2002), the prevalence of MetS in the United States is 39% among men and women aged 20 and above.[1] Among adolescents and using a similar definition, approximately 5.8% meet the established criteria.[2] In addition to an elevated risk for cardiovascular disease and diabetes, individuals with MetS report poorer health-related quality of life, both physically and mentally.[3]

DIAGNOSING DIABETES

The classic symptoms of T1DM are frequent urination, weight loss, impaired wound healing, infections, and excessive thirst and appetite. Such individuals may suffer from diabetic ketoacidosis upon diagnosis, and they are usually lean in presentation. In T2DM, the symptoms are generally milder and may go unnoticed. For that reason and others, many people with T2DM do not even know that they have the disease. Abdominal weight, fatigue, blurred vision, poor wound healing, periodontal disease, and frequent infections are often manifesting symptoms of T2DM.

The standard method for diagnosing diabetes involves the measurement of blood glucose levels. The initial measurement is generally a fasting blood glucose taken after the patient has avoided food for at least 10 hours but not more than 16. The normal reading is between 70 and 99 mg/dL. If a person has a fasting blood glucose measurement greater than 126 mg/dL (7 mmol/L) on two separate occasions, the diagnosis is diabetes. As mentioned above, a fasting glucose greater than 100 but less than 126 mg/dL is classified as prediabetes.

TABLE 161-2 **Criteria for Response to the Glucose Tolerance Test**

TYPE	CRITERIA
Normal	No elevation > 160 mg/dL (9 mmol/L); <150 mg/dL (8.3 mmol/L) at end of first hour, below 120 mg/dL (6.6 mmol/L) at end of second hour
Flat	No variation of more than ± 20 mg/dL (1.1 mmol/L) from fasting value
Prediabetic	Blood glucose levels of 140 mg/dL (7.8 mmol/L) to 180 mg/dL (10 mmol/L) at end of second hour
Diabetic	>180 mg/dL (10 mmol/L) during first hour, 200 mg/dL (11.1 mmol/L) or higher at end of first hour, 150 mg/dL (8.3 mmol/L) or higher at end of second hour

A postprandial and a random glucose determination are also helpful in diagnosing diabetes. A postprandial measurement is usually made 1 to 2 hours after a meal, whereas a random measurement is one that is made at any time during the day without regard to the time of the last meal. Any reading greater than 200 mg/dL (11 mmol/L) is considered indicative of diabetes (Table 161-2)

Glycosylated Hemoglobin

A valuable laboratory test for evaluating long-term blood glucose levels is the measurement glycosylated $HgbA_{1c}$. Proteins that have glucose molecules attached to them (glycosylated peptides) are elevated several-fold in diabetic patients. Normally, about 4.6% to 5.7% of hemoglobin is combined with glucose. An $HgbA_{1c}$ from 5.7% to 6.4% indicates prediabetes. An $HgbA_{1c}$ of 6.5% or higher, particularly when done as a screening test, can diagnose diabetes and is particularly helpful in patients with nondiagnostic fasting blood sugar levels.[4] Nonetheless, it is best coupled with a fasting blood glucose measurement and a 2-hour postprandial glucose level for a more accurate diagnosis. Because the average life of a red blood cell (RBC) is 120 days, the $HgbA_{1c}$ assay represents time-averaged values for blood glucose over the preceding 2 to 4 months. An $HgbA_{1c}$ at 5% indicates that the glucose median for the previous 3 months was around 100 mg/dL; for each digit of elevation in the percentage, a rough addition of 35 mg/dL is followed. Thus, an $HgbA_{1c}$ of 7% means that on average over the preceding 3 months the patient's blood glucose was 170 mg/dL. The $HgbA_{1c}$ index is extremely valuable in providing a simple, useful method for assessing the effectiveness of treatment as well as patient compliance; it should be checked every 3 to 6 months.

RISK FACTORS FOR TYPE 1 DIABETES

In T1DM the insulin-producing cells of the pancreas are ultimately destroyed, in most cases by the body's own immune system, but what triggers this destruction can vary from one case to another. Genetic factors may predispose a person to damage to the insulin-producing cells through either impaired defense mechanisms, immune system sensitivity, or a defect in tissue regeneration capacity. The entire set of genetic factors linked to T1DM have been termed "susceptibility genes," because they modify the risk of diabetes but are neither necessary nor sufficient for disease to develop.[5] Rather than acting as the primary cause, the genetic predisposition simply sets the stage for the environmental or dietary factor to initiate the destructive process.[6] The very term *predisposition* clearly indicates that something else must occur: less than 10% of those with increased genetic susceptibility for T1DM actually develop the disease.[7]

In detailed studies, the concordance rate for developing T1DM in identical twins was only 23% in one study[8] and 38% in another.[9] If one twin develops T1DM after age 24, the concordance rates drops all the way down to 6%, meaning that the other twin is at very low risk for developing the disease. These results and others indicate that in most cases, even where there is a true genetic predisposition, environmental and dietary factors may be more important in determining whether diabetes will develop.[10]

Additional evidence supporting the need to focus on dietary and environmental triggers follows:

- There has been a threefold to tenfold increase in the number of people with T1DM throughout the world over the past 40 years. Such a rise simply cannot be explained by an increased number of people genetically predisposed to T1DM. Changes to the human genetic code across large populations take more than one generation.[11]
- The rate of T1DM can increase dramatically when children in areas where T1DM is relatively rare move to developed countries.[12] For example, the rate of T1DM increased by nearly fourfold in one 10-year period in children of Asian origin moving to Great Britain, and the rate increased more than sevenfold in Polynesians migrating to New Zealand.[13,14] Genetic factors cannot explain such a rapid change.

Environmental and Dietary Risk Factors

Accumulating data indicate that abnormalities of the gut immune system may play a fundamental role in the development of the immune attack on beta cells and the subsequent development of T1DM.[15] The intestinal immune system serves a vital role in processing the many food and microbial antigens to protect the body from infection and allergy. What appears to happen in the development of some cases of T1DM is the development of antibodies by the gut immune system that ultimately attack the beta cells. Possibly an underlying factor that may contribute to T1DM is poor protein digestion.

Poorly digested dietary proteins can cross-react with antigens on or within the beta cells of the pancreas. In humans, two proteins that have had the highest degree of incrimination are those found in milk (which contains bovine serum albumin and bovine insulin) and wheat (which contains gluten). For example, dietary bovine insulin differs from human insulin by only three amino acids. If a person develops antibodies to bovine insulin, there is a good chance that these antibodies will also attack their own insulin. In addition to causing antibody-mediated destruction of the beta cells, bovine insulin is able to activate T cells in those predisposed to diabetes in a manner that can also lead to beta-cell destruction by direct attack from T-killer cells.

Strong evidence implicates dietary factors like cow's milk and gluten as important triggers of the autoimmune process that leads to T1DM. In contrast, breastfeeding has been identified as an important factor in establishing proper intestinal immune function and reducing the risk of T1DM. It is well known that breastfeeding confers a reduction in the risk of food allergies as well as better protection against both bacterial and viral intestinal infections. In case-controlled studies, patients with T1DM were more likely to have been breastfed for less than 3 months and to have been exposed to cow's milk or solid foods before 4 months of age. A critical review and analysis of all relevant citations in the medical literature indicate that early cow's milk exposure may increase the risk by about 1.5 times.[14,16] In addition, although the risk of

diabetes associated with exposure to cow's milk was first thought to relate only to intake during infancy, additional studies showed that ingestion at any age may increase the risk of T1DM.

There is also considerable evidence that sensitivity to gluten—the major protein component of wheat, rye, and barley—may also play a role. Gluten sensitivity produces celiac disease, another autoimmune disorder. Celiac disease, like T1DM, is associated with abnormalities in intestinal immune function. And as in the case of diabetes, breastfeeding appears to have a preventive effect, whereas the early introduction of cow's milk is believed to be a major causative factor. The risk of developing T1DM is higher in children with celiac disease. Not surprisingly, the highest level of antibodies to cow's milk proteins is found in people with celiac disease.[17]

Enteroviruses and Type 1 Diabetes

Population-based studies as well as a prospective study have strengthened the hypothesis that T1DM can be the result of viral infection.[18,19] A working theory in this regard is that the immune system becomes slightly confused as to which proteins to attack—the food-based ones such as those from dairy or gluten or the similar proteins on the pancreatic beta cells or insulin. When the person then has a viral infection, the increased stimulation of the immune system is the key that prompts it to become more active, and those confused immune cells begin to damage the pancreas. Gastrointestinal infections due to enteroviruses (e.g., polioviruses, coxsackieviruses, echoviruses) and rotavirus are common, especially in children. All of these viruses replicate in the gut and stimulate the intestinal immune system, which may then activate the insulin-specific immune cells to seek out and destroy beta cells. These viruses and others are also capable of infecting pancreatic beta cells, causing the leukocytes to attack and destroy the beta cells in an attempt to kill the virus. Gastrointestinal viral infections may also increase intestinal permeability and enhance the antibody response to dietary bovine insulin as a result of increased absorption of the intact protein. The severe "leaky gut"—or increased permeability of the small intestine that occurs during and for some time following rotavirus infections (one of the most common causes of acute diarrheal illness in children)—exposes the gut-associated immune cells to large quantities of intact protein.

Vitamin D Deficiency

Cod liver oil may offer significant protection against the development of diabetes because of its high content of vitamin D. The use of cod liver oil became popular during the 1890s to treat rickets, a vitamin D–deficiency disease characterized by an inability to calcify the bone matrix, resulting in softening of the skull bones, bowing of the legs, spinal curvature, and enlarged joints. Beginning in the 1930s, vitamin D was added to milk at a level of 100 IU per 8 oz. As a result, rickets is now uncommon in most developed countries.

Emerging evidence indicates that vitamin D supplementation from cod liver oil and other sources during early childhood can prevent not only rickets but also T1DM.[20] In fact, vitamin D fortification may offset some of the "diabetogenic" effect of cow's milk, but the dosage level in milk may not be sufficient to do so, as the level that was shown to be protective was about 2000 IU—much higher than the amount typically ingested from the consumption of vitamin D–fortified milk.

The most extensive study looking at vitamin D and T1DM enrolled all pregnant women in northern Finland who were due to give birth in 1966 (more than 12,000 women), and their children were then monitored until December 1997.[21] Final analysis of 10,366 enrollees demonstrated that children who regularly took vitamin D, primarily from cod liver oil, had an 80% reduced risk of developing T1DM, whereas those who had a vitamin D deficiency actually had a 300% increased risk of developing the disease. One study found that the use of vitamin D from cod liver oil during pregnancy significantly reduced the frequency of T1DM in the offspring.[22] Furthermore, studies looking at vitamin D status in the blood of newly diagnosed individuals with T1DM have found much lower levels of the vitamin in these patients than in healthy controls. Because vitamin D can be produced in the body by the action of sunlight on the skin, lack of sun exposure during childhood may also play a role and partially explain the higher T1DM rates in northern countries. Vitamin D in recent research has been shown to prevent autoimmune conditions, including those that attack beta cells, from developing in the body, and observational studies have shown a dose-dependent degree of protection.[23]

This research indicates that ensuring adequate vitamin D supplementation during pregnancy and early childhood may reduce the risk of T1DM. Vitamin D is important for the normal development of the immune system. In addition, it has been shown that vitamin D inhibits some of the autoimmune reactions that target the beta cells.

Omega-3 Fatty Acid Deficiency

In addition to the strong case that can be made for vitamin D as a protective factor, an equally strong case can be made for the benefits of the omega-3 fatty acids in cod liver oil and other fish oils. Human studies have shown that when essential fatty acids (EFAs) are given, the onset of T1DM was significantly reduced. Also, higher levels of n-3 polyunsaturated fatty acids in RBCs have also been associated with reduced risk.[24] For one thing, cod liver oil also provides both EPA and DHA, which are vital EFAs in humans. Other studies support the benefit of supplementing EFAs in pregnant women and children. The mechanisms responsible for this effect may be related to improved cell membrane function, leading to enhanced antioxidant status and the reduced formation of inflammatory compounds called cytokines.[25]

Nitrates

Clear links between increased levels of nitrates (from both dietary sources and water) and an increased rate of T1DM have been established. Nitrates are produced by agricultural runoff from fertilizers and are found in cured or smoked meats such as ham, hot dogs, bacon, and jerky to keep the food from spoiling. Nitrates react within the body to form compounds known as nitrosamines. (Note: The USDA requires all manufacturers of processed meats to add vitamin C to their products to prevent the formation of nitrosamines.) Nitrates and nitrosamines are known to cause diabetes in animals. Infants and young children are believed to be particularly vulnerable to the harmful effects of nitrate exposure.

One of the most alarming features of T1DM is that it is becoming much more prevalent, with a current growth rate of 3% per year worldwide.[10] Some areas have been hit particularly hard, such as Finland, Great Britain, Canada, and the United States. Increased nitrate exposure may be a key factor, as the nitrate levels in ground and surface waters of agricultural regions have increased over the past 40 years owing to the use of nitrogen fertilizers. Nitrate contamination occurs in geographic patterns related to the amount of nitrogen contributed by fertilizers, manure, and airborne sources such as automobile and industrial emissions. Nitrate exposure may explain why some geographic pockets have substantially higher rates of T1DM.[26,27]

Circumstantial evidence from population-based studies also suggests that a higher dietary intake of nitrates from smoked/cured meats is associated with a significantly higher risk for T1DM. These foods severely stress body defense mechanisms and are to be avoided. The habit of feeding children hot dogs, cold cuts, and ham would be a good one for parents to break. Health food stores now carry nitrate-free alternatives to these toxic food choices. Also, investing in a high-quality water purifier is good insurance against ingesting nitrate-contaminated drinking water.



EARLY TREATMENT AND POSSIBLE REVERSAL OF TYPE 1 DIABETES

Early intervention in T1DM designed to affect the autoimmune or oxidative process theoretically may be capable of lengthening the "honeymoon" phase or even completely reversing the process. This goal appears to have two candidates: niacinamide and epicatechin.

There are some new data (see, for example, http://www.jdrf.org/index.cfm?page_id=110893) showing that people are now removing gluten and dairy from their diets and are supporting gut health as well as immune system balance.

Niacinamide

Niacinamide, also called nicotinamide, has been shown to prevent some of the immune-mediated destruction of the pancreatic beta cells and may actually help to reverse the process.[28,29] Observations that niacinamide can prevent the development of T1DM in experimental animals led to several pilot clinical trials that initially confirmed these observations and suggested that if given soon enough at the onset of diabetes, niacinamide could help restore beta cells or at least slow down their destruction. In one of the first pilot studies of people newly diagnosed with T1DM, 7 patients were given 3 g of niacinamide daily and 9 were given a placebo. After 6 months, 5 patients in the niacinamide group and 2 in the placebo group were still not taking insulin and had normal blood glucose and $HgbA_{1c}$. At 12 months, 3 patients in the niacinamide group but none in the placebo group were in clinical remission.[30]

The results of this pilot study and others suggest that niacinamide can prevent T1DM from progressing in some patients if given soon enough at the onset of diabetes by helping restore beta cells. As of 2004, there had been 12 studies of niacinamide treatment in recent-onset T1DM or T1DM of less than 5 years' duration and residual beta-cell mass. Ten of these were double-blind placebo-controlled studies, of which half showed a positive effect compared with placebo in terms of prolonged non–insulin-requiring remission, lower insulin requirements, improved metabolic control, and increased beta-cell function as determined by secretion of a substance known as C-peptide. The main differences between the positive and negative studies in recent-onset T1DM were older age and higher baseline fasting C-peptide in positive studies.[31-34]

Although some of the studies have shown positive results, it is important to point out that two large studies designed to evaluate the effectiveness of niacinamide in preventing the development of T1DM in high-risk individuals—such as siblings of children who developed T1DM or in individuals who already show elevations in antibodies directed against the beta cells—did not show niacinamide to be effective. The first of these, the German Nicotinamide Intervention Study, did not show much of an effect with 1.2 g of niacinamide daily, while results from the larger study, the European Nicotinamide Diabetes Intervention Trial, did not show benefit with dosages as high as 3 g a day.[35,36] A possible shortcoming of these studies was the choice of a timed-released niacinamide. It is possible that such a formulation did provide the peak levels of niacinamide required to block autoimmune mechanisms such as cytokine production.[37]

In the best-case scenario, niacinamide will likely work for only a few individuals with T1DM of recent onset. Nonetheless, the fact that some patients have had complete reversal of their disease makes a trial of niacinamide worth the effort, especially because there is currently no reasonable alternative.

The dosage recommendation is based on body weight: 25 to 50 mg of niacinamide for every 2.2 lb of body weight or a maximum dosage of 3 g/day in divided doses. Niacinamide is generally well tolerated and without side effects. In fact, no side effects have been reported in clinical trials in T1DM. It does not cause the flushing of skin characterized by high dosages of niacin. However, because it could possibly harm the liver, a blood test for liver enzymes should be performed every 3 months to rule out liver damage.

Epicatechin

The second natural compound that may offer benefit is epicatechin. The line of research on its potential role in T1DM of recent onset began with examining the bark of the Malabar kino tree *(Pterocarpus marsupium).* This botanical medicine has a long history of use in India as a treatment for diabetes. Initially, epicatechin extracted from the bark was shown to prevent beta-cell damage in rats. Further research indicated that both epicatechin and a crude alcohol extract of *P. marsupium* were actually able to promote the regeneration of functional pancreatic beta cells in diabetic animals.[38] Green tea *(Camellia sinensis)* extract appears to be a better choice than extracts of *P. marsupium,* as the epicatechin content in a high-quality green tea extract is actually higher than that found in extracts of *P. marsupium*. Second, green tea extract exerts a broader range of beneficial effects. Green tea polyphenols also exhibit significant antiviral activity against rotavirus and enterovirus—two viruses suspected of causing T1DM.[39] Last, green tea extract is considerably easier to find commercially than *P. marsupium*. Recommended dosages for children below age 6 is 50 to 150 mg; for those 6 to 12 years old, 100 to 200 mg; and for children older than 12 years old and adults, 150 to 300 mg. The green tea extract should have a polyphenol content of 80% and be decaffeinated.



RISK FACTORS IN TYPE 2 DIABETES

The major risk factor for T2DM is obesity or, more precisely, excess body fat. Approximately 80% to 90% of individuals with T2DM are obese (a body mass index above 30). When adipocytes, particularly those around the abdomen, become full of fat, they secrete a number of biological products (e.g., resistin, leptin, tumor necrosis factor, free fatty acids, cortisol) that dampen the effect of insulin, impair glucose utilization in skeletal muscle, promote glucose production by the liver, and impair insulin release by pancreatic beta cells. Also important is that as the number and size of adipocytes increase, there is a reduction in the secretion of compounds that promote insulin action, including a novel protein produced by fat cells known as adiponectin. (Adiponectin is associated not only with improved insulin sensitivity but also with antiinflammatory activity; moreover, it lowers triglycerides and blocks the development of atherosclerosis, or hardening of the arteries.) The net effect of all these negative actions of fat cells is that they severely stress blood glucose control mechanisms while

BOX 161-2 Risk Factors for Type 2 Diabetes Mellitus

- Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
- Obesity
- Increased waist-to-hip ratio
- Age: increasing age is associated with increased risk, beginning at age 45
- Race/ethnicity (e.g., African American, Hispanic American, Native American/Canadian, Native Australian or New Zealander, Asian American, Pacific Islander)
- Previously identified impaired fasting glucose or impaired glucose tolerance
- History of gestational diabetes (diabetes during pregnancy) or delivery of baby weighing more than 9 lb
- Hypertension (blood pressure >140/90 mm Hg)
- Triglyceride level >250 mg/dL
- Low levels of adiponectin, elevated levels of fasting insulin
- Polycystic ovary syndrome (to be considered in any adult woman who is overweight with both acne and infertility)

also leading to the development of the major complication of diabetes: atherosclerosis. Because of all of these newly discovered hormones secreted by adipocytes, many experts now consider the adipose tissue a member of the endocrine system (e.g., the pituitary, adrenals, and thyroid).[40,41] Measurements of blood levels of adiponectin and other hormones secreted by fat cells may turn out to be the most meaningful predictors of the likelihood of developing T2DM.[42,43]

In the early stages of the increased metabolic stress produced by the various secretions of adipocytes and the lack of adiponectin, blood glucose levels remain normal despite insulin resistance because pancreatic beta cells compensate by increasing insulin output. As metabolic stress increases and insulin resistance becomes more significant, the conventional explanation is that eventually the pancreas cannot compensate and elevations in blood glucose levels develop. As the disease progresses from insulin resistance to full-blown diabetes, the pancreas starts to "burn out" and produces less insulin. Under naturopathic care, however, the pancreas can recover just fine and continue to secrete insulin for the rest of the patient's life. However, with conventional care and especially allowing the patient to eat a high-carbohydrate diet, diabetes is not well controlled and the result is ultimately complete pancreatic failure to produce insulin, thus requiring full use of basal and bolus insulin. It cannot be sufficiently stressed that this scenario is preventable with good diabetes care and if a patient's $HgbA_{1c}$ remains at 5.7 or less. (See Box 161-2 for risk factors.)

Genetics of Type 2 Diabetes and Obesity

In studies of identical twins, the concordance rate was between 70% and 90% for T2DM. This high concordance points to a strong genetic relationship. Data from family studies also provide additional support, as children with one parent with T2DM have an increased risk of developing diabetes at some point in their lives. If both parents have the disease, the risk in offspring is nearly 40%.[44] However, even with the strongest predisposition, diabetes can be avoided in most cases.

The Case of the Pima Indians

The Pima Indians of Arizona have the highest rate of T2DM and obesity anywhere in the world. Research has demonstrated a strong genetic predisposition, but even with this strong tendency it is clear that the high rate of T2DM in this group is related to diet and lifestyle. The Pima Indians living traditionally in Mexico still cultivate corn, beans, and potatoes as their main staples, plus a limited amount of seasonal vegetables and fruits such as zucchini squash, tomatoes, garlic, green pepper, peaches, and apples. The Pimas of Mexico also make heavy use of wild and medicinal plants in their diet. They work hard, have no electricity or running water in their homes, and walk long distances to bring in drinking water or wash their clothes. They use no modern household devices; consequently, food preparation and household chores require extra effort from the women. In contrast, the Pima Indians of Arizona are largely sedentary and follow the dietary practices of typical Americans. The results are astounding. Although roughly 16% of U.S. Native Americans have T2DM, 50% of Arizona Pimas have T2DM and 95% of them are overweight or obese. T2DM is a rarity among the Mexican Pimas and only about 10% can be classified as obese. The average difference in body weight between the Arizona and Mexican Pima men and women was more than 60 lb.[45]

Further evidence that diet and lifestyle appear to be able to overcome even the strongest genetic predisposition is shown by some of the intervention studies among Pima Indians. When these people were placed on a more traditional diet along with physical exercise, their blood glucose levels improved dramatically and they lost weight. The focus right now, by various medical organizations such as the National Institute of Health, in dealing with the epidemic of diabetes and obesity among the Pima Indians is to educate children on the importance of exercise and dietary choices to reduce diabetes risk.

Other Genetic and Racial Factors

Other racial and ethnic groups beside Pima Indians that have a higher tendency to develop T2DM include other Native Americans, African Americans, Hispanic Americans, Asian Americans, Australian Aborigines, and Pacific Islanders. It is important for all of these higher-risk groups to learn that when they follow the traditional dietary and lifestyle practices of their original cultures, their rates of diabetes will be extremely low. It appears that these groups are simply highly sensitive to the "Western diet" and lifestyle.

Diet, Exercise, Lifestyle, and Diabetes Risk

Findings from the U.S. government's Third National Health and Nutrition Examination Survey (NHANES III) make it clear that diabetes is a disease of diet and lifestyle. Of individuals with T2DM, 69% did not exercise at all or did not engage in regular exercise; 62% ate fewer than five servings of fruits and vegetables per day; 65% consumed more than 30% of their daily calories from fat and more than 10% of total calories from saturated fat; and 82% were either overweight or obese.[46]

Insights into the independent role of the modern lifestyle versus diet and obesity in the development of T2DM can be gleaned from the Old Order Amish. These 30,000 or so individuals, whose ancestors arrived on U.S. shores in the eighteenth century, maintain religious and cultural beliefs that preclude regular use of modern conveniences such as electrical appliances, telephones, and cars, and they have a physically active lifestyle. By comparison, the 200 million typical Americans living alongside them have, over the past 250 years, willingly adopted the advances of modern technology, making life less physically demanding.

Although the typical Amish diet and rate of obesity do not differ from those of the typical American, the rate of diabetes among the Amish is considerably less—about 50% lower. Although the percentage of Amish with impaired glucose tolerance (prediabetes) is

about the same as in other whites in America, apparently not as many Amish go on to develop diabetes. This suggests that physical activity has a protective effect against T2DM independent of obesity or percentage of body fat.[47,48]

Results from other studies corroborate this hypothesis. Lifestyle changes alone are associated with a 58% reduced risk of developing diabetes among those at high risk because they show evidence of impaired glucose tolerance (as based on results from the Diabetes Prevention Program—a large intervention trial of more than 1000 subjects). The two major goals of the program were a minimum of 7% weight loss/weight maintenance and a minimum of 150 min/week of physical activity similar in intensity to brisk walking.[49]

A Diet High in Refined Carbohydrates

Dietary carbohydrates play a central role in the causes, prevention, and treatment of T2DM. In an effort to qualify carbohydrate sources as acceptable or not, two indices have been developed: the glycemic index (GI) and glycemic load (GL). The GI is a numerical value that expresses the rise in blood glucose after a particular food is eaten. The standard value of 100 is based on the rise seen with the ingestion of glucose. The GI ranges from about 20 for fructose and whole barley to about 98 for a baked potato. The insulin response to carbohydrate-containing foods is similar to the rise in blood sugar. The GI is often used as a guideline in dietary recommendations for people with either diabetes or hypoglycemia. In addition, eating foods with a lower GI is associated with a reduced risk for obesity and diabetes.[50-52]

One of the shortcomings of the GI is that it tells us only about the quality of the carbohydrates, not the quantity. Obviously quantity matters too, but measurement of the GI of a food is not related to portion size. That is where the GL comes into play. The GL takes the GI into account but provides much more accurate information than the GI alone. The GL is calculated by multiplying the amount of carbohydrate in a serving of food by that food's GI (as compared with glucose) and then dividing it by 100. The higher the GL, the greater the stress on insulin. In Appendix 6, we provide the GI and GL for many common foods.

Research studies are just starting to use the GL as a more sensitive marker for the role of diet in chronic conditions like diabetes and heart disease. The preliminary results are showing an even stronger link in predicting diabetes than the one shown for the GI.[50,52] Researchers are also showing that a high-GL diet is also associated with an increased risk for heart disease. For example, when researchers from the Nurse's Health Study used GL measures to assess the impact of carbohydrate consumption on women, they found that high-GL diets (and, by extension, high-GI foods and greater total carbohydrate intake) correlated with even more significantly greater risk for heart disease than the GI because of lower levels of protective HDL cholesterol and higher triglyceride levels.[53] Increased risk for diabetes and heart disease started, on average, at a daily GL of 161. Therefore, we recommend using the information in Appendix 5 to help determine how to prevent the total daily GL from exceeding 150. Keep in mind that the GL is based on the stated serving size; the larger the serving size, the greater the GL.

The Importance of Dietary Fiber in Reducing the Risk of Developing Diabetes

Population studies as well as clinical and experimental data show diabetes to be one of the diseases most clearly related to an inadequate intake of dietary fiber. Different types of fibers possess different actions. The type of fiber that exerts the most beneficial effects on blood sugar control is the water-soluble form. Included in this class are hemicelluloses, mucilages, gums, and pectins. These types of fiber are capable of slowing down the digestion and absorption of carbohydrates, thereby preventing rapid rises in blood sugar. They are also associated with increasing the sensitivity of tissues to insulin and improving the uptake of glucose by the muscles, liver, and other tissues, thereby preventing a sustained elevation of blood sugar.[54,55]

Particularly good sources of water-soluble fiber are legumes, oat bran, nuts, seeds, psyllium seed husks, pears, apples, and most vegetables. Large amounts of plant foods must be consumed to obtain adequate levels of dietary fiber, although beans, peas, and legumes are overall the best sources for high fiber intake in relatively easy amounts to ingest. Even the simple change from white flour products to whole-grain versions is associated with a reduced risk for T2DM,[56,57] our recommendation is to consume at least 35 g of fiber a day from various food sources, especially vegetables. Fiber supplements can also be taken to achieve greater effects in lowering the GI.

The Wrong Types of Fats

Dietary fat also plays a central role in the likelihood of developing T2DM. Large controlled trials have shown that a reduction of fat intake as part of a healthy lifestyle, combined with weight reduction and exercise, reduces the risk for T2DM. However, more important than the amount of fat in the diet is the *type* of fat consumed.[58] The types of dietary fats linked to T2DM include saturated fats and trans fatty acids (partially hydrogenated vegetable oils) taken in large amounts along with a relative insufficiency of monounsaturated and omega-3 fatty acids.

One of the key reasons why dietary fats appear to be related to the risk for T2DM is that they determine cell membrane composition. That is, a "bad fat" pattern leads to reduced membrane fluidity, which in turn causes reduced insulin binding to receptors on cellular membranes, reduced insulin action, or both. Particularly harmful to cell membrane function are margarine, vegetable oil shortening, and other foods containing trans fatty acids and partially hydrogenated oils. These fatty acids interfere with the body's ability to use important essential fatty acids (EFAs). One study estimated that by substituting polyunsaturated vegetable oils for margarine containing partially hydrogenated vegetable oil, the likelihood of developing T2DM could be reduced by 40%.[59]

In contrast to the dampening of insulin sensitivity caused by margarine and saturated fats, clinical studies have shown that monounsaturated fats and omega-3 oils improve insulin action.[60] Adding further support is the fact that population studies have also indicated that the frequent consumption of monounsaturated fats such as olive oil, raw or lightly roasted nuts and seeds, nut oils, and omega-3 fatty acids from fish protect against the development of T2DM. Healthy omega-3 fish include wild salmon, trout, sardines, halibut, and herring. All of this evidence indicates that altered cell membrane composition and fluidity play a critical role in the development of T2DM.

One of the most useful food groups to reduce the risk of T2DM is nuts. Studies have shown that consumption of nuts is inversely associated with the risk of T2DM, independent of known risk factors for T2DM including age, obesity, family history of diabetes, physical activity, smoking, and other dietary factors.[61] In addition to providing the beneficial monounsaturated and polyunsaturated fats that improve insulin sensitivity, nuts are also rich in fiber and magnesium and have a low GI. Higher intakes of fiber and magnesium and foods with a low GI has been associated with a reduced risk of T2DM in several population-based studies. Eating mostly raw or lightly roasted fresh nuts and seeds rather than commercially roasted and salted nuts and seeds should be advocated.

Low Intake of Antioxidant Nutrients

Cumulative free radical damage leads to cellular aging and is a major factor contributing to T2DM as well as many other chronic degenerative diseases. Several large population-based studies have shown that the higher the intake of fruit and vegetables, the better blood glucose levels are controlled and the lower the risk for T2DM.[62] Many factors could explain this inverse correlation. Fruits and vegetables are good sources of fiber and also provide many nutrients and antioxidants. Even something as simple as the regular consumption of salads is associated with a reduced risk for T2DM.[63]

Studies looking at levels of individualized antioxidants have also shown similar inverse correlations—the higher the level of vitamin C, vitamin E, or carotenes, for example, the lower the risk for T2DM.[64-66] Likewise, the lower the levels of antioxidants and higher the levels of fats damaged by free radicals (lipid peroxides), the greater the risk for T2DM.[67] In one study, 944 men 42 to 60 years of age were followed closely for 4 years. None of them had diabetes at the beginning of the study. At the end of this time, 45 men had developed diabetes. The researchers found that a low vitamin E concentration was associated with 3.9-fold (390%) increased risk for T2DM in the study subjects.[68]

Free Radicals and Diabetes

One of the hallmark features of T2DM is the presence of higher levels of free radicals and prooxidants,[69] particularly an increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS).[70] These compounds are also activated by high blood glucose and elevated levels of saturated fat and, as already mentioned, are produced in the abdominal fat cells of individuals who are overweight or obese.

These compounds greatly stress antioxidant mechanisms, as they directly oxidize and damage cellular components such as DNA, proteins, and cell membrane fatty acids. In addition to their ability to directly inflict damage on these structures, ROS and RNS indirectly induce damage to tissues by activating a number of inflammatory compounds such as nuclear factor-kappa B, which ultimately leads to both insulin resistance and impaired insulin secretion.

Persistent Organic Pollutants

Persistent organic pollutants (POPs) include such chemical compounds as polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), hexachlorobenzene (HCB), organophosphates, DDE, and bisphenol A. These compounds have been linked to the development of T2DM. In addition, research indicates that the body load of POPs is not only a significant predictor of T2DM but may also be a more significant risk factor than obesity.[71] Those with levels of organochlorine pesticides in the top quartile have an odds ratio of 5.3 for metabolic syndrome.[72]

Unfortunately, direct measurement of POP levels is difficult and very expensive. However, a good indirect measure is gamma-glutamyltransferase (GGTP). An elevated level of GGTP is a strong predictor of diabetes risk. Those with levels above 40 IU/L have a 20-fold increased risk.[73]

Lifestyle Management versus Drugs to Prevent Type 2 Diabetes

Several well-designed large trials have shown that lifestyle and dietary modifications can be used to effectively prevent T2DM. That fact has not dissuaded drug companies from sponsoring studies attempting to prevent diabetes with drugs. However, the degree of prevention with drugs pales in comparison with that of diet and lifestyle. For example, in one of the most celebrated studies, 3234 subjects with impaired glucose tolerance (prediabetes) were randomly assigned to be in a group receiving a placebo, the blood glucose–lowering drug metformin (850 mg twice daily), or a lifestyle modification program with the goals of at least a 7% weight loss and at least 150 minutes of physical activity per week. The average follow-up was 2.8 years. The incidence of diabetes was 11, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively. The lifestyle intervention reduced the incidence of diabetes by 58% and metformin by 31% as compared with placebo. Clearly, the lifestyle intervention was significantly more effective than metformin—a drug with sometimes serious side effects.[74]

Environmental Toxicity

Given the fact that environmental pollutants can increase the risk of developing T2DM, steps can be taken to reduce patients' exposure to them. This can be done, for example, through the use of organic foods and natural cleaning agents in the home and the avoidance of chemical pesticides. These are all valid steps in preventing environmental toxins undermining the regulation of insulin.

CLINICAL MONITORING OF DIABETES

Knowledge and awareness are the greatest allies of people with diabetes. An individual with diabetes who makes a strong commitment to learning about his or her condition and accepts the lead role in a carefully supervised monitoring program that breaks away from the standard recommended by the American Diabetes Association (ADA) greatly improves the likelihood that he or she will lead a long and healthy life. On the other hand, individuals who remain blissfully ignorant about their disease and refuse to undergo regular testing or self-monitoring are far more likely to face years of unnecessary suffering and, more often than not, catastrophic health problems.

Unless it is properly managed and supervised, diabetes can be viewed as a state of biochemical and hormonal anarchy that will lead to organ injury and accelerated aging. Many of the complex control systems that faithfully govern and protect the body are damaged in the diabetic individual. In order for such a person to regain control, he or she must learn how to maintain an intimate awareness of blood sugar, risk factors for atherosclerosis (hardening of the arteries), blood pressure, body mass index, level of fitness, and other factors that determine the risk of developing diabetic complications and experiencing an erosion of his or her quality of life.

Fortunately, diabetic patients who do develop a keen awareness of these risk factors through regular testing and a properly supervised self-monitoring program are also those who are much more likely to benefit from changes in lifestyle: diet, supplements, and, when necessary, medications.

Urinary Glucose Monitoring

The measurement of glucose in the urine is now entirely passé. Until the mid-1970s, the only option that diabetic patients had to monitor blood glucose was indirectly through urine glucose testing. Normally, the kidneys are able to conserve all of the glucose in the blood that they constantly filter. However, if blood glucose gets too high, the kidneys become unable to conserve all of the glucose, which then begins to appear in the urine. Because the average diabetic patient's kidneys can completely conserve glucose until the blood glucose reaches about 200 to 250 mg/dL (10 mmol/L), a

negative urine glucose reading indicates that the blood glucose since the time of previous voiding has been less than 200 to 250 mg/dL (10 mmol/L). Therefore, the measurement of glucose in the urine is only a crude measurement of blood glucose control and is completely worthless in detecting severe hypo- or hyperglycemia.[75] Thus, urinary glucose monitoring is of little value in determining the success of blood glucose control, and it does not provide adequate feedback when lifestyle, diet, or other treatments are adjusted. These days, all diabetic patients should own a glucometer and know how to test their own blood glucose levels.

Urinary Ketone Testing

In any circumstance when the body must derive its primary source of energy from fat, ketones are produced as a by-product. If the level of ketone production is high enough, ketones appear in the urine. In the patient with T1DM or T2DM who cannot produce any innate insulin, ketones appear in the urine when there is a severe deficiency in or activity of insulin. In general this is associated only with T1DM, because the vast majority of patients with T2DM do not develop ketoacidosis. This can occur if a patient with insulin-dependent diabetes accidentally or purposefully forgets to take insulin. It can also occur when such a patient becomes ill or injured or is given high doses of cortisone-related drugs. All of these phenomena may result in a severe loss of insulin effectiveness, resulting in the cells' inability to take up and use glucose. In such circumstances, blood glucose rises to high levels, high amounts of fat are used by cells that cannot take in glucose, and the blood becomes polluted with toxic levels of acidic ketones. Severe dehydration occurs rapidly because the kidneys are unable to conserve water in the presence of such extraordinary levels of blood glucose. This dangerous state is referred to as diabetic ketoacidosis, and it must be treated as a medical emergency, usually necessitating intravenous insulin, large amounts of intravenous fluids, and careful monitoring, usually in an intensive care unit. Ignoring ketoacidosis can rapidly lead to death.

Because of the events outlined above, the testing of urine or, even better, blood for ketones (using the Precision Xtra glucometer, which can also test for ketones) remains an important part of monitoring only in patients with T1DM who have no remaining pancreatic function. The presence of urine or blood ketones accompanied by high blood sugar readings can be interpreted to determine how far along the ketoacidosis has developed and what type of medical attention is required. For this reason, all patients with T1DM should test their urine for ketones frequently during acute illness or severe stress, especially when blood glucose levels are consistently elevated (>300 mg/dL [16.7 mmol/L]), regularly during pregnancy, or when symptoms suggestive of ketoacidosis such as nausea, vomiting, or abdominal pain are present.

Self-Monitoring of Blood Glucose

Since its introduction, self-monitoring of blood glucose (SMBG) has revolutionized the management of diabetes.[76] The publication of the landmark Diabetes Control and Complications Trial,[77] which examined intensive glucose control in people with T1DM, and the United Kingdom Prospective Diabetes Study,[78] which examined intensive glucose control in those with T2DM, scientifically proved that the most important factor in determining the long-term risk of serious diabetic complications in both types of diabetes is blood glucose control. Patients who do not maintain vigilant awareness of their blood glucose and who do not make every effort to keep their blood sugar under tight control can expect a significant increase in their risk of serious health problems such as eye, kidney, and heart disease as well as a whole host of other problems including depression, fatigue, impotence, and chronic infections. SMBG is important for a number of reasons:[79]

1. Modifications of treatment to achieve appropriate blood glucose control
2. Detection and diagnosis of hypoglycemia
3. Adjusting care in response to daily life circumstances (e.g., food intake, exercise, stress, illness)
4. Detection and treatment of severe hyperglycemia
5. Increasing compliance with therapy (helps to combat apathy and denial)
6. Improvement in motivation because of immediate positive and negative feedback (Boxes 161-3 and 161-4)

BOX 161-3 Optimal Range for Self-Monitored Blood Glucose

- Fasting or before meals: 80 to 110 mg/dL (4.4-6.7 mmol/L)
- 2 hours after eating (postprandial): <140 mg/dL (7.8 mmol/L)
- At bedtime: 100 to 140 mg/dL (5.6-7.8 mmol/L)
- Note that these are whole-blood values that typically run 10 mg/dL (0.6 mmol/L) higher than serum values. To avoid confusing numbers, some home glucose-monitoring kits, even those using whole-blood samples, are now calibrating to serum levels. Check the glucose monitor's documentation to find out if it is set up to determine whole-blood or serum glucose levels.
- Slightly higher values may be acceptable in the elderly or in young children because of their higher risk of developing dangerous hypoglycemia.

BOX 161-4 Optimal Schedule for Self-Monitored Blood Glucose

1. Test on awakening and just before each meal. Ideal blood sugar before meals is <120 mg/dL (6.7 mmol/L).
2. Test 2 hours after each meal. Ideal blood sugar 2 hours after meals is <140 mg/dL (7.7 mmol/L).
3. Test at bedtime. Ideal blood sugar at bedtime is <140 mg/dL (7.7 mmol/L).

Type 1 Diabetes and Self-Monitoring of Blood Glucose

Without a doubt all individuals with T1DM must monitor their blood glucose frequently if they want to achieve and maintain good health. In the absence of diabetes, the pancreas monitors blood glucose continuously and adjusts its insulin output depending on moment-by-moment changes. In order to achieve blood glucose levels that are consistently as close to normal as possible, those with T1DM must replicate this natural situation as closely as possible. This means that they must monitor their blood glucose frequently, and they must learn to use this information to make ongoing adjustments to their insulin injections, diet, and exercise.

Intensive insulin therapy allows a diabetic patient to achieve near normal levels of blood glucose along with enjoying improved lifestyle flexibility. With conventional, infrequent insulin injections, the diabetic patient must structure meals and other aspects of lifestyle around his or her injections or face serious abnormalities of blood glucose. On the other hand, with intensive insulin therapy that relies on rapid-acting, short-duration insulin or the use of an insulin pump (an electronic device that provides a

continuous injection of short-acting insulins with extra boluses before meals), the timing and size of doses can be adjusted to suit the events of the day.[80] Even though it may involve multiple injections (usually before each meal and often at bedtime) and blood glucose measurements up to six times or more each day, intensive insulin therapy results in greater dietary and lifestyle freedom, a higher quality of life and well-being, and near nondiabetic blood glucose control, which is vital for long-term health.

Type 2 Diabetes and Self-Monitoring of Blood Glucose

Self-monitoring of blood glucose has an important place in the management of T2DM as well. Each such patient lies somewhere on a spectrum that ranges from mild glucose intolerance (accompanied by insulin resistance and higher-than-normal levels of insulin) to more advanced forms (with more severe insulin resistance, the potential for high levels of blood glucose, ketoacidosis, and partial or nearly complete pancreatic failure with an accompanying lack of insulin). Depending on the severity of the individual's diabetes, SMBG plays a varying role. Each such patient should own a blood glucose monitor and have become intimately familiar with its use. Even those whose blood glucose is well controlled through diet, lifestyle, and supplements should measure their blood glucose regularly.

Numerous dietary factors, supplements, exercise, stress, and illness can all have a significant impact on blood glucose control. Becoming intimately aware of how all these factors influence diabetes will help motivate these patients to make positive changes and provide immediate feedback as to the success of any changes that have been made.

Those whose disease is more advanced and who have diminished pancreatic insulin production may also benefit from efforts to establish consistently near normal blood glucose control using intensive insulin therapy similar to that of patients with T1DM.[81] A C-peptide blood test can provide an estimate of how much insulin a patient is producing and is one way to help determine the appropriateness of using insulin. If T2DM patients are placed on an intensive insulin therapy program, they must perform SMBG as frequently as those with T1DM who are receiving intensive insulin therapy (usually before and 2 hours after each meal).

Many patients with advanced T2DM have diminished insulin production (evidenced by lower-than-normal C-peptide levels). A common way to achieve optimal blood glucose in these individuals is to give one injection of the new, long-acting insulin glargine (Lantus), which provides a smooth, continual release of insulin for 24 hours, along with diet and other medication. Patients on this type of program must measure their blood glucose frequently (usually before and 2 hours after each meal).

C-Peptide Determination

Often it is important to know whether a diabetic patient's pancreas is making insulin, and if so, how much. This assessment can greatly influence treatment, especially in a patient hoping to avoid or cease using injected insulin. The level of pancreatic insulin production can also partially determine the type of medication or natural health products that are more likely to be effective. Once it is known how well the pancreas is producing insulin, the focus may be shifted toward replacing deficiencies in insulin production, stimulating insulin production, preserving pancreatic function, reducing insulin resistance, or a combination of these therapeutic efforts.

One way to determine the level of insulin production is by measuring C-peptide. The pancreas manufactures a large protein called *proinsulin* first. A piece of this protein (C-peptide) is then snipped off by enzymes, and both C-peptide and the remaining insulin are released into the bloodstream. Injected insulin has no C-peptide, nor does the body ever produce antibodies against it, as it can against insulin. T1DM patients and those who have injected insulin even once are at high risk of having developed insulin antibodies, which can destroy the molecule. The benefits of measuring C-peptide are helpful for both T1DM and T2DM patients, but generally more so for those with T2DM. C-peptide can uncover how much insulin the pancreas is making, which may help to determine how much of a T1DM pancreas is still active. It may even sometimes make it possible, with alternative care, to stabilize the patient's condition. In T2DM, high C-peptide levels confirm that the patient is highly insulin resistant. If the C-peptide is low, it indicates that the pancreas is so damaged that some type of insulin therapy will be required (Table 161-3).

TABLE 161-3 **Interpreting Levels of C-Peptide**

C-PEPTIDE RESULTS	INTERPRETATION
Normal	Insulin production at normal level
Below normal	Newly diagnosed type 1 diabetic or chronic, long-term type 2 diabetic
Above normal	Newly diagnosed type 2 diabetic or a benign pancreatic tumor (insulinoma; rare)
Undetectable	Chronic type 1 diabetic or postsurgical removal of pancreas (rare)

Physician Monitoring

Although diabetic patients must take charge of their illness and be in control of their diet, lifestyle, and glucose monitoring, they are rarely successful without professional guidance. Numerous studies have determined that physician monitoring through laboratory measurements of blood glucose levels can have a major impact on a diabetic patient's long-term health.

One of the key determinants of blood glucose control is the $HgbA_{1c}$ test (see earlier). Unlike direct measurements of blood glucose, which detect the level at the moment of testing, the $HgbA_{1c}$ test reflects the average level of blood glucose over the preceding 3 months. Studies have shown that the level of $HgbA_{1c}$ closely correlates with the level of risk for diabetic complications. However, an $HgbA_{1c}$ may not be entirely accurate. A patient may have steady, regulated blood sugars that return an $HgbA_{1c}$ of 6%, or he or she may have very high numbers in combination with hypoglycemic events, which can also—because the $HgbA_{1c}$ is an average, median index—show the same $HgbA_{1c}$ of 6%.[6] Having an $HgbA_{1c}$ level of less than 5.5% or less is ideal and indicates that blood glucose levels have averaged in a range that is essentially nondiabetic (meaning that the patient is suffering no damage because of his or her glucose level). Owing to the great importance of adequate glucose control, all diabetic patients, should have their $HgbA_{1c}$ levels measured every 3 to 4 months, depending on the stability of their condition. If the $HgbA_{1c}$ number is not clearly known to be the result of good control or fluctuating highs and lows, then a second laboratory test, called Glycomark, is a good one to consider.[81a] The GlycoMark assay measures blood levels of 1,5-anhydroglucitol. 1,5-AG is found in nearly all foods and is ingested in a regular diet. Once ingested, 1,5-AG is nearly 100% non-metabolized and remains in a

relatively constant amount in the blood and tissues. When blood glucose exceeds 180 mg/dL for any period of time, the kidney attempts to reabsorb as much glucose back into the blood as it can. During times of glucosuria, the additional amount of glucose in the kidney blocks 1,5-AG from being reabsorbed into the blood and 1,5-AG is excreted in the urine at a higher rate than normal. Due to the lack of 1,5-AG being reabsorbed, blood levels of 1,5-AG decrease immediately, and continue to decrease until glucose values go below 180 mg/dL. It is this competitive inhibition of 1,5-AG from glucose that allows GlycoMark to accurately reflect any hyperglycemic episodes over 180 mg/dL. The Glycomark test has been shown to be more accurate than an HgbA1c and offers the physician a clearer picture of how well a patient's glucose levels are being controlled and also shows postprandial spikes more clearly.

Although it is clear that optimal blood glucose control is critical to the health of diabetic patients, several other risk factors must be carefully monitored in all diabetic patients. Early detection of problems through a program of regular screening and monitoring will enable preventive efforts and treatments to be put in place before serious complications or catastrophic problems occur. Table 161-4 provides a checklist for the proper evaluation and monitoring of patients with diabetes.

TABLE 161-4 **Clinical Management of the Patient with Diabetes**

	QUARTERLY	ANNUALLY
Review Management Plan		
Blood glucose self-monitoring results	X	X
Medication/insulin regimen	X	X
Nutritional plan	X	X
Exercise program	X	X
Psychosocial support	X	X
Physical Examination		
Weight	X	X
Height (for child/adolescent)	X	X
Sexual maturation (for child/adolescent)	X	X
Skin, including insulin injection sites	X	X
Feet: pulses, capillary refill, color, sensation, nails, skin, ulcers	X	X
Neurologic: reflexes, proprioception, vibratory sensation, touch (distal temperature sensation, distal pinprick or pressure sensation, standardized monofilament)		X
Regular retinal examination	X	X
Dilated retinal examination		X
Electrocardiogram		X
Laboratory Tests		
Fasting or random plasma glucose (normal/target range: 80-120 mg/dL before meals)	X	X
Glycosolated hemoglobin (A_1C) (target range: <7% in adults, 7.5 to 8.5, age dependent)	X	X
Urinalysis (glucose, ketones, microalbumin, protein, sediment)	X	X
Complete Cardiovascular Profile		
Test/Target		X
Cholesterol <200 mg/dL		X
Triglycerides <200 mg/dL		X
Low-density lipoprotein <130 mg/dL		X
High-density lipoprotein <35 mg/dL		X
Lipoprotein (a) <40 mg/dL		X
C-reactive protein <1.69 mg/L		X
Fibrinogen <400 mg/L		X
Homocysteine <16 µmole/L		X
Ferritin 60-200 mcg/L (if elevated, transferrin saturation; if elevated, genetic testing for hemochromatosis only once)		X
Lipid peroxides <normal		X
Serum creatinine (in adults; in children only if protein is present in urine)	X	X

THE COMPLICATIONS OF DIABETES

In diabetes, problematic regulation of glucose levels can lead to acute complications, and long-term elevations of blood glucose cause inflammatory and oxidative damage that will lead to chronic disease progression and the development of complications (Box 161-5).

Acute Complications

As described above, the acute complications of diabetes may represent a medical emergency and possibly a life-or-death situation. Any diabetic patient experiencing any symptom even remotely suggestive of an acute complication should consult medical care immediately. The major acute complications of diabetes are hypoglycemia, ketoacidosis, and nonketogenic hyperosmolar syndrome.

Hypoglycemia

Hypoglycemia is usually seen in T1DM. It is the result of excessive insulin injection, decreased or delayed food ingestion, use of alcohol or drugs that interfere with the liver's production of glucose, or an unaccustomed increase in exercise. Severe hypoglycemia can also occur unpredictably in patients with "brittle" T1DM or in any patient on insulin or sulfonylurea drugs who neglects the need for the proper monitoring of blood glucose. Daytime hypoglycemic episodes are usually recognized by symptoms including sweating, nervousness, tremor, and hunger. Nighttime hypoglycemia may be without symptoms or manifest as night sweats, unpleasant dreams, or early-morning headache.

The earliest autonomic symptom of hypoglycemia is hunger, and occurs when the glucose is at or below 65 to 70 mg/dL. Patients may also experience irritability, anxiety, heart palpitations, pallor, and sweating. Neuroglycopenic symptoms, which occur when the brain becomes starved of glucose, start with blurry vision and can progress to headache, tiredness, abnormal behavior, slurred speech, unconsciousness, and seizures. Treatment of hypoglycemia follows the 15-15 rule, whereby patients are told to ingest 15 g of carbohydrate and then recheck their glucose in 15 minutes. If the glucose is still below 80 mg/dL, another 15 g of carbohydrate should be taken and the glucose rechecked in an hour. When glucose sinks below 55 mg/dL, the patient will probably need help from another person, and when it is below 20 mg/dL, a seizure is highly likely to follow and glucagon should be injected. Any hypoglycemic event should be recorded and reported to a physician.

BOX 161-5 Acute and Chronic Complications of Diabetes

Acute complications:
- Hypoglycemia
- Diabetic ketoacidosis
- Nonketotic hyperosmolar hyperglycemia

Chronic complications:
- Atherosclerosis and other vascular lesions
- Retinopathy and cataracts
- Neuropathy
- Nephropathy
- Poor wound healing
- Foot ulcers

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is most commonly seen in patients with newly diagnosed T1DM when they have infections, when they have deliberately or accidentally omitted their insulin, and under other circumstances including trauma, myocardial infarction or stroke, during surgery, and with dental abscess and other types of physiologic stress. The lack of insulin leads to extremely high levels of blood glucose and a buildup of acidic ketone molecules as fat stores are burned to provide energy. If progressive, ketoacidosis can lead to numerous metabolic problems and even coma or death. Because ketoacidosis is a medical emergency, its prompt recognition is imperative. Patients should be taught to check for ketones in their urine or blood when their glucose is above 250 mg/dL for more than a few hours, if they are feverish or have an infection, if they do not "feel well," and regularly during pregnancy, as DKA is usually fatal to the fetus. The symptoms of DKA include fruity breath, disorientation, abdominal tenderness, polyuria and polydipsia, hyperventilation, and signs of dehydration. Treatment of DKA depends on the severity of the situation and where the glucose level is—it can require injecting insulin, eating as well as insulin injection, or referral to an emergency department.

Hyperosmolar Hyperglycemic State

The hyperosmolar hyperglycemic state (HHS) occurs mostly in older T2DM patients, usually in the seventh decade of life. It develops gradually, taking days to weeks to manifest itself. There is no ketoacidosis with this condition, but it has a higher mortality, as it tends to occur in patients who have other serious problems, such as acute illness, recent surgery, congestive heart failure, renal dysfunction, or cardiovascular disease or who are taking certain drugs, are victims of elder abuse or neglect, or are simply noncompliant with their diabetic therapy protocols. The diagnostic criteria include a glucose level above 600 mg/dL, profound dehydration, other changes in pH, and some alteration in consciousness. Patients may present with drowsiness, coma, visual changes, sensory deficits, and even paralysis or seizures.

HHS is a medical emergency, and the patient must be taken to an emergency room. Injecting insulin can cause severe complications so hospital care is best.

Chronic Complications

Much more common than the acute complications of diabetes are certain long-term complications, described as follows. The main four areas of the body affected most by diabetic complications are the eyes, kidneys, nerves, and endothelial lining. These four areas do not require insulin in order to absorb glucose into their cells, as do the liver, muscle, and fat cells, so when glucose levels are elevated in uncontrolled diabetes, unregulated glucose floods those cells and causes significant damage. Thus, they are the key sites for diabetic complications.

Atherosclerosis

Atherosclerosis and other vascular lesions are the underlying factors in the development of many chronic complications of diabetes. Individuals with diabetes have a four- to sixfold higher risk of dying prematurely of heart disease or stroke than do nondiabetic individuals, and 55% of deaths among diabetes patients are caused by cardiovascular disease. The majority of those with T2DM have hypertension, and many of the diet and lifestyle habits of diabetic patients—such as eating poorly and not exercising—combined with nutrient deficiencies can accelerate the risk of developing cardiovascular disease.

Retinopathy

Diabetic retinopathy is the leading cause of blindness in the United States for people between the ages of 20 and 64. In this condition the retina is damaged by microhemorrhages, scarring, and the attachment of glucose molecules (glycosylation) to structural proteins in the retina. Studies have shown that 20 years after a diagnosis of diabetes, 80% of those with T1DM and 20% of those with T2DM have significant retinopathy. Diabetic patients are also prone to developing cataracts—opacities that occur in the lens of the eye as a result of oxidative damage to the delicate protein structures of the lens.

Neuropathy

Neuropathy usually involves the loss of peripheral nerve function and is characterized by tingling sensations, numbness, and a characteristic burning pain (neuropathic pain). It commonly occurs noticeably in the feet but can also spread elsewhere in the body, as to the autonomic nerves of the gastrointestinal tract, causing diarrhea, constipation, and/or gastroparesis. If it progresses, it can affect deeper nerves of the autonomic nervous system, resulting in disturbances in stomach emptying and, later, impaired cardiac function, alternating bouts of diarrhea and constipation, and an inability to empty the bladder. Impotence is a common occurrence and is caused by damage to the small blood vessels of the penis as well as neuropathy of the autonomic nerves controlling blood flow into the penis. Approximately 60% of all people with diabetes eventually develop neuropathy. The main problem of peripheral neuropathy is that lack of feeling in the feet can lead patients to develop sores and lesions that they do not notice. These may then ulcerate, leading to gangrene and amputation.

Nephropathy

Nephropathy due to diabetes accounts for 40% of the cases of severe kidney disease and, in the United States, is the most common reason for end-stage renal disease, hemodialysis, and kidney transplantation. In addition to monitoring blood glucose levels, it is important to monitor kidney function with various laboratory measurements (random microalbuminuria, 24-hour urine protein, blood urea nitrogen, uric acid, creatinine and creatinine clearance, and glomerular filtration rate). Angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are part of standard care because they have been shown to protect the kidneys from diabetic damage.

Poor Wound Healing and Foot Ulcers

Poor wound healing is common in diabetics for several reasons, such as the microvascular changes leading to poor circulation and the functional deficiency of nutrients. Foot ulcers are common in individuals with diabetes because of microvasculature changes leading to a poor blood supply, peripheral neuropathy, poor wound healing, poor nutrition, and immune system dysfunction, all of which can promote chronic infections in the feet. Apart from trauma, diabetic wounds are the leading cause of limb amputations in the United States. More than 50% of lower limb amputations in the United States (70,000 each year) are due to diabetic foot ulcers.

Immune System Dysfunction

Immune system dysfunction often begins long before a diagnosis of diabetes is made. In fact, in many cases a recurrent yeast infection of the vagina or skin is the first clue leading to the detection of diabetes. Immune system problems are made worse by poor glucose control, which puts the diabetic patient at risk for serious infections or complications of simple infections. Susceptibility to chronic, hidden infections in the oral cavity, blood, or respiratory tract may be a primary underlying cause of the increased risk for cardiovascular disease among diabetic patients.

Depression and Cognitive Difficulties

Depression and cognitive difficulties are common among those with diabetes. In fact, depression may begin to occur when the individual first starts to develop insulin resistance, decades before the onset of T2DM. The brain is more sensitive to its need for glucose than any other organ, and it appears that brain cells may suffer from some degree of glucose deprivation when insulin resistance occurs.[82] Depression is also much more common among overweight and obese individuals, probably owing to the combined effect of insulin resistance and diminished self-esteem. Cognitive changes begin to occur after the first severe hypoglycemic episode in people with diabetes. Hypoglycemia is profoundly stressful to the brain and, if severe hypoglycemia occurs many times, significant cognitive impairment can ensue. Uncontrolled diabetes is also associated with an increased risk of developing Alzheimer's disease.

Contributors to the Long-Term Complications of Diabetes

The major contributors to the long-term complications of diabetes are listed here, followed by a brief description of each factor along with coping measures:

- Poor glucose control
- Glycosylation of proteins
- Intracellular accumulation of sorbitol
- Increased oxidative damage
- Nutrient deficiency
- Elevated levels of homocysteine
- Hypertension
- Endothelial cell dysfunction

Poor Glucose Control

A large body of evidence indicates that good blood glucose control significantly reduces the development of complications. The largest and most extensive study to date in T1DM is the Diabetes Control and Complications Trial, whereas the largest and longest study on patients with T2DM is the United Kingdom Prospective Diabetes Study. Both studies conclusively demonstrated that improved blood glucose control reduces the risk of developing the long-term complications of diabetes, especially retinopathy, nephropathy, and neuropathy. Maintaining $HgbA_{1c}$ levels near normal (equal to or less than 7%) can dramatically help reduce the risk of eye problems (up to 76%), nerve damage (up to 60%), and kidney disease (up to 56%).

Glycosylation of Proteins

As described previously, the term *glycosylation* refers to the binding of glucose to proteins. The poorer the glucose control, the greater the binding of glucose molecules to proteins. This binding leads to changes in the structure and function of the protein. Among the adverse effects of excessive glycosylation are inactivation of enzymes, inhibition of regulatory molecule binding, and the formation of abnormal protein structures. For example, when glucose molecules bind to cholesterol-carrying low-density-lipoprotein (LDL) molecules, they block LDL from binding to receptors on the liver that tell the liver to cease manufacturing cholesterol. As a result, the liver "thinks" that there is a shortage of cholesterol in the body and continues to produce more and to release it into the blood. This is one reason why diabetes is almost always associated with high cholesterol levels.

In addition to keeping blood glucose levels as close to ideal as possible, high intakes of antioxidants—especially vitamins C and E, flavonoids, and alpha-lipoic acid (discussed later)—help to reduce glycosylation.

Intracellular Accumulation of Sorbitol

Sorbitol is a sugar molecule formed from glucose within cells. In people without diabetes, once sorbitol is formed, it is quickly broken down into fructose. This conversion to fructose is critical because it allows any excess sorbitol to be excreted from the cell, and sorbitol cannot exit the cell once it is formed. If sorbitol levels continue to increase within cells, they create an osmotic effect.

When there is an increase in the concentration of soluble compounds (e.g., sorbitol) that the cell cannot get rid of, the cell leaks small molecules like amino acids, inositol, glutathione, niacin, vitamin C, magnesium, and potassium in order to maintain osmotic balance. Because these compounds function to protect cells from damage, their loss results in increased susceptibility to damage.

Intracellular accumulation of sorbitol is a major factor in the development of most complications of diabetes, as evidenced by the fact that elevated sorbitol levels are found in high concentrations in the tissues commonly involved in the major diabetic complications: the lens of the eye, nerve cells, kidney cells, and the cells that line blood vessels.

In addition to controlling blood glucose levels, vitamin C and flavonoids like quercetin, grape seed extract, and bilberry extract can help lower intracellular sorbitol levels. Sorbitol accumulation, by the way, has nothing to do with eating foods that contain sorbitol.

Increased Oxidative Damage

Increased oxidative stress is a major factor in the development of the chronic complications of diabetes. As previously stated, individuals with diabetes typically have elevated levels of free radicals and oxidative compounds.[83] These highly reactive compounds bind to and destroy cellular compounds, cause damage all over the body, and increase insulin resistance. They also greatly increase the inflammatory process by adding fuel to their destructive fire via the increased formation of inflammatory mediators like C-reactive protein, interleukin-6, and tumor

necrosis factor-alpha.[84] One of the critical goals in diabetes prevention and treatment is to flood the body with a high level of antioxidant compounds to counteract the negative effects of free radicals and prooxidants. Implementation of this goal is achieved by following the dietary and supplementary strategies given, which promote weight loss, establish better glucose control, and replete antioxidants in the body. In addition to the basic supplementation program, supplementing the diet with superantioxidants like alpha-lipoic acid and flavonoid-rich extracts is often useful in further boosting antioxidant protection.

Nutrient Deficiency

A deficiency of any one of several nutrients has been shown to contribute to several chronic complications of diabetes. Studies have found that nutrient supplementation helps diabetic patients to control their glucose levels; it can also lower their blood pressure and protect their bodies from diabetic complications. In general, the risk of long-term complications of diabetes is inversely proportional to micronutrient status. Sometimes the symptoms of nutrient deficiency can closely mimic those of a chronic complication of diabetes. For example, vitamin B_{12} deficiency is characterized by numbness, "pins and needles" sensations, or a burning feeling in the hands or feet—symptoms virtually identical to diabetic neuropathy. Although vitamin B_{12} supplementation has been used with some success in treating diabetic neuropathy, it is not clear whether this success is due to correction of a vitamin B_{12} deficiency state or the normalization of the deranged vitamin B_{12} metabolism seen in diabetic patients.

High-potency multivitamin/multimineral supplementation is critical to the management of diabetes. Supplying the diabetic patient with additional key nutrients improves blood glucose control and reduces the development of the major long-term complications of diabetes.

Elevated Levels of Homocysteine

Elevated homocysteine levels constitute an independent risk factor for heart attack, stroke, and peripheral vascular disease. In addition, recent research has implicated elevations of homocysteine in the development of long-term complications of diabetes, especially diabetic retinopathy.[85]

Hypertension

Blood pressure control is essential in preventing the complications of diabetes, especially renal disease, retinopathy, and stroke. Maintaining blood pressure in the normal range (120/80 to 140/80 mm Hg) can reduce the risk of heart disease and stroke by approximately 33% to 50% and can reduce microvascular disease (eye, kidney, and nerve disease) by approximately 33%.

Endothelial Cell Dysfunction

A single layer of endothelial cells lines all the body's blood vessels, serving as a metabolically active interface between the components of blood and the blood vessel. These cells regulate many important aspects of blood flow: coagulation, clot formation, and the formation of key regulatory compounds including those that control blood pressure. Endothelial cells are susceptible to damage by oxidized LDL cholesterol and other free radicals—hence the importance of a high dietary intake of antioxidants, flavonoids, key supplemental antioxidants like vitamins C and E, and alpha-lipoic acid. All of these factors have been shown to improve endothelial cell function and are critical in the battle against vascular disease in diabetes.[86-89]

THERAPEUTIC CONSIDERATIONS

Diet Therapy in Managing Diabetes

The optimal diet for the treatment of diabetes is virtually the same as the program presented in Chapter 44. The difference is that there must often be an even stricter avoidance of foods with a high carbohydrate concentration (see Appendix 6). The strictness of the diet with regard to the intake of carbohydrates must be based on the patient's ability to maintain satisfactory blood glucose measurements and $HgbA_{1c}$ levels and to achieve/maintain ideal body weight. Obviously, the poorer the control, the more the carbohydrate intake must be restricted. Initially, some people with diabetes—especially those who have poorly controlled blood glucose levels—may have to avoid meals with a total GL of more than 20 and space these meals at least 3 hours apart. Higher-GL meals can be consumed if one of the special natural products designed to slow gastric emptying and blunt after-meal blood glucose levels is used (these compounds are discussed later).

Clinical Studies with Diet Therapy in Type 1 Diabetes

Numerous clinical studies have shown impressive results in improving blood glucose control when diets high in fiber and low in GL are followed. This holds true in both adults and children as well as in both T1DM and T2DM. In a study involving children, 8- to 13-year-olds in Melbourne, Australia were divided into two groups: one group followed the ADA's exchange-program diet and the other was instructed to eat low-GI foods.[90] Although there was no change in A_{1c} in the exchange diet (8.6%), the group eating the low-GI diet dropped from 8.6% to 8%—an acceptable value in children. Rates of excessive blood glucose levels were 66% for the exchange diet versus 35% for those eating low-GI foods. Although these results are good, what the study really highlighted was the impact of eating a low-GI diet on the quality of life. There were significantly fewer family conflicts, fewer limitations placed on family activities, and fewer difficulties in meal selections. Furthermore, parents and children alike showed a clear preference for the low-GI diet.

Similar results have been seen in adults, including pregnant women with T1DM following a high-fiber, low-GI diet.[91-94] What these studies and others indicate is that low-GI and low-GL diets are emerging as the most scientifically proved dietary support for T1DM. We have taken the proved diet to a much higher level by also considering the role of fats on insulin action.

Clinical Studies with Diet Therapy in Type 2 Diabetes

Diet alone can often be effective as the sole factor in treating and reversing T2DM. Other lifestyle factors and supplements are important, but treatment of T2DM begins with diet. And just as in T1DM, there is considerable evidence from clinical trials that diets low in GI and GL are emerging as the most scientifically proved approach, especially considering not only the diet's effect on blood glucose levels but also its effects in reducing the sequelae of diabetes, such as high cholesterol levels, cardiovascular disease, hypertension, and complications of diabetes.[95]

One of the key goals is to get the total fiber intake from foods to at least 25 to 40 g/day. In one study, the effects of two diets on blood glucose levels were compared,[96] because higher fiber intake was known to lower average daily glucose levels. One diet contained 24 g of dietary fiber as 8 g of soluble fiber and 16 g of insoluble fiber on the basis of ADA recommendations, whereas the other provided a total of 50 g as 25 g of soluble fiber and 25 g of insoluble fiber. Both diets had the same calorie level and

percentages of fat, carbohydrate, and protein. After 6 weeks, the average daily blood glucose levels were 13 mg/dL lower in the group on the higher-fiber diet.

Furthermore, a high-fiber diet has also been found to lower the total area under the curve for 24-hour blood glucose levels; in addition, it lowered insulin concentrations and reduced total cholesterol concentrations by 6.7%, triglyceride concentrations by 10.2%, and very low density lipoprotein cholesterol concentrations by 12.5%. This study showed that a high intake of dietary fiber, particularly of the soluble type, above the level recommended by the ADA improves glycemic control, decreases hyperinsulinemia, and lowers plasma lipid concentrations in patients with T2DM. Similar studies looking at a low versus a high-GI diet have clearly shown the advantages of the former.[97,98]

Psychological Support in Diabetes

Helping people with diabetes deal with their diagnosis, develop a sense of empowerment, and make important lifestyle changes is an extremely important aspect of proper medical care. It is imperative to analyze the emotional aspects of diabetes and manage any negativity or sense of being overwhelmed, which is very common in diabetic patients and can impair their capacity to follow their protocols and maintain good blood sugar control. A book called *Diabetes Burnout: What to Do When You Can't Take It Anymore,* by William Polonsky, published by the ADA, is highly useful reading matter for diabetes patients when they are feeling stressed by their condition. Cognitive behavioral therapy has proved to be especially effective in helping adolescents with T1DM deal with their disease, leading to improvements in both mood and blood glucose control.[99]

Dealing with Stress

Stress adversely affects blood glucose control because higher stress levels are associated with higher blood glucose levels in both T1DM and T2DM.[100] There is a simple explanation for this. Exposure to stress—whether it be physical, mental, or emotional—leads to activation of the body's "stress response" and causes increased secretion of the adrenal gland hormones adrenaline and cortisol. Among other things, these hormones cause blood glucose levels to rise and also blunt the response to insulin. In addition, they have a negative effect on the immune system. Because stress seems to be an inevitable part of modern living, it is critical to develop effective methods to deal with it. Some studies have shown that positive methods for dealing with stress, such as relaxation training, can improve blood glucose control, especially in individuals who are anxious or are experiencing significant stress in their lives.[101,102]

Exercise and Diabetes

Exercise is absolutely essential in the prevention and management of diabetes. Exercise directly improves insulin sensitivity and blood glucose control from a combination of increased lean muscle mass and an improvement in muscle cell metabolism.[103] Exercise also has profound benefits for the cardiovascular system directly as well as indirectly by improvements in blood lipids (especially an improvement in HDL, the "good cholesterol"). Exercise also decreases symptoms of anxiety and depression, improves sexual functioning, and improves confidence and self-esteem. Importantly, exercise has been shown to help attain and sustain weight loss.[104] Three types of exercise are important for people with diabetes: aerobic, strength training, and stretching.

Aerobic Exercises

Aerobic exercises such as walking, jogging, aerobic dance classes, cycling, and swimming produce rises in heart and respiratory rates. These sorts of activities are foundational in both the prevention and treatment of diabetes. In its simplest form, an aerobic exercise program would consist of a schedule of regular walking combined with cycling, swimming, or the use of low-impact indoor exercise equipment such as an elliptical trainer. Patients should engage in at least 30 minutes of aerobic exercise five times a week.

Strength Training

Strength training should occur for 15 to 30 minutes five times a week. Working initially with a trainer to learn proper technique and a rotating regimen of weights is the healthiest way to go. Anaerobic weight training can burn 19 times the amount of glucose as aerobic exercise and protects against the loss of lean body mass while also increasing its size. The loss of lean muscle mass means that there is less tissue to actively absorb glucose. The more muscle one has, the easier it becomes to control blood glucose. Also, diabetic patients are particularly prone to developing chronic musculoskeletal complaints. Most of these problems are related to increased susceptibility to injuries of joints, ligaments, and muscles due to the loss of muscle mass.

Stretching Exercises

Stretching exercises should be done daily. Stretching is extremely important because most people with diabetes suffer from premature stiffening of the spine and joints. Stretching on a daily basis helps to maintain flexibility and avoid the chronic pain problems that occur frequently in diabetic patients due to stiff muscles and joints.

Nutritional Supplements

The proper treatment of diabetes with natural medicine involves trying to achieve ideal blood glucose control and to reach metabolic targets as well as to reduce the risk of complications by focusing on the following four areas:

1. Providing optimal nutrient status
2. Reducing after-meal elevations in blood glucose levels
3. Improving insulin function and sensitivity
4. Preventing nutritional and oxidative stress

Even though natural products can have significant effects on their own, the proper and effective treatment of diabetes requires the careful integration of diet and lifestyle changes along with any required medication and then natural medicines. Furthermore, all those with T1DM and many with T2DM also require conventional medical treatment (with oral drugs or insulin), depending on adequacy of pancreatic insulin production (this can be determined by the C-peptide level) and the individual's response to dietary and lifestyle measures. The most important determining factor as to whether or not a patient will require the use of drugs or insulin is the adequacy of blood glucose control.

Providing Optimal Nutritional Status

In addition to eating a nutrient-dense diet, a high-potency multivitamin/multimineral (MV) supplement is an absolute must for people with diabetes. Follow the guidelines given in Appendix 8. The person with diabetes has such an increased need for many nutrients that supplementation is critical. Supplying him or her with additional key nutrients has been shown to improve blood glucose control as well as to help prevent or reduce the development of the major complications of diabetes. Taking an MV supplement has also been shown to

boost immune function and reduce infections in diabetic patients.[105] The best MV is not a "one a day" but instead a high-potency product recommended by a physician who specializes in alternative medicine. Specific examples of nutrients for which the diabetic has increased requirements include chromium, vitamin C, vitamin E, certain B vitamins, manganese, magnesium, potassium, and zinc.

Whenever a diabetic patient adds significant nutrient, fiber, or botanical medicines to his or her protocol, glucose monitoring is recommended because oral or injectable medicines may have to be reduced. A physician should be involved in all decisions regarding natural supplementation.

Chromium

Chromium is vital to proper blood glucose control because it functions in the body as a key constituent of what is referred to as the "glucose tolerance factor." Chromium works closely with insulin in facilitating the uptake of glucose into cells. Without chromium, insulin's action is blocked and glucose levels are elevated. Evidence indicates that marginal chromium status is common in the United States. A chromium deficiency may be an underlying contributing factor to the tremendous number of Americans who have diabetes and hypoglycemia and are obese.

More than 20 clinical studies have focused on chromium supplementation in diabetes. In some of these studies in T2DM, supplementing the diet with chromium has been shown to decrease fasting glucose levels, improve glucose tolerance, lower insulin levels, and decrease total cholesterol and triglyceride levels while increasing HDL-cholesterol levels. Although there are also studies that have not shown chromium to exert much effect in improving glucose tolerance in diabetes, there is no argument that chromium is an important mineral in blood glucose metabolism. At this time, however, it appears that chromium supplementation is likely to produce meaningful improvements in glycemic control only in people who are deficient in this essential trace element.[106]

Although there is no recommended daily allowance (RDA) for chromium, it appears that at least 200 mg each day in the diet is required. People with diabetes must supplement between 400 and 600 mg per day. Chromium polynicotinate and chromium picolinate may offer the best results, since chromium-rich yeast failed to produce any significant benefit in the most recent trials.[107] In contrast, several recent studies with chromium picolinate in combination with biotin at dosages of 600 mcg and 2 mg, respectively, showed considerable benefit in helping patients with T2DM improve blood sugar control, as fasting glucose levels dropped 10 mg/dL and $HgbA_{1C}$ levels dropped 0.54%.[108] Improvements in blood lipids and atherogenic indices were also noted in other studies.[109]

Vitamin C

Because the transport of vitamin C into cells is enhanced by insulin,[110] many people with diabetes suffer from a relative deficiency of vitamin C within their cells even if they consume an adequate amount of vitamin C in their diets. As a result, people with diabetes must take extra vitamin C.

In addition to its role as an antioxidant, vitamin C is required in immune functions and the manufacture of collagen, the main protein substance of the human body. Because collagen is such an important protein for the structures that hold the body together (e.g., connective tissue, cartilage, tendons), vitamin C is vital for wound repair, healthy gums, and the prevention of easy bruising. A chronic, latent vitamin C deficiency leads to a number of problems for the diabetic patient, including increased capillary permeability, poor wound healing, elevated cholesterol levels, and a depressed immune system. Vitamin C supplementation has been shown to exert a mild effect in improving glucose control, as evident by a slightly lower $HgbA_{1c}$ in the vitamin C group (8.5%) compared with placebo (9.3%) in one double-blind study.[111] Probably more important than any significant effect on improving blood glucose control is the fact that vitamin C supplementation has been shown to reduce the formation of compounds linked to the development of diabetic complications.

In one study of vitamin C supplementation in T2DM, 30 patients who were 45 to 70 years old and had not only T2DM but also hypertension were randomly assigned in a double-blind manner to take either 500 mg of ascorbic acid by mouth or a placebo daily for 4 weeks. Vitamin C supplementation decreased systolic blood pressure from 142.1 to 132.3 mm Hg and diastolic blood pressure from 83.9 to 79.5 mm Hg. Additional analytic methods designed to measure vascular resistance also demonstrated significant improvements in arterial stiffness in the group taking vitamin C. These results indicate that vitamin C supplementation is effective in improving the elasticity and function of blood vessels in patients with T2DM.[112]

The attempt to prevent sorbitol accumulation with drugs has failed because of severe side effects. In contrast, vitamin C can accomplish what these drugs could not—provide safe and effective inhibition of sorbitol accumulation. In one study comprising young adults with T1DM, the baseline measurement of sorbitol in RBCs was nearly double in these patients compared with those without diabetes despite "adequate" dietary intakes of vitamin C. Vitamin C supplementation at a dose of either 100 or 600 mg normalized RBC sorbitol within 30 days. This correction was independent of changes in diabetic control as monitored by fasting glucose or $HgbA_{1c}$. In fact, overall diabetic control during the study was moderate to poor, indicating that vitamin C's effect was not dependent on glucose concentration.

These results indicate that vitamin C may inhibit the enzyme aldose reductase, which converts glucose to sorbitol. To investigate this, an in vitro study was conducted to determine the concentration of vitamin C that would be required to inhibit aldose reductase in RBCs.[113] At concentrations higher than 100 µmol, vitamin C reduced sorbitol production by about 30%. Levels between 600 and 900 µmol reduced sorbitol production by about 50%. These concentrations are attainable with vitamin C supplementation. In fact, the normal level of vitamin C in plasma and RBCs is 40 to 120 µmol. Supplementing with 500 to 1500 mg of vitamin C a day may boost blood levels into the higher range required to inhibit sorbitol production.

Although vitamin C supplementation is necessary, patients should not rely exclusively on it to meet all their vitamin C requirements. Vitamin C–rich foods are also rich in compounds such as flavonoids and carotenes, which work to enhance the effects of vitamin C while also exerting favorable effects of their own.

Vitamin E

Vitamin E functions primarily as an antioxidant in protecting against damage to cell membranes. Without vitamin E, the body's cells would be quite susceptible to damage. Nerve cells are particularly vulnerable. Diabetic patients appear to have an increased requirement for vitamin E, which not only improves the action of insulin but also, when taken at doses ranging from 400 to 800 IU, has a number of beneficial effects that may aid in preventing the long-term complications of diabetes. It:

- Prevents free radical damage to LDL cholesterol and the vascular lining[114-116]
- Improves the functioning of blood vessels and the cells that line them[117,118]
- Increases the concentration of magnesium within cells[119,120]

D
E
F

- Decreases the level of C-reactive protein and other inflammatory compounds[121,122]
- Increases the level of glutathione—an important intracellular antioxidant—within cells[123]
- Improves the rate of conduction of electrical impulses through the nervous system[124]
- Improves blood flow to the eye and mitigates diabetic retinopathy
- Improves kidney function and normalizes creatinine clearance—an indicator of kidney function—in patients with mild elevations[125]

Vitamin E supplementation may be particularly helpful for patients with the Hp 2-2 genotype, a subgroup that comprises 2% to 3% of the general population. Haptoglobin (Hp), a major antioxidant protein, is a determinant of cardiovascular events in patients with T2DM. The Hp gene is polymorphic with two common alleles, 1 and 2. The Hp 2 allelic protein product provides inferior antioxidant protection compared with the Hp 1 product. In a large study of over 1400 diabetic patients 55 years of age or older with the Hp 2-2 genotype randomized to vitamin E (400 IU a day) or placebo, the rates of myocardial infarction, stroke, and cardiovascular death 18 months after initiating the study were significantly reduced in those receiving vitamin E (2.2%) compared with placebo (4.7%), a greater than 50% reduction.[126]

It should be noted that in one study in patients with T2DM, treatment with either 500 mg of α-tocopherol or mixed tocopherols significantly increased systolic blood pressure (approximately 6-7 mm Hg) versus placebo, indicating that some patients may have a hypertensive reaction.[127] Patients should be monitored to rule out this negative effect.

Niacin and Niacinamide

Enzymes that contain niacin (vitamin B_3) play an important role in energy production; fat, cholesterol, and carbohydrate metabolism; and the manufacture of many body compounds including sex and adrenal hormones. Niacin, like chromium, is an essential component of the glucose tolerance factor, making it a key nutrient for hypoglycemia and diabetes.

In addition to offering possible benefits in T1DM, niacinamide may also help in T2DM. Eighteen patients with T2DM of normal body weight who failed to respond to oral antihyperglycemic drugs were randomly assigned to one of three treatments for 6 months: (1) insulin plus nicotinamide (500 mg three times daily); (2) insulin plus placebo; or (3) an oral antihyperglycemic drug plus niacinamide (500 mg three times daily). The parameters assessed included C-peptide, $HgbA_{1c}$, and both fasting and mean daily blood glucose levels. With detailed analysis, niacinamide administration was the only significant factor accounting for the improvement of C-peptide release. The data indicated that niacinamide improves C-peptide release and blood glucose control in patients with T2DM who had previously failed to respond to oral antihyperglycemic drugs alone.[128]

Vitamin B_6

Vitamin B_6 supplementation appears to offer significant protection against the development of diabetic neuropathy.[129] Diabetic patients with neuropathy have been shown to be deficient in vitamin B_6 and to benefit from supplementation.[130] The neuropathy of a vitamin B_6 deficiency is indistinguishable from diabetic neuropathy. Individuals with long-standing diabetes or who are developing signs of peripheral nerve abnormalities should definitely supplement their diets with vitamin B_6, which is also important in preventing other diabetic complications.

Vitamin B_6 supplementation can be a safe and effective treatment for gestational diabetes (diabetes caused by pregnancy). When 14 women with gestational diabetes were given 100 mg of vitamin B_6 daily for 2 weeks in one study, the diagnosis was eliminated in 12 of the 14 women.[131]

Magnesium

Like manganese and chromium, magnesium is also involved in glucose metabolism. Considerable evidence indicates that diabetic patients should take supplemental magnesium, the reasons being that more than one half of all people with diabetes show evidence of magnesium deficiency, and magnesium may prevent some of the complications of diabetes, such as retinopathy and heart disease. Magnesium levels are usually low in diabetic patients and lowest in those with diabetic complications like retinopathy and neuropathy. Clinical studies have shown that magnesium supplementation (usually 400 to 500 mg/day) improves insulin response and action, glucose tolerance, and the fluidity of the RBC membrane in patients with diabetes.[132,133]

The RDA for magnesium is 350 mg/day for adult males and 300 mg/day for adult females. Diabetic patients may need twice this amount because they tend to lose excessive magnesium through their kidneys.[134] Most of the magnesium should be derived from the diet. The average intake of magnesium by healthy U.S. adults ranges from 143 to 266 mg/day. This is obviously far below the RDA. Food choices are the main reason. Although magnesium occurs abundantly in whole foods, food processing refines out a large portion of it. The best dietary sources of magnesium are tofu, seeds, nuts, and green leafy vegetables. Fish, meat, milk, and the most commonly eaten fruits are low in magnesium. Most Americans consume a low-magnesium diet because they eat a lot of refined foods, meat, and dairy products.

In addition to favoring a diet rich in magnesium, diabetic patients should supplement it with 300 to 500 mg of magnesium. For best results, highly absorbable sources of magnesium like magnesium aspartate or citrate should be taken. Diabetic patients should also be sure to get at least 25 mg of vitamin B_6 per day because the level of vitamin B_6 within body cells appears to be intricately linked to the cells' magnesium content. In other words, without vitamin B_6 (as well as vitamin E), magnesium will not get inside the cells and will therefore be useless.

Zinc

Zinc functions in more enzymatic reactions than any other mineral because it is a cofactor in more than 200 different enzymes. Although severe zinc deficiency is rare in developed countries, many individuals in the United States have marginal zinc deficiency. This is particularly common in the elderly population as well as in people with diabetes. Low body levels of zinc are associated with an increased susceptibility to infection, poor wound healing, a decreased sense of taste or smell, and skin disorders. Zinc deficiency, like chromium deficiency, has also been suggested to play a role in the development of diabetes.[135]

Zinc is involved in virtually all aspects of insulin metabolism: synthesis, secretion, and utilization. Zinc also has a protective effect against beta-cell destruction and has well-known antiviral effects. Diabetic patients typically excrete too much zinc in the urine and therefore require supplementation. They should take at least 30 mg of zinc daily. Zinc is also found in good amounts in nuts and seeds.

Manganese

Manganese functions in many enzyme systems, including those involved in blood glucose control, energy metabolism, and thyroid hormone function. Manganese also functions in the antioxidant enzyme superoxide dismutase (SOD). In guinea pigs, a deficiency

of manganese results in diabetes and the frequent birth of offspring who develop pancreatic abnormalities or have no pancreas at all. Diabetic patients have been shown to have only one half the manganese of normal individuals. A good daily dose of manganese for a diabetic is 3 to 5 mg.

Biotin

Biotin is a member of the B-vitamin family; it functions in the manufacture and utilization of carbohydrates, fats, and amino acids. Without biotin, sugar metabolism is severely impaired. Biotin supplementation has been shown to enhance insulin sensitivity and increase the activity of the enzyme glucokinase—which is responsible for the first step in the utilization of glucose by the liver. Glucokinase concentrations in diabetic patients are low. Evidently supplementing the diet with high doses of biotin improves glucokinase activity and glucose metabolism. In one study, 16 mg of biotin daily resulted in a significant lowering of fasting blood glucose levels and improvements in blood glucose control in patients with T1DM. In another study in patients with T2DM, similar effects were noted with 9 mg of biotin daily.[136] Biotin therapy has also been shown to be helpful in the treatment of diabetic neuropathy.[137]

Omega-3 Fatty Acids from Fish Oil Supplements

Omega-3 fatty acids are vital supplements for diabetic patients. They offer significant protection against heart disease in diabetics, helping to lower lipids and blood pressure. They are antiinflammatory and promote insulin sensitivity. Omega-3 oils are usually almost completely lacking in the basic diet of a diabetic patient. Foods that contain these oils include oily fish such as wild salmon, sardines, herring, trout, and mackerel; walnuts; grass-fed beef; wild game; omega-3 eggs; and ground flax, hemp, and chia seeds. Initially there were concerns that omega-3 fatty acid supplementation might adversely affect blood glucose control, but two intensive investigations, one conducted at Oxford University and the other at the Mayo Clinic, analyzed data from 18 double-blind clinical trials involving 823 participants followed for an average of 12 weeks.[138,139] Doses of fish oil (18% eicosapentaenoic acid [EPA] and 12% docosahexanoic acid [DHA]) ranged from 3 to 18 g/day. Both evaluations came to the same conclusions. Fish oil supplementation has no adverse effect on glycemic control, but it does appears to offer the same protection against cardiovascular disease in people with diabetes that it does in people without diabetes.[140] Importantly, many studies in patients with diabetes were conducted with lower-quality fish oil products that contained significant amounts of cholesterol and lipid peroxides. As a result, in some of these studies an elevation in LDL cholesterol was noted. It is important for diabetic patients to ingest a high-quality fish oil product that is guaranteed not to be rancid or to contain mercury, solvents, PCBs, or other toxins. The combined total EPA+DHA level should be approximately 1000 mg daily.

Reducing After-Meal Elevations in Blood Glucose Levels

Elevations of blood glucose levels after a meal can wreak biochemical havoc in any diabetic patient. In fact, an elevation in postprandial blood glucose levels is the major contributor to the development of diabetic complications, especially cardiovascular disease and diseases of the microvasculature (retinopathy, neuropathy, and nephropathy). For example, patients who have a normal fasting blood glucose measurement but an average 2-hour postprandial glucose level greater than 200 mg/dL (11 mmol/L) have a threefold increase in the incidence of diabetic retinopathy.[141] Therefore, blunting of the after-meal increase in blood glucose levels is an important goal.

In addition to following low-carb dietary guidelines to reduce postprandial blood glucose levels (eating low-GI/low-GL meals), several natural products can be used. The best supplements in this regard are fiber supplements and natural glucosidase inhibitors.

Fiber Supplements

Fiber supplements have been shown to enhance blood glucose control, decrease insulin levels, and reduce the number of calories absorbed by the body. The best fiber sources for reducing postprandial blood glucose levels, lowering cholesterol levels, and promoting weight loss are those that are rich in water-soluble fibers, such as glucomannan (from konjac root), psyllium, guar gum, defatted fenugreek seed powder or fiber, seaweed fibers (alginate and carrageenan), and pectin.

Clinical studies have repeatedly shown that after-meal blood glucose levels decrease as soluble fiber viscosity increases.[142,143] This relationship has also been shown to hold true for the other physiologic benefits produced by soluble fibers, including increased insulin sensitivity, diminished appetite, significant weight control, improved bowel movements, and decreased serum cholesterol.[144]

When taken with water before meals, these types of fiber bind to the water in the stomach and small intestine to form a gelatinous, viscous mass that not only slows down the absorption of glucose but also induces a sense of satiety (fullness) and reduces the absorption of calories.

One of the most viscous naturally occurring dietary fibers is glucomannan, a soluble fiber obtained from grinding the root of konjac, a plant that has been used as a food and remedy for thousands of years in Asia. Highly refined and uniquely processed glucomannan possesses the greatest viscosity of any single dietary fiber. It is three times more viscous than guar and approximately seven times more viscous than psyllium. Konjac fiber is now easily available in the form of noodles made with konjac root.

PGX is a novel natural polysaccharide matrix composed of three natural compounds (glucomannan, alginate, and xanthum gum) combined in a proprietary process that leads them to coalesce and form an entirely new matrix that is the most viscous fiber ever discovered.[145,146] By combining glucomannan with alginate and xanthum gum, the viscosity of glucomannan can be amplified to a viscosity three to five times higher than that of glucomannan alone. PGX reduces the glycemic index of any food or beverage by 15% to 70% and also reduces postprandial glucose levels when added to or taken with foods.[147,148] In a double-blind study with an earlier version of PGX, 3 weeks of supplementation with meals was shown to lower postprandial blood glucose by approximately 20% and insulin secretion by approximately 40%, producing a whole-body insulin-sensitivity index improvement of nearly 50%.[149] It was also shown to reduce total cholesterol (12.4%), LDL cholesterol (22.3%), the LDL:HDL cholesterol ratio (15%), and serum fructosamine (5%).[149] In another study in similar patients, postprandial blood glucose (27%), insulin levels (41%), and insulin resistance were estimated to be improved by 56%.[150] The typical dosage for PGX is 2.5 to 5 grams before meals. PGX is discussed further in Chapter 192.

Natural Glucosidase Inhibitors

Starches, complex carbohydrates, and even simple sugars (disaccharides) like sucrose are broken down in the digestive tract into glucose by the action of certain enzymes. Among the most important of these are the α-glucosidases that line the intestines. Because these enzymes are essential for the breakdown of starches, complex carbohydrates, maltose, and sucrose into absorbable glucose

molecules, their inhibition can diminish the after-meal rise in both glucose and insulin.

Acarbose (Precose) and miglitol (Glyset) are approved drugs for treating diabetes by inhibiting α-glucosidase. Although clinical studies have shown them to be effective, they are also characterized by a high frequency of mild-to-moderate gastrointestinal side effects such as flatulence, diarrhea, and abdominal discomfort. Although these side effects generally diminish in frequency and intensity with time, few patients are willing to deal with them.

Instead of the drugs acarbose and miglitol we recommend either touchi or mulberry extracts, which are natural and superior to their drug counterparts.

Touchi Extract

Touchi is a fermented soybean product that has been used in China and Japan for more than 3000 years. Touchi extract is concentrated to possess high levels of naturally occurring α-glucosidase inhibitors, and several clinical studies have documented its effectiveness in reducing postprandial elevations in blood glucose levels.[151] Longer-term studies have also shown benefit.[152,153] For example, when T2DM patients took 300 mg of touchi extract before each meal for 6 months, there were moderate changes in fasting blood glucose and $HgbA_{1c}$ levels—effects that were apparent after only 1 month of use. After 6 months, the fasting blood glucose dropped more than 10 mg/dL in nearly 80% of the patients, and $HgbA_{1c}$ levels fell by more than 0.5% in 60% of patients. Surprisingly, touchi extract also had a mild effect in lowering triglyceride and cholesterol levels, probably through a decrease in insulin resistance.

Unlike the α-glucosidase inhibitor drugs, no side effects have been seen with touchi extract and no one participating in the clinical trials has complained of the gastrointestinal side effects that are so characteristic of acarbose.

Morus indica

The mulberry plant *(Morus indica)* is probably best known as food for silkworms, but it has also been highly regarded in traditional Chinese and Japanese medicine for human use. It has been shown to possess significant hypoglycemic effects in animal studies, and it contains an effective α-glucosidase inhibitor along with other compounds that appear to improve blood glucose control.[154,155] Mulberry extract has been studied in T2DM, and the results are excellent. In one study, researchers decided to investigate its effect on blood and RBC lipids as well as to compare its blood glucose–lowering actions with those of the oral antihyperglycemic drug glyburide.[156] Patients were given either dried mulberry leaves at a dosage of 3 g/day or one tablet of glyburide (5 mg/day) for 4 weeks. Mulberry therapy significantly improved diabetic control in patients with T2DM (Table 161-5). The results clearly show that fasting blood glucose concentrations were significantly lowered with mulberry therapy, suggesting that it is effective in controlling diabetes. Compared with glyburide treatment, mulberry therapy significantly reduced fasting blood glucose concentrations of diabetic patients (27%; $P < 0.01$). However, no significant differences were observed in blood glucose concentrations between pretreatments and post treatments with glyburide ($P > 0.05$). Mulberry extract was also superior to the approved drug in its ability to decrease $HgbA_{1c}$, total cholesterol, LDL, and triglycerides. It also resulted in an increase in HDL (the "good cholesterol"). Although these changes were not statistically significant ($P > 0.05$), there are strong suggestions that this natural product is clearly superior to an established pharmaceutical agent (see Table 161-5).

In addition to the benefits for blood glucose levels and blood lipids, mulberry therapy was also shown to reduce the amount of lipid peroxidation to the cell membranes of RBCs, indicating a significant antioxidant effect. Additionally, mulberry therapy significantly decreased membrane cholesterol in patients with T2DM.

Improving Insulin Function and Sensitivity

The first step in improving insulin function and sensitivity is achieving ideal body weight and following the dietary and lifestyle recommendations given earlier, including taking a high-potency multivitamin/multimineral supplement to make sure that the body has all essential vitamins and minerals required for proper insulin sensitivity. If additional support is necessary to bring blood glucose levels under control, we would recommend using in isolation or in scientifically formulated combinations one or more of the following: *Gymnema sylvestre* extract, bitter melon, *P. quinquefolius* (American ginseng) or *Panax ginseng,* and fenugreek seed extract. We also recommend increasing the intake of onions and garlic.

Gymnema sylvestre

Gymnema is a plant from India that has long been used as a treatment for diabetes. Recent scientific investigation has upheld its effectiveness in both T1DM and T2DM. Gymnema extracts have been shown to enhance glucose control in diabetic dogs and rabbits. Interestingly, in animals that have their pancreas removed, gymnema has no apparent effects, suggesting that it enhances the production or activity of insulin. There is evidence in animal studies that gymnema promotes the regeneration of insulin-producing beta cells in the pancreas. Studies in humans also seem to support the possibility of pancreatic regeneration.[157]

TABLE 161-5 **Influence of Mulberry and Glyburide Treatments on Blood Glucose, Glycosylated Hemoglobin, and Serum Lipids of Patients with Type 2 Diabetes**

	Glyburide			Mulberry		
PARAMETER	BEFORE	AFTER	CHANGE (%)	BEFORE	AFTER	CHANGE (%)
Fasting blood glucose (mg/dL)	154.4	141.8	-8	152.7	110.5	-27
$HgbA_{1c}$ (%)	12.5	12.4	0	12.5	11.2	-10
Cholesterol (mg/dL)	190	182	-4	193.7	170.3	-12
LDL cholesterol (mg/dL)	102.5	95.5	-7	102.1	78.7	-23
HDL cholesterol (mg/dL)	49.8	51.3	+3	50.1	59.2	+18
Triglycerides (mg/dL)	199.5	180	-10	200.4	168	-16
Free fatty acids (pmol/dL)	589.8	580	-2	590.1	520	-12

An extract of the leaves of *G. sylvestre* given to 27 patients with T1DM on insulin therapy was shown to reduce insulin requirements and fasting blood glucose levels as well as to improve blood glucose control.[158] These results indicate that gymnema enhances the action of insulin because these diabetic patients were not recently diagnosed. Clinical experience also shows that gymnema has a significant benefit in decreasing cravings for carbohydrates and enabling patients to follow a lower-carb diet.

With regard to T2DM, gymnema extract appears to work by enhancing the action of insulin. In one study, 22 patients with T2DM were given gymnema extract along with their oral antihyperglycemic drugs.[159] All demonstrated improved blood glucose control, 21 of the 22 were able to reduce their drug dosage considerably, and 5 were able to discontinue their medication and maintain blood glucose control with the gymnema extract alone.

The dosage for gymnema extract (standardized to contain 24% gymnemic acid) can range from 200 mg twice a day to 2400 mg/day. No side effects have been reported from gymnema extract.

Momordica charantia

In addition to being eaten as a vegetable in Asia, unripe bitter melon has been used extensively in folk medicine as a remedy for diabetes. The blood glucose–lowering action of the fresh juice or extract of the unripe fruit has been clearly established in modern scientific studies in both T1DM and T2DM.

Bitter melon is composed of several compounds with confirmed blood glucose–lowering properties. Charantin, extracted by alcohol, is a hypoglycemic agent composed of mixed steroids that is more potent than the oral hypoglycemic drug tolbutamide. Bitter melon also contains an insulin-like polypeptide, polypeptide-P, which lowers blood glucose levels when injected like insulin into patients with T1DM. Because it appears to have fewer side effects than insulin, bitter melon has been suggested as a replacement therapy for some patients, although there is little likelihood of this application ever being developed. Fortunately, drinking as little as 2 oz of the juice has shown good results in clinical trials.[160,161]

Unripe bitter melon is available primarily at Asian grocery stores. Health food stores may have bitter melon extracts, but the fresh juice is probably the best to use, because this was what was used in the studies. Bitter melon juice is difficult to make palatable. As its name implies, it is quite bitter, so it is recommended that patients plug their noses and take a 2-oz shot of the juice. The dosage of other forms should approximate this dose.

Panax quinquefolium and Panax ginseng

Research conducted at the University of Toronto's Risk Factor Modification Center has uncovered important properties of some ancient natural medicines. In their first studies and published reports, the group used whole powdered American ginseng root *(Panax quinquefolium)* and found that a dose of about 3 g before each meal reduced postprandial blood glucose significantly in patients with T2DM.[162-166] American ginseng is now considered by authorities to be the most evidence-based herbal therapy for T2DM.[167]

P. ginseng can also be helpful. In a double-blind controlled study, 36 non–insulin-dependent diabetic patients were treated for 8 weeks with ginseng extract at 100 or 200 mg or with a placebo. Ginseng elevated mood, improved psychophysiologic performance, and reduced fasting blood glucose and body weight. The 200-mg dose improved glycated hemoglobin, serum aminoterminalpropetide concentrations, and physical activity.[168]

Fenugreek

Fenugreek seeds have demonstrated significant antidiabetic effects in experimental and clinical studies. The active principles are the special soluble fiber of fenugreek along with the alkaloid trigonelline and 4-hydroxyisoleucine. Fenugreek appears to be helpful in both types of diabetes. Defatted fenugreek seed powder given twice daily at a 50-g dose to patients with T1DM led to a significant reduction in fasting blood glucose and improved the results of glucose tolerance tests.[169] A 54% reduction in 24-hour urinary glucose excretion and significant reductions in LDL and very low density lipoprotein cholesterol and triglyceride values also occurred. In patients with T2DM, the addition of 15 g of powdered fenugreek seeds soaked in water significantly reduced postprandial glucose levels during the meal tolerance test.[170] However, that is a very large dose and impractical for daily supplementation. In another study, 25 patients with T2DM randomly received 1 g/day of fenugreek seed extract or placebo capsules for 2 months.[171] Complex analysis of the data found that the group taking the fenugreek seed extract had improved blood glucose measurements (e.g., fasting blood glucose levels dropped from 148.3 to 119.9 mg/dL), but there was also a significant decrease in insulin output. This finding indicates that there was a significant improvement in insulin sensitivity, an effect that is most likely due to the 4-hydroxyleucine.

Allium cepa and Allium sativum

Onions and garlic appear to have significant blood glucose–lowering action. The active principles are believed to be the sulfur-containing compounds allyl propyl disulfide and diallyl disulfide oxide (allicin), respectively, although other constituents such as flavonoids may play a role as well.

Although garlic generally has more potent effects, onions can be given at higher doses, and the active compounds appear to be more stable than allicin. Graded doses of onion extracts (1 mL of extract = 1 g of whole onion) at levels sometimes found in the diet (i.e., 1 to 7 oz of onion) reduced blood glucose levels during an oral glucose tolerance test in a dose-dependent manner. The effects are similar in both raw and boiled onion extracts, indicating that the active components are probably stable.[172]

Garlic has a wide range of additional well-documented effects that are useful for the diabetic including helping to improve blood glucose control, lower cholesterol and blood pressure, and inhibit some of the factors associated with increased risk for vascular complications of diabetes, such as increased fibrinogen levels.

Preventing Nutritional and Oxidative Stress

Diabetes is characterized by increased nutritional and oxidative stress. Because individuals with diabetes typically have elevated levels of free radicals and oxidative compounds, they are much more likely to experience damage. These highly reactive compounds bind to and destroy cellular compounds. They also greatly increase the inflammatory process by adding fuel to their destructive fire via increased formation of inflammatory mediators like C-reactive protein.

One of the critical goals in nutritionally supporting individuals with diabetes is to flood the body with a high level of antioxidant compounds to counteract the negative effects of free radicals and prooxidants. This goal is implemented by using the recommendations given earlier, along with taking a flavonoid-rich extract and alpha-lipoic acid.

Flavonoids

Research suggests that flavonoids may be useful in treating diabetes as well as in preventing long-term complications. Flavonoids such as quercetin promote insulin secretion and are potent inhibitors of

glycosylation and sorbitol accumulation, whereas flavonoid-rich extracts like bilberry and hawthorn extracts have been shown to be helpful in diabetic retinopathy and microvascular abnormalities.[173]

The beneficial effects of flavonoids in battling the complications of diabetes are numerous and include the fact that as antioxidants, flavonoids are generally more potent and effective against a broader range of oxidants than the traditional antioxidant nutrients vitamins C and E, beta-carotene, selenium, and zinc. Other beneficial effects include increasing intracellular vitamin C levels, decreasing the leakiness and breakage of small blood vessels, preventing easy bruising, promoting wound healing, and providing immune system support. Good dietary sources of flavonoids include citrus fruits, berries, onions, parsley, legumes, green tea, and red wine.

In individuals with diabetes who are already showing signs of long-term complications, it is extremely important to take a flavonoid-rich extract. Because certain flavonoids concentrate in specific tissues, it is possible to take flavonoids that target those tissues. For example, because the flavonoids of bilberry *(Vaccinium myrtillus)* have an affinity for the eye, including the retina, bilberry is probably the best choice in a diabetic patient who is already exhibiting signs of diabetic retinopathy. The point is to identify which flavonoid or flavonoid-rich extract is most appropriate for the patient and then to direct him or her to take it according to the recommended dosage. There is tremendous overlap among the mechanisms of action and benefits of flavonoid-rich extracts; it is important to take the one that is most specific to the individual's needs (Table 161-6).

Alpha-lipoic Acid

Alpha-lipoic acid is a vitamin-like substance that is often described as "nature's perfect antioxidant." Alpha-lipoic acid is a small molecule that is efficiently absorbed and easily crosses cell membranes. Unlike vitamin E, which is primarily fat-soluble, and vitamin C, which is water-soluble, α-lipoic acid can quench either water- or fat-soluble free radicals both inside the cell and in the intracellular spaces. Furthermore, α-lipoic acid extends the biochemical lives of vitamins C and E as well as other antioxidants.

Alpha-lipoic acid is an approved drug in Germany for the treatment of diabetic neuropathy. In fact, it has been successfully used in Germany for more than 30 years. The beneficial effects of α-lipoic acid in diabetic neuropathy at a dosage of 400 to 600 mg daily have been confirmed in several double-blind studies.[174,175] Although α-lipoic acid's primary effect in improving diabetic neuropathy is thought to be due to its antioxidant effects, it has also been shown to lead to improvement in blood glucose metabolism as well as blood flow to peripheral nerves and even to stimulate the regeneration of nerve fibers. Its ability to improve blood glucose metabolism is a result of its effects on glucose metabolism and its ability to increase insulin sensitivity. Its importance in treating diabetic neuropathy cannot be overstated.

Recommendations for Specific Chronic Complications

Following are additional recommendations for dealing with the specific complications of diabetes. The most important method for reducing the risk of these complications is achieving optimal blood glucose control.

Elevated Cholesterol

Key natural products used to lower cholesterol levels in diabetes are soluble fiber, garlic, and niacin. These agents are discussed fully in Chapter 148. Because taking niacin at higher doses (e.g., 3000 mg or more) can impair glucose tolerance, many physicians have avoided niacin therapy in diabetic patients. However, newer studies with slightly lower doses (1000 to 2000 mg) have not shown that niacin affects the regulation of blood glucose adversely.[176] For example, during a 16-week double-blind placebo-controlled trial, 148 T2DM patients were randomized to placebo or 1000 or 1500 mg/day of niacin; in the niacin-treated groups there was no significant loss of glycemic control and the favorable effects on blood lipids were still apparent.[177] Other studies have actually shown $HgbA_{1c}$ to drop, indicating improved glycemic control.[178]

The most common blood lipid abnormality in patients with T2DM is elevated triglyceride levels; decreased HDL cholesterol levels; and a preponderance of smaller, denser LDL particles. Niacin has been shown to address all of these areas much more significantly than statins or other lipid-lowering drugs. However, one reason that niacin may not be as popular as it should be is the side effect of skin flushing—rather like a prickly heat rash—which typically occurs 20 to 30 minutes after the niacin is taken and disappears within about the same time frame. Other occasional side effects include gastric irritation, nausea, and liver damage. The risk of liver damage is especially pertinent. Diabetic patients who are overweight often develop fatty livers, which are now considered to be as damaging as livers injured by alcoholism and hepatitis C. Moreover, the fatty liver may facilitate the

TABLE 161-6 **Flavonoids Used in the Treatment of Diabetes and Diabetic Complications**

FLAVONOID-RICH EXTRACT	DAILY DOSE	INDICATION
Bilberry extract (25% anthocyanidins)	160-320 mg	Best choice in diabetic retinopathy or cataracts.
Ginkgo biloba extract (24% *Ginkgo* flavonglycosides)	120-240 mg	Best choice for most people >age 50. Protects the brain and vascular lining. Very important in improving blood flow to the extremities in treating neuropathy and foot ulcers.
Grape-seed or pine-bark extract (95% procyanidolic oligomers)	150-300 mg	Systemic antioxidant; best choice for most people < age 50, especially if retinopathy, hypertension, easy bruising, and poor wound healing exist. Also specific for the lungs, varicose veins, and protection against cardiovascular disease.
Green tea extract (60%-70% total polyphenols)	150-300 mg	Best choice in the early stage of type 1 diabetes or if there is a family history of cancer.
Hawthorn extract (10% procyanidins)	150-300 mg	Best choice in cardiovascular disease or hypertension.
Milk thistle extract (70% silymarin)	100-300 mg	Best choice if there are signs of impaired liver function.
Mixed citrus flavonoids	1000-2000 mg	Least expensive choice but may not provide same level of benefit; use if no complication is present.
Quercetin	150-300 mg	Good choice if allergies, symptoms of prostate enlargement or bladder irritation, or eczema are also present.

development of fibrosis and cirrhosis. Giving niacin to a patient with a fatty liver may put extra stress on that vital organ. Therefore, in an overweight diabetic patient, high-dose niacin is to be used only under a physician's supervision. To reduce the side effect of skin flushing, an intermediate-release niacin may be prescribed, one that is identical in its dissolution pattern to the prescription product Niaspan. This product is best taken just before going to bed, as most people sleep right through any flushing reaction that might occur. Another approach to reduce flushing is to use inositol hexaniacinate. This form of niacin has long been used in Europe to lower cholesterol levels and also to improve blood flow in intermittent claudication—a peripheral vascular disease that is common in diabetes.[179] If inositol hexaniacinate does not work, regular niacin can be tried.

If regular niacin or inositol hexaniacinate is being used, a dosage of 500 mg a night may be tried for 1 week. The dose can then be increased to 1000 mg the next week and 1500 mg the following week. The 1500-mg dose should be given for 2 months before checking the response, and the dose can then be adjusted up or down as needed. Time-release niacin products like Niaspan can be used at the full dosage of 1000 to 2000 mg at night from the beginning. Regardless of the form of niacin being used, periodic checking (at least every 3 months) of cholesterol, $HgbA_{1c}$, and liver function is strongly indicated.

Retinopathy and Cataracts

Diabetic retinopathy has two forms: (1) "simple" retinopathy consisting of burst blood vessels, hemorrhages, and swelling and (2) proliferative retinopathy with newly formed vessels, scarring, more serious hemorrhage, and retinal detachment. Laser photocoagulation therapy is an important treatment for the more severe type of proliferative retinopathy but is still not indicated in milder forms because of the risk of vision loss. That is, there is a risk that the side effects of this treatment may outweigh the benefits.

As with other complications of diabetes, prevention is the best treatment, with the key factor being the maintenance of optimal blood glucose control. $HgbA_{1c}$ should be monitored frequently.

Extremely important in the battle against retinopathy are flavonoid-rich extracts, especially bilberry, pine bark, and grape seed extracts. The flavonoids in these extracts exert many benefits in diabetes, including an ability to increase intracellular vitamin C levels, decrease the leakiness and breakage of capillaries, prevent easy bruising, and serve as potent antioxidants. These effects are of particular value in dealing with the microvascular abnormalities of diabetes. Because the flavonoids in bilberry, pine bark, and grape seed extract have an affinity for the blood vessels of the eye and improve circulation to the retina, they are particularly helpful in slowing the progression of diabetic retinopathy, as evidenced by positive results in more than a dozen clinical trials.[180,181]

Neuropathy

In addition to α-lipoic acid and the basic supplementation program, three additional natural medicines along with acupuncture deserve mention:

Gamma-linolenic acid (GLA) has been shown to improve and prevent diabetic neuropathy. Diabetes is associated with a substantial disturbance in EFA metabolism. One of the key disturbances is the impairment in the process of converting linoleic acid to GLA. As a result, providing GLA in the form of borage, evening primrose, or black currant oil can bypass some of this disturbance. In the GLA Multicenter Trial, 111 patients with mild diabetic neuropathy were given either GLA at a dose of 480 mg/day or a placebo for 1 year. Sixteen parameters were assessed, including conduction velocities, hot and cold thresholds, sensation, tendon reflexes, and muscle strength. After 1 year, all 16 parameters improved, 13 of them to a statistically significant degree. Treatment was more effective in diabetic patients who were relatively well controlled than in those who were poorly controlled. The latter finding highlights the need for a comprehensive approach in controlling blood glucose levels rather than expecting a single physiologic aid (i.e., GLA) to compensate for poor control.

Benfotiamine is a fat-soluble form of thiamine, or vitamin B_1, that is more effective in raising blood thiamine levels (up to 120% to 240% vs. regular thiamine). In studies in diabetic patients, benfotiamine decreased advanced glycosylated end-product formation, decreased the aldose reductase pathway, and reduced oxidative cellular damage.[182] However, results in the treatment of diabetic neuropathy and nephropathy in small clinical trials with benfotiamine alone have shown modest to no benefit.[183,184] It is possible that benfotiamine can be usefully combined with α-lipoic acid. In a small study in patients with T1DM, treatment with 600 mg of benfotiamine plus 300 mg of α-lipoic acid produced better results in reducing the effects of hyperglycemia than benfotiamine alone.[185]

Capsaicin is the active component of cayenne pepper *(Capsicum frutescens),* which stimulates and then blocks the small nerve fibers that transmit the pain impulse by depleting these fibers of a transmitting substance known as substance P.[186] In numerous double-blind studies, topically applied capsaicin has been shown to be of considerable benefit in relieving the pain of diabetic neuropathy. Roughly 80% of people with diabetic neuropathy experience great relief in this way.[187] Commercial ointments containing 0.025% or 0.075% capsaicin are available over the counter. The patient should apply the 0.075% cream twice daily to the affected area (the first covering his or her hand with plastic wrap to prevent the capsaicin from coming in contact with the eyes or mucous membranes). It may take a few days for the cream to start working, and it will continue to work only with regular application.

Acupuncture can also be helpful in improving neuropathy. The scientific investigation of acupuncture in diabetes includes both experimental and clinical studies. For example, animal experiments have shown that acupuncture can act on the pancreas to enhance insulin synthesis, increase the number of receptors on target cells, and accelerate the utilization of glucose, resulting in the lowering of blood glucose.[188] However, the best documentation for the clinical application of acupuncture is in treating chronic painful diabetic neuropathy. In one clinical study, 77% of patients treated with acupuncture noted significant improvement in their symptoms, with 21% noting that their symptoms were completely eliminated.[189] That success rate is excellent considering the long-standing nature of the condition in most of the cases and the fact that no side effects were observed.

Nephropathy

Many of the previous recommendations also apply to preventing diabetic nephropathy. In fact, a strong reason for adhering to the dietary principles outlined above is to protect the diabetic kidneys. Especially important again is dietary fiber. Dietary fibers (especially the water-soluble type) are fermented in the colon to produce short-chain fatty acids. These by-products are the primary fuel for colonic cells and, if present in high amounts, greatly increase the colon's waste removal capabilities. It has been shown that in the presence of a diet high in fermentable fiber, the colon turns into the "second kidney" as it collects nitrogenous wastes out of the blood and disposes of them via the feces. This has been shown to greatly reduce the workload and stress on the kidneys themselves.[190]

Highlighting just how important some basic supplement recommendations are in halting the progression of diabetic nephropathy are the results of a study of 30 T2DM patients with elevated albumin in their urine. These patients received vitamin C (1250 mg) and vitamin E (680 IU) daily or a matching placebo for 4 weeks followed by a 3-week washout period before being switched to the other arm.[191] The results were that the vitamins were successful in reducing urinary albumin levels by an average of nearly 20%, indicating that antioxidant therapy may halt or slow down the progression of kidney disease in patients with diabetes.

If a patient has developed serious kidney failure, then following the low-protein, low-potassium standard diet becomes necessary; unfortunately that does not promote good glucose control, which can then worsen kidney function. The main goal is to prevent end-stage renal disease from developing in the first place.

If drugs are necessary, the ACE inhibitors and ACE receptor blockers offer the greatest benefits in dealing with diabetic nephropathy.[192] They are now often prescribed in low doses to help prevent nephropathy even in the absence of high blood pressure. Alternatively, a special preparation of bonito peptides has been shown to exert anti-ACE activity (see Chapter 174 for more information) and may prevent the need for ACE-inhibitor drugs.

Poor Wound Healing

A deficiency of virtually any essential nutrient can lead to impaired wound healing. Key nutrients include vitamin C and zinc, both of which are often deficient in the diabetic patient. Taking a high-potency multivitamin/multimineral formula should improve nutritional status and promote proper wound healing. For topical application, pure (100%) *Aloe vera* gel can be used. The wound-healing effects of *Aloe vera* are well known. It contains a number of compounds that promote wound healing, including vitamin C, vitamin E, and zinc. It has been shown to stimulate many factors important to wound repair and should be applied to affected areas (not open wounds) two to three times daily. Another option is a topical ointment called Amerigel, featuring an oak extract (*Quercus rubra*), which contains tannins including quercitannic acid, catechin, ellagitannin, and proanthocyanidin, which are readily absorbed into damaged skin.

Foot Ulcers

Lack of blood supply, poor wound healing, and peripheral neuropathy are key factors in the development of diabetic foot ulcers. Key strategies in prevention and treatment are proper foot care (including professional care of nails and calluses), preferably by a podiatrist; regular physician's examination of the feet, avoidance of injury, avoidance of tobacco in any form, and the use of methods to improve the local circulation. Proper foot care includes keeping the feet clean, dry, and warm and wearing well-fitting shoes. Tobacco use in any form constricts the peripheral blood vessels and can lead to more serious peripheral vascular disease, including severe arterial blockages. Diabetes and smoking are like nitro plus glycerin—a sure recipe for catastrophe. Circulation can be improved by exercising regularly, avoiding sitting cross-legged or in other positions that compromise circulation, and massaging the feet lightly upward. *Ginkgo biloba* or grape seed extract can also be used to support optimal circulation.

THERAPEUTIC APPROACH

Effective treatment of the diabetic patient requires the careful integration of wide-ranging therapies and patients who are willing to substantially improve their lifestyles. T2DM is usually the result of many years of chronic metabolic insult and, although treatable with the natural metabolic approach presented here, requires persistence for its ultimate resolution. Although much of the information presented in this chapter focuses on T2DM, it is equally appropriate for T1DM with the exception that, according to current information, the patient with T1DM will always require insulin.

The first step in the therapy of either T1DM or T2DM is a thorough diagnostic workup. Of particular importance is identifying any of the complications of diabetes. The patient's diet, environment, and lifestyle should be carefully studied to rule out any exposure to agents that may be inducing his or her glucose intolerance.

A diet, exercise, and supplement program that meets the patient's individual needs and his or her current level of glucose tolerance should be developed. For maximum efficacy, the patient's ideal body weight must be achieved (see Chapter 192 for additional recommendations).

In treating patients with severe or uncontrolled diabetes, a high level of awareness of the acute diabetic complications must be maintained. If the patient is on insulin, the physician should be adept at using, changing, and adapting insulin types and doses according to the individual's particular needs.

Finally, the patient must be monitored carefully, particularly if he or she is on insulin or has relatively uncontrolled diabetes. Patient symptomatology, home glucose monitoring, and the $HgbA_{1c}$ test are at present the best ways to monitor progress. It is important to recognize that as these therapies take effect, the patient's drug dosages must be altered and that a good working relationship with the physician will greatly aid the healing process. The ultimate goal is to reestablish normal glycemia and prevent the development of (or ameliorate) the complications of diabetes.

Note: Under no circumstances should a patient be suddenly taken off diabetes drugs, especially insulin. According to current information, an insulin-dependent patient will never be able to stop taking insulin.

Diet

The optimal healthy diet detailed in Chapter 44 is clearly the diet of choice. All simple, processed, and concentrated carbohydrates must be avoided. A low glycemic diet rich in high-fiber foods should be stressed, and sources of healthy fats should be ingested. Low glycemic vegetables, particularly onions and garlic, are useful and their liberal ingestion should be encouraged.

Supplementation for Type 1 Diabetes

The recommended supplementation program depends on the degree of blood glucose control as evident by self-monitored blood glucose and $HgbA_{1c}$ levels.

Recently diagnosed T1DM:

- Foundation supplements
 - High-potency multivitamin/multimineral supplement
 - Fish oils: 1000 mg each of EPA and DHA a day
 - Vitamin C: 500 to 1500 mg a day
 - Vitamin E: 400 to 800 IU a day
- Vitamin D: 4000 to 8000 IU a day
- Niacinamide: 25 to 50 mg/kg a day
- Green tea extract: The recommended dosage for children 6 years of age or younger is 50 to 150 mg; for children 6 to 12 years old, 100 to 200 mg; for children older than 12 years of age and adults, 150 to 300 mg. The green tea extract should have a polyphenol content of 80% and be decaffeinated.

Level 1: achievement of targeted blood glucose levels, $HgbA_{1c}$ levels less than 7%, no lipid abnormalities, no signs of complications

- High-potency multivitamin/multimineral supplement
- Fish oils: 600 mg each of EPA and DHA a day
- Vitamin C: 500 to 1500 mg a day
- Vitamin E: 400 to 800 IU a day
- Alpha-lipoic acid: 400 to 600 mg a day
- Grape seed, pine bark, or green tea extract (or other appropriate flavonoid-rich extract): 100 to 300 mg a day

Level 2: Failure to achieve targeted blood glucose levels, $HgbA_{1c}$ between above 7%

- Level 1 supplements plus:
- *G. sylvestre* extract (24% gymnemic acid): 200 mg twice a day
- Biotin: 8 mg twice a day
- Optional:
 - Bitter melon juice: 2 to 4 oz a day

Supplementation for Type 2 Diabetes

The recommended supplementation program depends on the degree of blood glucose control as evident by self-monitored blood glucose and $HgbA_{1c}$ levels.

Level 1: Achievement of targeted blood glucose and $HgbA_{1c}$ levels less than 7%, no lipid abnormalities, no signs of complications

- High-potency multivitamin/multimineral supplement
- Greens drink: one serving a day
- Fish oils: 600 mg each of EPA and DHA a day
- Vitamin C: 500 to 1500 mg a day
- Vitamin E: 400 to 800 IU a day
- Grape seed, pine bark, or green tea extract (or other appropriate flavonoid-rich extract): 100 to 150 mg a day
- Alpha-lipoic acid: 400 to 600 mg a day
- PGX (glucomannan, or other soluble source at equivalent dosage to PGX): 2500 to 5000 mg before meals

Level 2: Failure to achieve targeted blood glucose levels, $HgbA_{1c}$ above 7%

- Level 1 support plus:
- One of the following insulin enhancers:
 - *G. sylvestre* extract (24% gymnemic acid): 200 mg twice a day
 - Fenugreek extract: 1 g a day
- Garlic: minimum of 4000 mcg of allicin per day
- Use one of the following glucosidase inhibitors:
 - Touchi extract: 300 mg three times a day with meals
 - Mulberry extract: equivalent to 1000 mg dried leaf three times a day

If self-monitored blood glucose levels do not improve after 4 weeks of following the recommendations for the current level, move to the next highest level. For example, if the patient starts out having an $HgbA_{1c}$ level of 8.2% and a fasting blood glucose level of 130 mg/dL, he or she should start on level 2 support. After 4 weeks, if the average reading has not dropped to less than 110 mg/dL, a prescription medication (either an oral hypoglycemic drug or insulin) will be required.

Additional Supplements for the Prevention and Treatment of Diabetic Complications

For high cholesterol levels and other cardiovascular risk factors Total cholesterol greater than 200 mg/dL or LDL cholesterol greater than 135 mg (100 mg if history of heart attack); HDL cholesterol below 45 mg/dL; lipoprotein(a) above 40 mg/dL; or triglycerides above 150 mg/dL

- Niacin (or inositol hexaniacinate): 1000 to 2000 mg at bedtime
- Garlic: minimum of 4000 mcg of allicin a day

For hypertension

- Garlic: minimum of 4000 mcg of allicin a day
- Coenzyme Q10: 100 to 200 mg a day
- Anti-ACE peptides from bonito: 1500 mg/day
- Take one of the following:
 - Hawthorn extract (10% procyanidins or 1.8% vitexin with 4% rhamnoside): 100 to 250 mg three times a day
 - Olive leaf extract (17% to 23% oleuropein content): 500 mg twice a day
 - Hibiscus: three 240-mL servings a day or an extract providing 10 to 20 mg anthocyanidins a day

For diabetic retinopathy:

- Bilberry extract: 160 to 320 mg daily or grape seed extract 150 to 300 mg a day

For diabetic neuropathy

- Gamma-linolenic acid from borage, evening primrose, or blackcurrant oil: 480 mg a day
- Benfotiamine: 600 mg a day
- Capsaicin (0.075%) cream: applied to affected area twice a day

For diabetic nephropathy

- Follow recommendations for high blood pressure above unless kidney function falls below 40% of normal. Be cautious in recommending magnesium and potassium supplements.
- Benfotiamine: 600 mg a day

For poor wound healing

- Aloe vera gel: Applied to affected areas twice a day

For diabetic foot ulcers

- *G. biloba* extract: 120 to 240 mg a day or grape seed extract 150 to 300 mg a day

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CHAPTER 162

Endometriosis

Tori Hudson, ND

DIAGNOSTIC SUMMARY

- Triad of symptoms: dysmenorrhea, dyspareunia, and infertility
- Physical examination reveals one or more of the following: tenderness of the pelvic area, cul-de-sac, or both; enlarged or tender ovaries; a uterus that tips backward and lacks mobility; fixed pelvic structures; adhesions
- Pelvic ultrasound: detection and consistency of endometriomas
- Definitive diagnosis: a laparoscopy or laparotomy visualizing endometrial implants within the pelvic cavity

GENERAL CONSIDERATIONS

Endometriosis affects 10% to 15% of menstruating women between 24 and 40 years of age. The main risk factor for endometriosis is heredity. Women with a mother or a sister who has endometriosis have an increased risk. Also, women with shorter menstrual cycles and a longer duration of flow have been found to be at higher risk for endometriosis. Lack of exercise from an early age, a high-fat diet, use of intrauterine devices, increased or unbalanced estrogen levels, and even natural red hair color have been suggested as factors in the development of endometriosis. A greater number of women with adhesions, endometriosis, or both have reported abuse in their histories. Increased immune action within the pelvic cavity and the possibility of antibody reactions to sperm has prompted recognition of an immunologic basis for endometriosis.

Additional possible risk factors are immune dysfunction; prenatal exposure to high levels of estrogens; exposure to environmental estrogens or endocrine disruptors (polychlorinated biphenyls [PCBs], weed killers, plastics, detergents, household cleaners, tin can liners); long-term dioxin exposure; and inappropriate liver metabolism and excretion of estrogens.

Etiologic Theories

Retrograde flow, the predominant theory first proposed in 1927, suggests that during menses blood flows backward and provides seeds of implants in the pelvic cavity. The problem with this theory is that more than 90% of menstruating women without endometriosis have retrograde flow; thus, this theory was challenged and questions were raised as to the biochemical and immunologic factors causing the implantation of endometrial tissue within the pelvic environment.[1] Some theories are based on findings that endometrial implants from women with endometriosis are biochemically different from those from normal women.[2]

Other findings suggest that cells may implant only in women with altered cell immunity.[1] Implants found in odd locations, such as the nose and lungs, suggest the transportation of endometrial tissue through lymphatic channels and blood vessels. Some researchers believe the implants to be of embryologic origin, when pieces of the uterus were left behind during development, and that these implants, when activated, secrete a chemical causing the nearby capillaries to bleed.[3]

Other research on endometriosis in baboons suggests activation by environmental toxins that mimic estrogens.[4] Exposure to radiation and dioxin has been associated with a higher frequency of endometriosis.[5,6] The highest incidence of endometriosis appears to be in Belgium, which is also the home to the highest level of dioxin pollution in the world.[7]

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Two studies, however, one in Belgium, found no significantly increased risk with dioxins or polychlorinated biphenyls.[8] The other study, in Italy, found no significantly increased risk of endometriosis in women who had high levels of dioxin in their blood.[9] Although there is currently no definitive epidemiologic evidence linking any one class of chemicals to the risk of endometriosis, there does appear to be some suggestion of a link with estrogen-like compounds in the environment,[10] called xenoestrogens, which can disrupt estrogen and estrogen metabolism. Substances that have been shown to have estrogenic effects in the body include PCBs, weed killers, liners in tin cans, plastics, detergents, and household cleaners.[11]

Immunologic alterations may exist in women with endometriosis. Increasingly, we are finding evidence that a lack of proper immune surveillance in the pelvic area is the cause of endometriosis and that impairment in other aspects of the immune system function are involved in the progression of the disease.[12]

Women with endometriosis have been found to have suppressed natural killer cell activity in their peritoneal fluid,[13,14] high levels of immunoglobulins IgG and IgM,[15] and high levels of autoantibodies against ovary and endometrial cells.[16,17]

Both types of immunity, cell-mediated and humoral, have been implicated in endometriosis, with immunologic defects present even in the mildest forms of the disease.[18] Macrophages are found in greater numbers in the early stages of endometriosis.[19]

Cytokines, macrophages, T lymphocytes, and tumor necrosis factors have all been found to be increased in the peritoneal fluid in women with endometriosis,[20-22] and their increase correlates with the severity of the disease. Growth factors, angiogenic factors, and lipid peroxidation in the peritoneal fluid may stimulate endometrial cell growth. Targeting of these proinflammatory compounds and blocking their action with antioxidants and other compounds provide a good rationale for new treatment strategies, both conventional and with natural compounds.

Genetic influences the area also likely involved in endometriosis. Grouping of endometriosis within families has been found in clinical studies,[23,24] populations-based studies,[25] and even studies of twins.[26-28] Several abnormalities in detoxification enzymes, tumor suppressor genes, and other genetic factors occurring in multistep fashion may be involved both in the development and the progression of the disease.[29]

DIAGNOSIS

In some cases symptoms begin with the onset of menstruation, but in most symptoms begin later and worsen progressively over time. The triad of symptoms is dysmenorrhea (pain with menses), dyspareunia (pain with vaginal intercourse), and infertility. Acute pain occurs before the onset of menses; it can last for a day or two during the menses or throughout the month. In some women, vomiting, diarrhea, and fainting can occur concurrently with the intense pelvic/abdominal cramping and even labor-like pains. Other pains can involve a chronic bearing-down pain and pressure in the lower back, with pain sometimes radiating down the legs. There is not necessarily any correlation between pain and the extent of disease. Women with fixed ovaries and large endometriomas may report only mild discomfort, whereas those with visibly smaller lesions may report severe chronic pain. Upon surgery, these lesions are found to extend more deeply; they are possibly more influenced by circulating estrogens.[30] Research has found that the severity of symptoms is correlated with the depth of the lesions rather than the number of lesions.[31]

Other symptoms may include pain with urination or bowel movements, bleeding from the nose/bladder or bowels, and fatigue.

Endometriomas, enlarged areas of ectopic endometrial involvement on the ovaries, are found in two of three patients with endometriosis. Infertility may be a cause of endometriosis rather than a result. There may be immune action within the pelvic cavity and the possibility of antibody reactions to sperm, which would suggest an immunologic basis for endometriosis.

Endometriosis can result in infertility and miscarriage. Data suggest that excessive amounts of free radicals are produced in endometriosis. Other findings suggest that infertility is a cause of endometriosis, due to the unruptured follicle, rather than a result. Whether infertility is a cause or result of endometriosis, tubal scarring, adhesions, and unruptured follicles are common findings in women having endometriosis and infertility problems.

Physical examination reveals one or more of the following: tenderness of the pelvic area, cul-de-sac, or both; enlarged or tender ovaries; a uterus that tips backward and lacks mobility; fixed pelvic structure; and adhesions. Endometrial tissue can be found on surgical scar tissue, in the vagina, and on the cervix. Physical examination during the first or second day of menses highlights tender areas in the septum between the rectum and vagina, most likely correlated with endometriosis.

An ultrasound examination of the pelvis can be useful in assessing pelvic pain and tumors but is not a definitive tool in diagnosing endometriosis. It can detect a mass on the ovary and determine size, characteristics, and consistency of the endometriomas. A blood test, CA-125, can have positive results in endometriosis but cannot differentiate among that and uterine fibroids, malignancies, and even normal tissue.

Definitive diagnosis of endometriosis can only be accomplished with a biopsy via either laparoscopy or laparotomy. Endometrial implants, endometriomas, or both are then visualized.

THERAPEUTIC CONSIDERATIONS

No single theory explains the development of endometriosis in all cases. More than likely, it stems from a combination of these postulated mechanisms with variable influences from case to case. The therapeutic plan may vary while targeting one or more of these possible mechanisms.

Diet

Several dietary principles are key in a natural medicine approach to endometriosis:

- Reduce inflammatory foods and increase antiinflammatory foods.
- Enhance detoxification mechanisms.
- Increase dietary fiber to promote optimal transit time and optimal gut flora.
- Increase omega-3 fatty acids and reduce trans fats.

The consumption of trans fats appears to increase the risk of endometriosis, whereas long-chain omega-3 fats appear to be protective. Twelve years of prospective data from the Nurses' Health Study II, which began in 1989, weres analyzed for dietary fat and its association with many health problems, including endometriosis.[32] Although there was no association with total fat consumption and endometriosis risk, those women with the highest consumption of long-chain omega-3 fatty acids were 22% less likely to be diagnosed with endometriosis compared with women who had the lowest intake of these fats. Those women who had the highest intake of trans unsaturated fats were 48% more likely to be diagnosed with endometriosis.

Foods high in fiber are associated with optimal transit time in the intestines and an optimal balance of friendly microorganisms within the large intestines (see Chapter 52). These microorganisms, better known as gut flora, crowd out the other types of flora that deconjugate estrogens and allow estrogens to recycle back through the body. Studies suggest that a predominantly vegetarian diet emphasizing less protein and more fiber can lead to a decrease of biologically active unconjugated estrogens in the blood plasma.[33] Although higher-protein diets are found to provide enzymes for the detoxification pathways of estradiol,[34] vegetarian diets are of greater value owing to their lower fat content. Diets containing large amounts of animal protein, especially in the form of red meat, contain large amounts of arachidonic acid, which promotes inflammatory prostaglandins and thus inflammation and pain. By adding vegetable protein, soy, nut butters such as almond, and salmon to our diets, we tip the inflammatory pathway toward antiinflammatory prostaglandins that inhibit tumor growth—and possibly endometrial growth.

By increasing the intake of vegetables, specifically those that enhance liver function, cell damage from toxins and metabolites is prevented. "Liver foods" to be increased include carrots, beets, and cabbage-family vegetables, owing to their role in aiding phase 2 of the liver's detoxification pathway. Indole-3-carbinol—found in broccoli, Brussels sprouts, cabbage, and cauliflower—favors the less active metabolite of estrogen.[35] Other liver-cleansing foods are carrots, artichokes, lemons, dandelion greens, watercress, and burdock root. Onions, garlic, and leeks contain organosulfur compounds, which enhance the immune system and induce enzymes that detoxify in the liver. In addition, they contain the bioflavonoid quercetin, which is known to stimulate the immune response, protect against oxidation, block the inflammatory response, and inhibit tumor growth.[36] Organically grown vegetables are expected to contain lower levels of pesticides that may also mimic estrogen.

The isoflavones in soy products and the lignans in flax seeds may also be important in a dietary approach to endometriosis. Many people might claim that these phytoestrogen compounds should be avoided, thinking that they would stimulate the growth of endometriotic implants, much as estrogen might. However, the evidence supports the inclusion of soy in the diets of women with endometriosis. A Japanese study demonstrated that a moderate intake of soy isoflavones was associated with a decreased risk of premenopausal hysterectomy. Because some of the surgeries involved endometriosis, these results led the authors to conclude that moderate soy intake may decrease the risk for endometriosis.[37]

Seasonings such as turmeric (curcumin) protect against environmental carcinogens, decrease inflammation, and increase bile secretion. Adding a tablespoon of milk thistle seeds that have been soaked and ground can also help with liver function. Fresh flax seeds increase antiinflammatory fatty acids. Seasoning with *Fucus* (a seaweed) helps to stimulate T-cell production and absorb toxins.[38]

Foods to decrease include sugar, caffeine, dairy, red meat, and alcohol. Sugar is known to increase estrogen levels in males.[39] A study of 50 women with endometriosis examined the effect of the reduction of higher glycemic carbohydrates, the addition of omega-3 and omega-9 fatty acids, and the elimination of foods containing caffeine and tyramine; after 8 weeks, there was a significant reduction in symptoms.[40] Endometriosis is found to be specifically correlated with caffeine consumption. Women consuming 5 to 7 g of caffeine monthly had a 1.2-times greater incidence of endometriosis, whereas those consuming more than 7 g had a 1.6-times greater increase.[41] The Environmental Protection Agency estimates that 90% of human dioxin exposure is through food, primarily meat and dairy products.[42] Cheese, particularly cottage cheese, and milk cause the lipid pathway to be tipped toward prostaglandins and leukotrienes, which cause inflammation, smooth muscle contraction, and vascular constriction. Alcohol consumption depletes stores of B vitamins in the liver and slows the metabolism of estrogen.

D
E
F

Nutritional Supplements

Vitamin C

Studies with the use of vitamin C show increases in cellular immunity, decreases in autoimmune progression, and decreases in fatigue.[43] In addition, vitamin C enhances immunity and decreases capillary fragility and tumor growth, all of which are evident at varying levels in women with endometriosis. Studies on autoimmune progression point to the effectiveness of high levels of vitamin C.[44]

Beta-Carotene

Beta-carotene helps enhance immunity. Studies show that the use of beta-carotene increased T-cell levels after 7 days.[45] In addition, beta-carotene was shown to be protective against early stages of tumor growth.[46] Retinoids can moderate the effects of interleukin-6, an inflammatory mediator, which has been implicated in endometriosis.[47] Impairment of phagocytosis is seen in vitamin A–deficient states.[48] Although vitamin A was used in the latter study, one third of beta-carotene is converted to the active form of vitamin A, that of retinol. Additional studies suggest that immune function is affected more by carotenoids than by vitamin A.[49] However, a significant portion of the population poorly converts beta-carotene to vitamin A, so supplemental vitamin A is still often needed (see Chapter 69) to ensure proper immune system function.

Vitamin E

Vitamin E helps to correct abnormal progesterone:estradiol ratios in patients with mammary dysplasia (increased growth of cells).[50] Because parallels have been found between abnormal tumor growth in cancer and abnormal growth of lesions in endometriosis, vitamin E supplementation may be advantageous. Although secondary dysmenorrhea is usually involved with endometriosis, studies on the use of vitamin E with primary dysmenorrhea[51] show benefit, perhaps through the inhibition of the arachidonic lipid pathway. Inhibition of the arachidonic pathway helps to prevent the release of chemicals that would normally cause edema, inflammation, and smooth muscle contraction.

Free radicals may contribute to the inflammation and excessive growth of endometrial tissue; vitamin E and N-acetyl cysteine, another antioxidant, can act to inhibit this proliferation.[52,53]

Pine Bark (Pycnogenol)

Pycnogenol is a special standardized extract from the bark of the French maritime pine. It is composed of polyphenols, several phenolic acids, catechins, taxifolin, and procyanidins. In laboratory research, Pycnogenol was found to selectively inhibit matrix metalloproteinases and other inflammatory cells; specifically, it inhibits cyclooxygenases 1 and 2. Its role in endometriosis was evaluated in a study of 58 women who were surgically diagnosed with endometriosis and then, after confirming regular menstruation and ovulation for 3 months, started on Pycnogenol within 6 months of surgery.[54] These women were randomized to receive either Pycnogenol 30 mg twice daily for 48 weeks or a gonadotropin-releasing

hormone agonist, leuprorelin acetate depot, 3.75 mg IM every 4 weeks for 24 weeks. After 4 weeks on Pycnogenol, patients slowly but steadily improved, reducing symptoms from severe to moderate. Overall, this group experienced a 33% reduction in symptoms of their endometriosis. The leuprorelin group had a greater response within the treatment period but relapsed after 24 weeks post treatment. The Pycnogenol group maintained regular menses and normal estrogen levels during treatment and, as expected, the leuprorelin group had suppressed menstruation and drastically lowered estrogen levels during treatment. In addition, five of the women taking Pycnogenol became pregnant.

Essential Fatty Acids

Gamma-linoleic acid (from borage, black currant, and evening primrose oil) and alpha-linolenic acid (from flax seed, canola, pumpkin, soy, and walnuts) help to decrease the inflammatory response on the tissue level through pathways that produce prostaglandins. Prostaglandins are potent hormone-like unsaturated fatty acids that act on target organs to increase or decrease inflammation depending on the kind of prostaglandins. Similarly, they can be pro-spasmodic or anti spasmodic, again depending on the prostaglandins that are being produced, as well as inhibit or promote tumor growth and other functions. Depending on one of three main pathways of prostaglandin production, the effects are helpful or harmful to the body. Animal fats lead to the production of prostaglandin products that increase inflammation, muscle constriction, and edema. However, when larger amounts of fats from the other two pathways, those of gamma-linoleic acid and alpha-linolenic acid, are taken, the opposite effects can occur. This means that these fatty acids can produce the prostaglandins involved in inhibiting tumor growth, dilating smooth muscle, and decreasing inflammation.[55] Because endometriotic implants are thought to secrete chemicals that cause leakage from nearby capillary beds, decreasing the permeability of these vessels could help control tissue destruction and adhesions, thus decreasing irritation in the pelvis. (See Chapter 90 for a more complete discussion of this complex topic.)

An interesting illustrative study looked directly at the role of essential fatty acid ratios and the viability of endometrial cells, including their production of inflammatory cytokines.[56] This in vitro study took endometrial cells from women with and without endometriosis attending an infertility clinic. In vitro cell cultures used culture media supplemented with various ratios of omega-3 polyunsaturated fatty acids and omega-6 polyunsaturated fatty acids. As a result, the investigators found that the higher the ratio of omega-6 to omega-3 fatty acids, the longer the survival time and secretion of interleukin-8 (IL-8) in cells from both women with and without endometriosis. Of particular significance was their observation that the cells from women with endometriosis secreted higher levels of IL-8 and that these levels were proportionately higher at higher ratios of omega-6 to omega-3.

B Vitamins

B vitamins help the liver to inactivate estrogen. Studies suggest that supplementation of B vitamins may cause the liver to become more efficient in processing estrogen.[57]

Selenium

Selenium aids in the synthesis of antioxidant enzymes responsible for detoxification reactions within the liver. In addition, selenium stimulates white blood cells and thymic function.[58] Individuals with decreased selenium levels have suboptimal cell-mediated immunity, decreased T cells, and associated inflammation.[59]

Lipotropic Factors

Lipotropic factors aid in enhancing liver function and detoxification reactions. Supplements that contain choline, betaine, and methionine promote the flow of fat and bile (containing estrogen metabolites) from the liver out through the large intestine.[60]

Botanical Medicines

The herbs appropriate for acute pain relief in endometriosis are the same herbs commonly used for menstrual cramps such as valerian, crampbark, and black cohosh, in addition to other traditional herbs that might be helpful, such as wild yam, chamomile, blue cohosh, ginger, passion flower, and false unicorn root.

Vitex agnus castus

Vitex agnus castus, also known as chaste tree, has traditionally been used as a treatment for hormonal imbalances in women. Through its action on the pituitary gland, chaste tree increases progesterone production via an increase in luteinizing hormone. This herb is useful for fibroids, premenstrual syndrome, and perimenopausal times of increased estrogen. With its use, less estrogen is available to stimulate endometrial tissue.[61]

Taraxacum officinale

Taraxacum officinale, also known as dandelion root, is one of the most detoxifying herbs. It works principally on the liver and gallbladder to help remove waste products. By supporting the liver, excessive estrogens and toxins can be deactivated. Researchers in Japan have found a link between dandelion and antitumor activity.[62] In addition, dandelion leaf contains vitamins A, C, and K; calcium; and choline.

Xanthoxylum americanum

Xanthoxylum americanum, or prickly ash, is known for its specific effects on capillary engorgement and sluggish circulation. Prickly ash stimulates blood flow throughout the body and enhances the transport of oxygen and nutrients in addition to removing cellular waste products. For women with pelvic congestion, this herb enhances circulation throughout the pelvis.

Leonorus cardiaca

Leonorus, or motherwort, is antispasmodic and gently soothes the nerves. As women with endometriosis generally experience uterine cramps and pain, Motherwort is useful in promoting relaxation during times of extreme "bearing down" pain in the uterus and other regions.[63] As a mild sedative, motherwort helps women get needed rest during their menstrual periods.

Turska's Formula

Turska's formula is a well-used old-time naturopathic treatment for decreasing aberrant cancer cell growth. A tincture of this formula is useful in endometriosis owing to the similarities in cell growth found in the pelvis. This formula contains *Aconite napellus* (monkshood), *Gelsemium sempervirens* (yellow jasmine), *Bryonia alba* (bryony), and *Phytolacca americana* (poke root). Monkshood and yellow jasmine contain various alkaloids that have been known to disrupt the assembly of microtubules, which eventually aid the formation of undifferentiated mesenchymal cells. Quite possibly, these herbal alkaloids interfere with the induction of abnormal ectopic lesions within the pelvis (consistent with the theory of cells left behind in embryonic development). *Bryonia* is also known to provide antitumor effects. Poke root contains glycoproteins, which are known to stimulate lymphocyte transformation for immune

enhancement. In addition, Poke root also has antiinflammatory properties. Owing to its toxic properties, however, this tincture can be provided only by a licensed health professional.

Other Considerations

Bioidentical Progesterone

Progesterone has been known to modify the action of estradiol by decreasing the retention of receptors, causing a decline in levels of serum estradiol. Women without enough progesterone are unable to adequately oppose estrogen, which can then lead to problems resulting from a relative excess of estrogen. In addition, progesterone has the effect of sedating painful uterine contractions. It is possible that this uterine sedative effect extends to pain relief in the pelvic region in general. Bioidentical progesterone is usually not used alone as a treatment for endometriosis but as part of a comprehensive natural treatment plan. Bioidentical progesterone creams can be applied in various regimens. Some women get results from ¼ tsp twice daily for 3 weeks on and 1 week off (week off is the week of menses). Other women need to use it only the week before their menses is due. Still other cases require higher doses of natural oral micronized progesterone in a cyclic dosing pattern.

THERAPEUTIC APPROACH

Diet

The primary dietary recommendation is to increase the consumption of high-fiber fruits/whole grains, decrease sources of saturated and trans fats, and increase the consumption of foods rich in omega-3 fatty acids, especially fatty fish (salmon, tuna, herring, sardines, mackerel). Especially of value are foods rich in indole-3-carbinol, such as broccoli, Brussels sprouts, cabbage, and cauliflower. Sources of caffeine should be limited.

TABLE 162-1 **Progesterone Cream Schedule**

Option 1	Days 1 to 7	No cream
	Days 8 to 28	¼ to ½ tsp twice a day
Option 2	Days 1 to 14	No cream
	Days 15 to 28	¼ to ½ tsp twice a day
Option 3	Days 1 to 21	No cream
	Days 22 to 28	¼ to ½ tsp twice a day

Supplements

- Vitamin C: 6 to 10 g in divided doses
- Beta-carotene: 50,000 to 150,000 IU a day
- Vitamin E: 400 to 800 IU a day
- Fish oil: 1000 mg EPA+DHA a day
- B complex: 50 to 100 mg B vitamin complex a day
- Selenium: 200 to 400 mcg a day
- Lipotropics: 1000 mg choline and 1000 mg methionine or cysteine three times a day
- Pycnogenol: 60 to 150 mg a day

Botanical Medicines

- Chaste tree, dandelion root, prickly ash, and motherwort tincture (equal parts): 1½ tsp to 1 tsp three times a day
- Turska's formula (*Aconite* 1½ drams, *Bryonia* 1½ drams, *Gelsemium* 1½ drams, *Phytolacca* 3 drams, and ½ dram water): five drops four times a day

Topical

Progesterone cream (Table 162-1)

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CHAPTER 163

Epilepsy

Gaetano Morello, BSc, ND

DIAGNOSTIC SUMMARY

- Recurrent seizures
- Characteristic electroencephalographic changes accompanying seizures
- Mental status abnormalities or focal neurologic symptoms potentially persisting for hours postictally

GENERAL CONSIDERATIONS

The word *epilepsy* derives from the Greek word *epilepsia,* which means "to take hold of" or "to seize." Epilepsy is not a disease in itself but rather a symptom of disease. The epilepsies are a group of disorders characterized by sudden, recurrent, episodic changes in neurologic function caused by abnormalities in the electrical activity of the brain.[1-4] Each episode of neurologic dysfunction is called a seizure. Seizures are termed *convulsive* when accompanied by motor manifestations or *nonconvulsive* when accompanied by sensory, cognitive, or emotional events. Epilepsy can occur because of a number of abnormalities, such as neurologic injuries, structural brain lesions, or some systemic diseases. Epilepsy is termed *idiopathic* when there is neither a history of neurologic insult nor other apparent neurologic dysfunction.[3] Whatever the etiology, the common denominator in all these conditions is the epileptic attack or seizure.

Epidemiology

The reported incidence and prevalence rates of epilepsy have varied widely because of uncontrolled methodologic factors.[5] According to the best available data, the prevalence of chronic recurrent epilepsy is about 10 per 1000, and it has been estimated that 10% of the population will have one or more seizures at some point in life. The cumulative lifetime incidence of epilepsy is approximately 3%.[6] An additional 2% to 5% of children experience febrile convulsions during the first several years of life. About 10% of these children, especially those in whom the febrile seizure is prolonged, develop epilepsy later in life.[1] Prospective studies show that more than 60% of newly diagnosed patients enter remission with conventional treatment.[7]

Etiology

Epilepsy may be idiopathic, cryptogenic, or symptomatic.[8] Idiopathic epilepsies are generally genetic in origin and account for 70% to 80% of all cases of epilepsy. The role of genetic factors in the pathogenesis is complex because of diverse conditions leading to the common symptom of seizures. In general, the prevalence of seizures in close relatives is three times that of the overall population.[1] William Lennox meticulously studied the relationship of epilepsy to genetics from 1934 through 1958, using twin studies. He concluded that epilepsy was a condition in which genetic and exogenous factors interact in all patients, with variable weighting in each particular case.[9]

This understanding sparked the concept that many factors play a role in the epileptic condition. Cryptogenic epilepsies are those in which an underlying cause is suspected but the etiology remains undetected. Finally, epilepsies for which there is an underlying structural cause or major metabolic derangement are considered symptomatic, for a probable cause has been identified.[4] As shown in Table 163-1, probable

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TABLE 163-1 **Presumptive Causes of Epilepsy According to Age at Onset of First Seizure**

AGE AT ONSET	PRESUMPTIVE CAUSES
Birth to 2 years	Birth injury, degenerative brain disease
2-19 years	Congenital birth injury, febrile thrombosis, head trauma, infection (meningitis or encephalitis)
20-34 years	Head trauma, brain neoplasm
35-54 years	Brain neoplasm, head trauma, stroke
55 years and older	Stroke, brain neoplasm

Data from references 3 and 4.

BOX 163-1 **The Most Common Etiologic Factors in Epilepsy**

- Brain damage before or at birth (congenital malformations, anemia, fetal infection)
- Head trauma significant enough to injure the brain and cause gliosis
- Central nervous system infections such as meningitis, encephalitis, brain abscess, neurosyphilis, rabies, tetanus, falciparum malaria, toxoplasmosis, and cysticercosis of the brain
- Metabolic disorders: hypocalcemia, hypoglycemia, hypoparathyroidism, phenylketonuria, and withdrawal from alcohol and drugs
- Brain tumors and other space-occupying lesions
- Stroke and other vascular disorders
- Degenerative brain disease
- Genetic disease
- Toxic conditions
- Idiopathic causes

BOX 163-2 **Classification of Epileptic Seizures in Adults**

Partial (Focal, Local) Seizures
- Simple partial seizures (consciousness not impaired)
 - Motor signs
 - Somatosensory or special sensory symptoms
 - Autonomic symptoms or signs
 - Psychic symptoms
- Complex partial (consciousness impaired)
 - Simple partial onset followed by impaired consciousness
 - Consciousness impaired at onset
- Partial seizures evolving to generalized seizures (tonic, clonic, or tonic-clonic)
 - Simple partial seizures evolving to generalized seizures
 - Complex partial seizures evolving to generalized seizures
 - Simple partial seizures evolving to partial seizures evolving to generalized seizures

Generalized Seizures (Convulsive or Nonconvulsive)
- Absence seizures
 - Typical (brief stare, eye flickering, no emotion)
 - Atypical (associated with movement)
- Myoclonic seizures
- Clonic seizures
- Tonic seizures
- Tonic-clonic seizures
- Atonic seizures

Unclassified Seizures

Modified from Willmore LJ, Ferrendelli JA. Epilepsy. In Dale DC, Federman DD, eds. Scientific American medicine. New York: Scientific American, 1997:11, XII-1-14.

causes can be determined by age at onset of seizures. Box 163-1 lists the most common etiologic factors.

Classification

The current classification of epileptic seizures is based on clinical and electroencephalographic criteria proposed by the International League Against Epilepsy. Box 163-2 lists the clinical features.

DIAGNOSIS

Differentiating between partial or focal seizures and generalized seizures is of great clinical significance. Partial seizures begin focally with a specific sensory, motor, or psychic aberration that reflects the affected part of the cerebral hemisphere.[5] These types of seizures may remain localized, whereas generalized seizures appear to generalize from their onset and usually affect both consciousness and motor function.[2-5] Differentiation is important because partial seizures are usually indicative of focal brain disorders such as tumors or gliosis, whereas generalized seizures rarely have a definable etiology (although some studies now implicate metabolic disorders).

An eyewitness account of a typical attack can be of great value in classifying the seizure. Past trauma, infections, and the use of drugs and alcohol should be fully explored, as should the family history. A complete neurologic examination should be performed as a preliminary screen for neoplasms. Laboratory work should include the following[4]:
- Serum glucose and calcium
- Complete blood cell count
- Liver and kidney function tests
- Serologic test for syphilis
- Skull radiographs
- An electroencephalogram (EEG)
- A computed tomography (CT) scan
- Magnetic resonance imaging (MRI)

Examination of the cerebrospinal fluid is indicated if infection or meningeal neoplasm is suspected.[1] MRI is considered the gold standard in evaluating epilepsy, as the resolution is superior to that of the CT scan.[6] Newer studies also employ EEG recording during functional MRI scanning in order to map normal and pathologic brain function.[10] Epilepsy should not be diagnosed on the basis of a solitary seizure. The recurrence rate after a single seizure is approximately only 27% over 3 years.[11]

PATHOPHYSIOLOGY

The hallmark of the altered physiologic state of epilepsy is a rhythmic, repetitive, synchronous discharge of many neurons in a localized area of the brain.[3] This discharge pattern is easily recorded on the EEG during an attack. However, the cause of the abnormal discharges is still not known. Research shows that the synchronous depolarization of masses of neurons is the result of a combination of increased excitatory mechanisms and decreased inhibitory mechanisms.[12]

Seizures can be induced in experimental models by blocking inhibitory mechanisms. For example, agents that block the action of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) are potent convulsants in humans. Conversely, the antiepileptic

drugs phenobarbital and benzodiazepines enhance GABA, thus supporting the inhibitory mechanism. In some forms of chronic focal epilepsy, inhibitory terminals on neurons in areas around cortical gliotic lesions are in fact diminished.

Other research demonstrates the instability of the nerve cell membranes in epileptics. During seizure activity, intracellular Ca^{2+} stored in the cell organelles is released and moves toward the inner cell membranes, where it binds to specific Ca^{2+}-receptive proteins, causing conformational changes in the protein's structure. These changes cause the transmembranal Ca^{2+}, K^{+}, and Na^{+} channels to pathologically remain open, potentiating the excitatory state and hence the convulsive activity.[1,2]

The earliest symptomatology, or aura, that is generated by a focal discharge provides the best clue to the localization and occasionally to the characterization of the responsible lesion. For example, a generalized seizure following an aura of a peculiar abdominal sensation or ill-defined odor indicates a lesion in the temporal lobe. A Jacksonian seizure beginning in the fingers and spreading up the arm before becoming generalized and producing a coma indicates a focal lesion in the convexity of the opposite motor cortex.[1]

THERAPEUTIC CONSIDERATIONS

Environmental Toxins

Heavy Metals

Heavy metals such as lead, mercury, cadmium, and aluminum can induce seizures by disrupting neural function.[13] Heavy metal toxicity should be ruled out as a possible cause in all seizures. A hair mineral analysis provides the most cost-effective screening method for the detection of heavy metals. Urine analysis remains the best method for estimating the levels of stored heavy metals after the administration of a chelating agent such as calcium disodium ethylenediaminetetraacetic acid or dimercaptosuccinic acid (see Chapter 53).

Neurotoxic Chemicals

Many neuron-, axon-, and myelintoxic chemicals have now been released into the environment. These chemicals are finding their way into human tissues, contributing to neurologic dysfunction. Minimizing exposure and improving the body's ability to eliminate neurotoxic agents become important aspects of the therapeutics approach. Chapters 35 and 53 discuss the impact of these neurotoxins.

Dietary Considerations

Hypoglycemia

Focal neurologic deficits associated with hypoglycemia have been well described in adults with diabetes,[14] and some researchers believe that hypoglycemia is the most important metabolic cause of seizures.[13] Researchers have found the following[13,15-18]:

- Serum glucose levels are unusually low before a seizure.
- 50% to 90% of epileptics have constant or periodic low blood sugar.
- 70% or more of epileptics have abnormal glucose tolerance tests.

Although the correlation of blood sugar abnormalities and epilepsy seems well documented, the mechanism of action is unknown. It has been suggested that low blood sugar could impair adenosine triphosphate (ATP) production in nerve cells, reducing the efficacy of the sodium ATPase pump. A defective sodium pump allows for increased intracellular sodium concentrations, which depolarize the cell membrane and thus lowers the firing threshold.

More recent observational studies have pointed to leptin as a factor that may help in regulating the occurrence of seizures. Animal studies have confirmed that injecting leptin reduces the occurrence and severity of seizures. It is well established that low blood sugar results in low circulating leptins levels, leading to another possible mechanism of action.[19]

Single measurements of serum glucose levels are inadequate to determine glycemic status—only an extended glucose tolerance test will give a complete picture.

Ketogenic Diet

Originally introduced by Wilder in 1921,[20] the ketogenic diet (KD) has a long history of use for the reduction of seizure activity.[21-23]

The diet is composed of more than 90% fat by weight, low in carbohydrates, and adequate in proteins, vitamins, and minerals. The low carbohydrate intake inhibits fat metabolism, resulting in the production of excessive levels of ketone bodies (acetone, acetoacetic acid, and beta-hydroxybutyric acid), the intermediary oxidation products. Presumably the beneficial effects of such a diet are due to its induction of metabolic acidosis, which corrects an underlying tendency of epileptics toward the spontaneous development of alkalosis.[20-22] This acidification is thought to normalize nerve conductivity, irritability, and membrane permeability.

Another possible benefit of the KD may be in augmenting ATP production by utilizing ketone bodies in place of glucose. It has been documented that many epileptics are hypoglycemic, thus compromising mitochondrial ATP production. The KD may provide an alternative route for balancing this deficit.[24]

The two main types of KDs are (1) the classic diet and (2) the medium-chain triglyceride diet. The classic KD produces ketosis by limiting intake of carbohydrates and protein to less than 10% of energy combined. The medium-chain triglyceride diet uses medium-chain triglyceride fat to produce ketosis. This allows for a larger intake of carbohydrates and protein.[20]

Research continues to document the efficacy of these types of dietary therapy. For example, one study of 27 children from 1 to 16 years of age using the classic diet found that 40% experienced a reduction of seizures of more than 50%, with 25% becoming seizure-free.[25] However, 35% discontinued the diet owing to difficulty in following the rigorous guidelines. A review from 1996 concluded that the KD had efficacy in one third to one half of childhood epilepsy cases and was partially effective in another one-third of cases.[26] A review article from 1997 states that the KD's success rate "greatly exceeds that of the medications" and that its side effects are fewer and the therapy cheaper.[27]

One prospective nonrandomized study measured the nutrient intakes, growth, and biochemical indexes of 30 children from 1 to 16 years of age who had intractable epilepsy before and after a 4-month protocol using a KD. Fourteen children on the classic diet and 11 on the medium-chain triglyceride diet completed the study, for an 83% completion. The results indicated that linear growth was maintained in patients from baseline to 4 months on both therapies. However, body weight decreased for children on both diets, which could be a result of inadequate energy intake. Protein intake met recommendations for both diets. In the medium-chain triglyceride group, there was a 0.7 decrease in the ratio of total cholesterol to high-density lipoprotein ratios at 4 months. All biochemical indices including albumin levels remained within normal limits.[20] However, this was only a 4-month study. Longer-term evaluations may show eventual unwanted changes in these parameters. The authors concluded that the medium-chain triglyceride diet may be more nutritionally adequate and thus confer an advantage over the classic KD.

Although the previously mentioned study demonstrated a relatively short use of 4 months, the KD is not without side effects. The long-term risks of a high-fat diet are well known, and a KD may prove unhealthy for a growing child. One retrospective investigation found that the linear growth of some children might be retarded.[28] When treating children on a KD, clinicians should recommend adequate intake of energy and protein, a higher proportion of unsaturated to saturated dietary fats, and also consider vitamin and mineral supplements.[20] Also, children should not be allowed to eat large meals, because these may predispose them to seizures. Small, frequent meals may be appropriate and may decrease hypoglycemic episodes.

In a study appearing in *Seizure*, researchers evaluated the long-term efficacy and tolerability of the KD in pediatric drug-resistant epileptic patients. The authors concluded that despite the retrospective nature of the study and the inhomogeneous patient sample, their results pointed to good long-term effects of the KD on seizure frequency, EEG readings, and neurologic development.[29]

The Atkins diet, which has gained great popularity in past years as a weight-loss tool, theoretically may be useful to treat epilepsy.[30] Like the KD, it too produces a ketotic state but creates this effect with less restriction on protein intake. In one pilot study, 6 patients ranging from 7 to 52 years of age were prescribed the Atkins diet for intractable focal and multifocal epilepsy. Five of the patients maintained moderate to large ketosis for periods of 6 weeks to 24 months and 3 experienced seizure reduction. As a result, they were able to reduce their antiepileptic medications.[31] Larger trials are necessary to explore whether the Atkins diet may be useful to treat patients with epilepsy.

Leptin

Leptin is a protein hormone that plays a key role in regulating appetite and metabolism. Acting on the receptors of the hypothalamus, it inhibits hunger by counteracting the affects of neuropeptide Y and anandamide, two powerful feeding stimulants. Now research is demonstrating the ability of leptins to act on receptors that activate signaling proteins, which, in turn, trigger changes that reduce brain excitability and thus seizures frequency and intensity.[19,32]

The anticonvulsant action of leptin was tested in animal seizure models by either injecting leptin directly into the cortex or administering it intranasally. Focal seizures in these animals were induced by neocortical injections of 4-aminopyridine, an inhibitor of voltage-gated K^+ channels. Results showed that seizures were briefer and less frequent upon coinjection of 4-aminopyridine and leptin. In mice, intranasal administration of leptin produced elevated brain and serum leptin levels and delayed the onset of chemical convulsant pentylenetetrazole-induced generalized convulsive seizures.[33]

The theorized mechanism of action may involve leptin's effect in activating two signaling proteins known as JAK2 (Janus kinase) and PI3K (phosphotidylinositol 3-kinase). These proteins blocked nerve impulses triggered by the neurotransmitter glutamate, thus reducing the severity and frequency of seizures. PI3K is also involved in regulating GLUT4, a cytoplasmic protein essential for sugar regulation. This may be another important mechanism of action of elevated leptins.[33,34]

Although these preliminary studies show that leptin can reduce seizures in acute settings, leptin's usefulness in chronic cases is yet to be determined. One challenge would be the fact that leptin has a relatively short half-life (15-30 minutes), leading to dosing problems. However, creating a physiologic environment that improves blood leptin levels through dietary and supplemental intervention could prove therapeutic.

There appears to be a link to the KD, since this diet increases the amount of circulating leptins—perhaps another plausible mechanism of action of KD. Future research may involve testing foods that have a propensity to increase circulating leptins and examining their effect on seizure frequency and intensity.[34]

Another link to the anticonvulsant action of leptin is hypoglycemia. It has been established that low blood sugar is associated with an increase in seizure formation, and hypoglycemic individuals also have low leptin levels. This may explain in part why hypoglycemia is associated with the occurrence of seizures.

Although the use of leptin as an anticonvulsant is in its early stages of research, the strategy of increasing blood levels of leptin in order to reduce seizure formation warrants consideration.

Food Allergy

There has been little research into the correlation between food allergy and epilepsy, with only anecdotal case histories,[35,36] single-case double-blind placebo-controlled studies,[37,38] and uncontrolled studies being reported. It is postulated that epileptic patients may have allergic reactions in the brain that are similar to the swelling, anoxia, and inflammatory chemical reactions seen at other sites of local allergic reactions.[35]

One uncontrolled study evaluated oligoantigenic diets in 63 children with epilepsy. Of 45 children with recurrent headaches, hyperkinetic behavior, or abdominal symptoms, 25 ceased to have seizures and 11 had fewer seizures during diet therapy. Headaches, abdominal pain, and hyperkinetic behavior ceased in all patients whose seizures ceased and in some of those whose seizures did not cease. Reintroduction of foods reproduced symptoms. Of 24 children with generalized epilepsy, 18 recovered or improved, as did 18 of 21 children with partial epilepsy. In double-blind provocation, 15 of 16 children experienced recurrence of symptoms, including seizures in 8, whereas none improved in the placebo group. Another group of 18 children who had epilepsy alone had no improvement with dietary change.[39] This study suggests that food allergy should be suspected in epileptic patients who suffer from multiple other symptoms of food allergy (see Chapter 15).

Another study evaluated two females, 5 and 23 years of age, who had focal occipital epilepsy with cerebral calcifications and were not responding well to antiepileptic therapy. Both had celiac disease as well as documented folic acid deficiency (a common side effect of most antiepileptic drugs). A gluten-free diet combined with supplementation with folic acid (dosage not reported) led to complete normalization of the EEG in the 5-year-old and cessation of seizures. The 23-year-old experienced significant improvement in her EEG and enhanced seizure control. Folic acid returned to the normal range within several months.[40]

A larger study looked more closely at the association between celiac disease and epilepsy. A total of 43 patients (15 male) between 4 and 31 years of age were evaluated for the association between celiac disease, epilepsy, and cerebral calcifications. Intestinal biopsy on the 31 patients with cerebral calcifications of unexplained origin and epilepsy found a flat intestinal mucosa in 24, suggesting celiac disease. CT scans showed cerebral calcifications in 5 of the 12 patients with celiac disease and epilepsy. Antibodies to gluten and folic acid serum concentrations were measured, and histocompatibility leukocyte antigen typing was done in most patients. Only 2 patients with cerebral calcifications and epilepsy had gastrointestinal symptoms at the time of biopsy. A gluten-free diet in epilepsy was found to be inversely related to the duration of epilepsy before the diet and to the patient's age at the beginning of the diet.

The authors strongly recommend that celiac disease be considered in all cases of epilepsy and cerebral calcifications of unexplained

origin, especially when the epilepsy is characterized by occipital seizures and the calcification is located bilaterally in the posterior regions.[41] One work involving 72 epileptic children and 202 controls revealed significantly higher rates of eczema in the mothers and rhinitis in the siblings of the epileptic patients as well as a generally higher incidence of allergic pathologies in both of these groups compared with the controls. Additionally, a significantly higher incidence of allergy to cow's milk as well as asthma was documented in the epileptic children with respect to the control group. Prick tests gave a significantly higher rate of positive results for cow's milk proteins in the epileptic patients versus controls.[42]

Mitochondrial ATP

Direct research into the possible benefits, with regard to seizure formation, of optimizing mitochondrial ATP production is minimal. However, there is peripheral evidence supporting this idea. For example, it is well accepted that individuals with mitochondrial diseases compromising ATP production have an increase in seizure frequency. This may be related to ATP production and the importance of this respiratory chain substrate in controlling the stability of cell membranes.[43]

In one observational study, 37 family members with a genetic mitochondrial disease (a mild defect in the NADH-ubiquinone oxidoreductase step) showed a significant increase in seizures (22% of the group developed epilepsy).[44]

Studies of subjects with mitochondrial encephalopathies have consistently shown epileptic seizures as a main recognized symptom. Partial seizures, chiefly with elementary motor symptoms, and focal or multifocal EEG epileptiform activity characterized the epileptic presentation in 71% of these patients.[45]

These results support the possibility that compromised ATP production may be playing a role in provoking seizures.

Supplementation with ubiquinone has shown positive effects in improving symptomatology produced by mitochondrial encephalopathies. In a study of patients with mitochondrial encephalopathies (which can lead to seizures) showed a significant improvement in fatigability and muscle endurance after the administration of supplemental ubiquinone.

Ubiquinone has been shown to have significant benefits in several neurologic disorders (e.g., Parkinson's disease, Huntington's chorea). Thus, using this agent as part of the anticonvulsant protocol may have some merit.[46-48]

Even the positive effects of the ketogenic diet (KD) may have some relationship to mitochondrial functionality. A recent study showed that animals placed on a KD had a 46% increase in the density of mitochondria in neuronal tissues. KD has been hypothesized to work on several levels; it is plausible to assume that increasing mitochondrial density and thus ATP production could be one of them.[49,50]

Nutritional Considerations

Pyridoxine

Two types of vitamin B_6–related seizures are known in newborns and infants younger than 18 months of age: vitamin B_6-deficient and vitamin B_6-dependent. They cause similar neurologic symptoms and EEG abnormalities; if not treated, they carry a prognosis of mental retardation.[51]

Pyridoxine-dependent seizure is an autosomal, recessively inherited inborn error of metabolism. In affected patients, long-lasting seizures usually begin in infancy but they may also appear up to 3 years of age and recur. They are resistant to conventional anticonvulsants. The condition ends fatally if diagnosis and administration of pyridoxine in pharmacologic doses are delayed too long.[52] The diagnosis of pyridoxine dependency should be suspected in every infant with convulsions in the first 18 months of life. Certain clinical features may be especially suggestive, including the following:

- Seizures of unknown origin in a previously normal infant without an abnormal gestational or perinatal history
- A history of severe convulsive disorders
- The occurrence of long-lasting focal or unilateral seizures, often with partial preservation of consciousness
- Irritability, restlessness, crying, and vomiting preceding the actual seizure

MRI with spectroscopy may be a useful tool in the neuroimaging evaluation of parenchymal changes despite a normal-appearing brain MRI in patients with pyridoxine-dependent seizures.[53] Since atypical presentations of pyridoxine-responsive seizures have been reported, it has been recommended that an empiric trial of parenteral pyridoxine be tried in any neonate or infant with long-lasting convulsions, especially when no clear-cut etiology is present.[51,54] A 100- to 200-mg intravenous dose or 20-mg dose every 5 minutes to a total of 200 mg is recommended. If the seizures stop, it is likely that the child has pyridoxine-responsive seizures.[51,54] The chance to identify a pyridoxine-responsive seizure is lost if pyridoxine is given together with or after most anticonvulsant drugs.[54]

Although vitamin B_6-deficient seizures are promptly corrected by the administration of dietary amounts of pyridoxine, vitamin B_6-dependent seizures require continuous high-dose supplementation in the range of 25 to 50 mg/day.[51,54-56]

Although the mechanism by which pyridoxine decreases seizure activity is not fully understood, it is undoubtedly related to its role as a necessary cofactor in the metabolism of various neurotransmitters, the production of which depends on amino acid decarboxylation. Once absorbed, pyridoxine is phosphorylated to pyridoxal-5-phosphate, a coenzyme in the reaction converting glutamic acid to GABA (Figure 163-1). GABA, as mentioned earlier, is an important inhibitory neurotransmitter.

One proposed mechanism for pyridoxine dependency is that pyridoxal phosphate does not bind with its usual affinity to glutamic acid decarboxylase, resulting in reduced GABA production. In these patients, higher-than-normal levels of pyridoxine are required to allow for the activity of this enzyme.[51,54-56]

One uncontrolled study of infants and children with uncontrollable infantile spasms or their sequelae found improvement in 2 to 14 days using oral pyridoxine phosphate (20 to 50 mg/kg). Of the 17 total subjects, 3 had complete relief, 6 showed transient relief, and 8 showed marked reduction in seizures and improvement in their EEGs.[56] Some adverse reactions were seen, including elevated transaminases, nausea, and vomiting.

Administration of vitamin B_6 to epileptic patients must be strictly monitored. Although some improvements have been noted, daily doses in the range of 80 to 400 mg have been shown to interfere with commonly used anticonvulsants.[57]

Folic Acid

Serum and red blood cell folate are reduced in up to 90% patients receiving phenytoin, carbamazepine, or barbiturates. These drugs

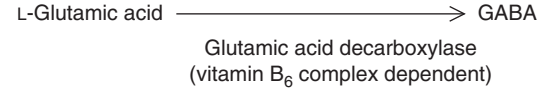


FIGURE 163-1 The conversion of glutamic acid to gamma-aminobutyric acid.

interfere with the intestinal uptake of folic acid at the mucosal level. Lamotrigine and zonisamide appear to not be associated with low levels of folic acid. Most reports state that valproate does not reduce folate levels, although some of the literature is inconsistent. A convincing argument now suggests that routine folic acid supplementation is important for adults receiving antiepileptic medication.[58]

The U.S. Food and Drug Administration has directed that oral tablets of folic acid not exceed 1 mg because of concerns brought forward more than 30 years ago that larger amounts might counteract the antiseizure effects of antiepileptic drugs and increase the frequency of seizures in some children.[59] Although that concern is no longer considered valid by epilepsy specialists, the dose restriction has not been lifted. Supplementation with folic acid appears safe even up to doses as high as 15 mg/day[58] and can protect both against birth defects for women of childbearing potential and also lower homocysteine levels, a risk factor for cardiac disease for adults using antiepileptic medications.

Thiamine

In an interesting study, 16 of 50 consecutive neurologic patients with a diagnosis of thiamine deficiency showed epileptic manifestations. It is possible that thiamine deficiency may promote epileptic episodes in those who have a subclinical predisposition to seizures. For example, the stimulation of nerve fibers in vitro causes them to lose significant amounts of thiamine pyrophosphate in the surrounding fluid, suggesting a significant role for thiamine in nerve-to-nerve conduction. In addition, thiamine deficiency may be accompanied by low concentrations of GABA, which, as noted earlier, is significant in seizure disorders. The authors suggested that, in patients with late-onset epilepsy, thiamine deficiency may be considered one of the possible causes.[60]

Taurine

Taurine is one of the most abundant amino acids in the mammalian brain.[61,62] It is involved in hyperpolarizing neurons by changing ion permeability and may mimic the effects of GABA and glycine.

Since the early 1970s, considerable clinical and experimental evidence has accumulated supporting the anticonvulsive activity of taurine.[61-74] The primary mode of action responsible for taurine's activity in epilepsy is its membrane-stabilizing effects (i.e., it seems to normalize the flow of Na^+, K^+, and Ca^{2+} into and out of the cell).[61-63]

In addition to acting as a GABA-like neurotransmitter,[61-64] taurine may also help to decrease seizure activity by increasing GABA levels by enhancing the action of glutamic acid decarboxylase.

Epileptic patients have been shown to have significantly lower levels of taurine in platelets than control patients.[65] Although several studies have shown lower taurine levels in the plasma, serum, and urine of epileptic patients, other research has yielded disparate results.[66-69] Cellular concentration of taurine as determined by platelet level is thought to be of much greater significance.

The first clinical trials of taurine were undertaken by Barbeau and Donaldson[70] in 1973 and Bergamini and colleagues[71] in 1974. The results were encouraging, and several additional reports have confirmed taurine's anticonvulsant effects.[61,63,70-76] However, the rate of effectiveness of taurine is far below the level where it could be recommended as a standard treatment for epilepsy. At this time, there is no consensus on the seizure types for which taurine is most suitable, nor is there agreement on appropriate dose. Even more, it is questionable whether taurine may even have the ability to effectively traverse the blood-brain barrier to gain an effect.[77]

At a daily oral dose of 0.05 to 0.3 g/kg in one study and 750 mg in another, taurine has demonstrated efficacy in some cases of intractable epilepsy, decreasing seizures by more than 30% in 11 of 34 subjects.[75,76] This is highly significant because these patients were unresponsive to any other anticonvulsants. Patients with partial epilepsy demonstrated the best results, with those achieving the highest taurine concentrations showing the best response.

The positive clinical response of some epileptic patients to supplemental taurine and the apparent cellular deficiency of taurine suggest that taurine supplementation be tried in most patients. Therapeutic monitoring of platelet or plasma taurine levels may prove useful.

Magnesium

Epileptic patients have been shown to have significantly lower serum magnesium levels than normals, with seizure severity correlating with the level of hypomagnesemia.[78-81] Although the mechanism of action is not fully understood, in uncontrolled trials magnesium has been shown to be of benefit in the control of seizures.[82,83] It has also been postulated that like those of folic acid, magnesium levels may be lowered by antiepileptic medications.[81]

Pfeiffer[82] found that a magnesium deficiency induces muscle tremors and convulsive seizures and reported success in controlling the seizure activity of 30 epileptic patients with 450 mg/day of magnesium.

Manganese

The link between epilepsy and manganese was first suggested in 1963, when Hurley and associates[84] observed that manganese-deficient rats were more susceptible to seizures than manganese-replete animals and that manganese-deficient animals exhibit an epileptic-like EEG. This prompted researchers to measure manganese concentrations in epileptic patients. Low manganese levels in whole blood and hair have been found in epileptic patients, and those with the lowest levels typically have the highest seizure activity.[85-89]

Manganese plays a significant role in cerebral function, as it is a critical cofactor for glucose utilization within the neuron, adenylate cyclase activity, and neurotransmitter control. Obviously optimal central nervous system function requires proper manganese levels. Manganese supplementation may be helpful in controlling seizure activity in some patients.[90]

Zinc

Children with epilepsy have been found to have significantly lower levels of serum zinc, especially those with West's or Lennox syndrome.[80,91] More importantly, it appears that epileptic patients may have an elevated copper:zinc ratio.[91] Seizures may be triggered when zinc levels fall, as in the absence of adequate taurine. Although the exact role of zinc or the copper:zinc ratio is not clearly understood, it appears to involve either the storage or binding of GABA.[91]

Zinc supplementation appears to be warranted, especially in light of the observation that anticonvulsants may cause zinc deficiency.[92]

Choline, Betaine, Dimethylglycine, and Sarcosine

Choline, betaine (N,N,N,-trimethylglycine), dimethylglycine (DMG), and sarcosine have exhibited some anticonvulsant activity in human and animal studies. Choline is converted to betaine when it acts as a methyl donor, whereas betaine is converted to DMG when it donates a methyl group. This is most evident in the transformation of homocysteine to methionine. Supplemental betaine has also been shown to be effective in preventing various induced seizures in rats and in alleviating seizures in humans with homocystinuria.[93-97]

DMG has also been shown to block induced seizures in rats and mice.[95,96] Roach and Carlin[98] reported a striking decrease in seizure

frequency in a patient with long-standing mental retardation when 90 mg of DMG was administered twice daily. Despite treatment with phenobarbital and carbamazepine, the patient had an average of 16 to 18 generalized seizures each week. Within 1 week of starting DMG, seizure frequency dropped to three per week. Two attempts to withdraw the DMG caused dramatic increases in seizure frequency.

It has been suggested that glycine and betaine may act indirectly on glycine metabolism and glycine-mediated neuronal inhibition, enhance GABA activity, or simply have a nonspecific effect on biological membranes.

Vitamin D

The association of anticonvulsant drugs with disorders of mineral metabolism—including hypocalcemia, rickets, and osteomalacia—is well documented.[99] Conflicting results have been published concerning the serum levels of vitamin D in patients with epilepsy. Studies have reported increased,[100] normal,[101] and decreased levels.[102]

Supplemental vitamin D intake is recommended when climatic conditions or the patient's lifestyle do not allow adequate exposure to sunlight.[103] Supplementing the diets of 23 epileptic patients with 4000 to 16,000 IUs of vitamin D resulted in a significant decrease in the number of seizures, indicating a possible therapeutic effect.[104] Doses of this magnitude can, however, be toxic, requiring careful monitoring.

Vitamin E, Selenium, and Antioxidants

Vitamin E and selenium function synergistically in many physiologic functions. Vitamin E deficiency is known to produce seizures,[105] and antiepileptic drugs have been shown to decrease the levels of vitamin E[106,107] as well as those of other antioxidants, like beta-carotene. Studies have shown both vitamin E and selenium to be low in epileptic patients.[105,108] Phosphate diesters of vitamins E and C have been shown to prevent the formation of epileptogenic foci and to attenuate seizure activity in animal models of epilepsy.[109] Supplementation with vitamin E and selenium may result in improved control of seizures.[105]

For example, a double-blind placebo-controlled study of 24 epileptic children unresponsive to antiepileptic drugs found that supplementation with 400 IU/day of vitamin E provided a significant reduction in the number of seizures in 10 of 12 children. The 2 unresponsive children were noncompliant. All the children continued their normal doses of antiepileptic drugs. No benefit was seen in the 12 placebo children, and, as expected, no negative side effects resulted from the vitamin E therapy.[110]

One report described four children with reduced glutathione peroxidase activity, intractable seizures, multiple infections, and resistance to anticonvulsant treatment. All had seizures within the first 6 months of life. There was no evidence of known inborn errors of metabolism; however, all four patients had low intracellular levels of glutathione peroxidase. Two had normal whole-blood selenium levels, whereas the other two had low levels. Once anticonvulsant therapy was stopped and selenium administered, all four patients experienced clinical improvement.[111]

For epileptic discharges induced in animal models, other antioxidants, such as alpha lipoic acid and those found in green tea, have been shown to scavenge radical oxygen species and may be prophylactic.[109,112]

Essential Fatty Acids

Animal studies have demonstrated that long-chain polyunsaturated fatty acids may alleviate or prevent cerebrovascular pathophysiology and can improve the competence of the blood-brain barrier.[113] One human 5-patient study using 5 g/day of a 65% omega-3 fatty acid spread demonstrated a marked reduction in both the frequency and strength of epileptic seizures.[114] However, three hospitalized schizophrenic patients treated with gamma-linolenic acid and linoleic acid in the form of evening primrose oil developed temporal lobe epilepsy following ingestion of the oil. This epilepsy ceased once carbamazepine treatment was initiated.[115] It may be important to monitor the use of oils and fatty acids in closely treating epilepsy; also, more research is needed to determine which agents are most beneficial. At this point, omega-3 fatty acids seem to be the best choice, and evening primrose oil should be used with caution.

Melatonin

It is well documented that melatonin (*N*-acetyl-5-methoxytryptamine) is a powerful antioxidant. Melatonin is often used to treat abnormalities in sleep-wake cycles, jet lag, cancer, and Parkinson's disease. Epileptic children have a higher incidence of sleep problems, and epilepsy is exacerbated by sleep deprivation.[116] Animal studies have demonstrated melatonin to have antiepileptic activity. Although not entirely clear, it is possible that melatonin exerts an antiexcitotoxic neuroprotective effect by lowering lipid peroxidation and raising coenzyme Q_{10} levels within the central nervous system.[117]

One randomized double-blind placebo-controlled trial included 31 children 3 to 12 years of age who had been taking sodium valproate (10 mg/kg per day) for 6 months and were seizure-free. Of these children 16 received a fast-release 3-mg melatonin tablet and 15 received a placebo, all 1 hour before bedtime. Using standard Quality of Life in Childhood Epilepsy scales, it was revealed that attention, memory, language, anxiety, behavior, and other cognitive processes all improved in the group receiving melatonin. The general health score also improved marginally. Although not objectively assessed, perceptible increases in appetite and the quality of sleep were reported by most in the melatonin group.[118] Given that high doses have been well tolerated in adults (up to 300 mg/day),[119] it may be possible to slowly increase the 3-mg dose of melatonin for even better results.

Botanical Medicines

Chinese Herbal Medicine

Botanical medicines have played a significant role in the treatment of epilepsy in both the Eastern and Western healing arts. Western scientific methodologies have been used to evaluate the efficacy of the Chinese herbal medicine combination known as saiko-keishi-to (SK).[120] SK demonstrated dramatic therapeutic effects on some difficult cases of epilepsy that had long been unsuccessfully treated with standard allopathic anticonvulsive drugs. SK is a combination of nine botanical drugs:

- *Bupleuri radix* (5 g)
- *Scutellaria radix* (3 g)
- *Pinelliae tuber* (5 g)
- *Paeoniae radix* (6 g)
- *Cinnamon cortex* (2 g)
- *Zizyphi fructus* (4 g)
- *Ginseng radix* (30 g)
- *Glycyrrhizae radix* (1.5 g)
- *Zingiber rhizoma* (2 g)

In one experiment, seizure-like activity was induced in snail neurons by the drug pentylenetetrazol.[121,122] SK was found to do the following:

- Inhibit the intracellular shift of Ca^{2+} toward the cell membrane
- Inhibit the binding of Ca^{2+} to Ca^{2+}-receptive membrane proteins and the Ca^{2+}-calmodulin complex

D
E
F

- Inhibit the conformational changes of the Ca^{2+}-receptive membrane proteins
- Inhibit the pathologic transmembrane current of Na^{+}, K^{+}, and Ca^{2+}

The researchers presumed that SK's experimental effects were similar to its mode of action in humans. When an attempt was made to isolate purified chemicals from the component herbs, the crude drug's efficacy was lost. This suggests a synergistic effect between the component botanical agents.

Clinical research has shown some benefit in epileptic patients. One study reported that 8 of 28 epileptic patients experienced a 25% decrease in number of seizures after 8 weeks of treatment.[122]

More recent research has shown that SK also has a protective effect on neuron damage produced by various factors including stress. This may point to possible antioxidant-specific compounds within the formula, affecting the central nervous system. Supporting this hypothesis is the fact that the same researchers found SK to have preventive effects on abnormal expression of one of the seizure-related genes.[123]

Coleus forskolii. Research showing that the cyclic nucleotides involved in the pathophysiology of seizures has elucidated a possible mechanism for the action of several botanical medicines used in the treatment of seizure activity.[124] Cyclic adenosine monophosphate (cAMP) has been demonstrated to depress electrical activity in cat hippocampal slices, whereas cyclic guanosine monophosphate can produce seizure-like discharge in the same tissues.[125] In addition, cAMP inhibits Ca^{2+} from binding to intracellular proteins like calmodulin, resulting in a decrease in the extrusion of neurotransmitters into the synapse.

The botanical *Coleus forskolii,* an important plant medicine in the Ayurvedic treatment of epilepsy, activates adenylate cyclase, thus increasing the levels of cAMP.[126,127] This action is thought to be due to forskolin, a diterpine, which has been found to increase adenylate cyclase activity by 530%.[127] This is the greatest activity found in 100 plants studied for the ability to increase cAMP. The same study found that seven of the nine botanicals in SK—*B. radix, C. cortex, G. radix, P. radix, G. radix, S. radix,* and *Z. rhizoma*—were found to display significant cAMP enhancement, either by enhancing adenylate cyclase or inhibiting cAMP phosphodiesterase.[127] *B. radix,* a key component of the SK formula, was found to increase cAMP by 170%.

Ginkgo biloba. *Ginkgo biloba* is well known for its usefulness as a memory aid, for cerebral insufficiency, and for its powerful antioxidant properties. However, some of the literature has cited the possibility that it may be responsible for precipitating seizures in two individuals with prior well-controlled seizures. In both patients (78 and 84 years of age), seizures commenced after taking gingko, and they were both seizure-free after the ginkgo was discontinued. The flavonoid components in gingko have been shown to exert GABAergic activity as partial agonists at benzodiazepine receptor sites, and this activity could play a role.[128] As a prudent measure, patients with a seizure history should probably stay away from this botanical until more research has been conducted.

Acupuncture

From work on animal models, it has been suggested that the mechanism of acupuncture in suppressing epileptic seizures involves the release of neurotransmitters such as endogenous opioid peptides, serotonin, and GABA.[129] Other studies have shown possible seizure inhibition through decreasing neuronal nitric oxide synthase transcription in the hippocampus.[130,131]

In humans, effective use of acupuncture, scalp needling, electroacupuncture, and embedding of acupuncture points to treat epilepsy and status epilepticus has been reported. However, one sham-controlled study of 34 patients found no benefit.[132] This research group reported similar results with a study of 29 patients. In a second study, many of the patients reported changes in their sense of well-being.[133] In both clinical trials, drug-resistant patients who had been considered intractable were given nearly identical treatments save one or two points, also without benefit. Given the individualized nature of traditional Chinese medicine, this may not be a reasonable representation of the acupuncture modality. Additionally, it may be possible that more benign cases of epilepsy may be more responsive even if intractable cases are not.

Auricular, or ear, acupuncture was developed by Nogier, a French neurologist, in the 1950s. Unlike traditional Chinese acupuncture, which uses the meridian system, ear acupuncture uses points on the ear that represent different areas on the body, similar to the way reflexology works with points on the foot. In one study, epileptiform behaviors in rats were induced by intrahippocampal injection of penicillin. Radioimmunoassay techniques demonstrated that levels of somatostatin, aspartic acid, glutamine, and GABA were increased. One hour later, the lower-half auricular lobules of seizure rats, containing the ear-points Pizhixia and Shenmen, were electrically stimulated. After auricular treatment, the convulsion behaviors of the rats improved. Concomitantly, the content of the somatostatin, aspartic acid, and glutamine in the seizure rats' hippocampi were significantly decreased, while the content of glycine, taurine, and GABA had increased. These results suggest that ear-point electrical stimulation has antiepilepsy effects. Physiologically, given that amino acid concentrations may be involved in the pathogenesis of an epileptic seizure, auricular treatment might be involved in decreasing the content of the somatostatin, aspartic acid, and glutamine and increasing that of glycine, taurine, and GABA in the hippocampi of seizure rats.[134,135]

Ear acupuncture may then be more effective than traditional body acupuncture. More studies are necessary to determine the effectiveness of both auricular and body acupuncture in the treatment of epilepsy. The negative side-effect profile of acupuncture is low, although one case report describes an episode of convulsive syncope, which occurred immediately after the insertion of acupuncture needles into the bilateral ST-36 acupuncture point.[136] Given the extraordinarily common use of these points and the extremely rare appearance of side effects due to acupuncture, this case report should be considered an anomaly.

Yoga and Meditation

A health trend that has become as popular as exercise is yoga. Yoga teaches a variety of physical postures, breathing exercises, and meditation techniques with the goal of improving both physical and mental health. There are a number of types of yoga emphasizing harmony between the physical and energetic aspects of the body. It has been documented that yoga has a physiologic impact that may offer benefit to the epileptic patient.[137]

Research has indicated that the meditative types of yoga (Sahajaea yoga) have the most benefits in reducing the intensity and occurrence of seizures. A Cochrane Review of yoga among epileptic patients showed significant improvement in one particular study involving 32 epileptic patients divided into an active group and two control groups. Results showed that the active group had a 50% reduction in the number of seizures at 1-year follow up. Although these results are statistically significant, the authors concluded that further research with larger numbers was needed.[137-139]

Trigeminal Nerve Stimulation

Intractable epilepsy, which affects more than 1 million Americans and is often resistant to drug treatment, may be ameliorated by a relatively new procedure known as trigeminal nerve stimulation (TNS). The trigeminal nerve, which extends into the brain from the face and forehead, is known to play a role in the inhibition of seizures, and it has been shown that stimulating this nerve can reduce their occurrence.[140] TNS involves using a stimulator the size of a cell phone that fits into a pocket; its wires are connected to the forehead with adhesives. Electrical impulses are transmitted to the nerve, resulting in reduced seizure frequency.[140]

In a recently completed clinical trial, patients experienced significant reductions in seizure occurrence. The study demonstrated that those participating in the study experienced 66% reduction of seizures in the first 3 months, 56% after 6 months, 59% reduction after 12 months, and, in one of the subjects, nearly 90% reduction in seizures after 1 year. The therapy shows promise as an alternative mode of neurostimulation, especially because it is not invasive (as compared with vagus nerve stimulation, which requires surgery).[141,142]

Exercise

There has been understandable caution in recommending exercise to epileptic patients owing to fear of injury and the possibility of seizure induction. However, a review of the literature shows that there is no increase in the frequency of seizures with exercise. Some studies have shown that exercise reduces seizure frequency, specifically in drug-resistant epileptic patients. In one study, 15 women resistant to drug therapy engaged in 1-hour physical exercise sessions twice a week for 15 weeks. As a result, 7 patients had 27 seizures during the 30 exercise sessions; self-reported seizure rate was significantly reduced by the end of the 15-week period (2.9 seizures per week had dropped to 1.7 seizures per week). There were also other benefits to the exercise program, including reduced muscle spasms, improved sleep, and increased energy.[143]

In a recent review, the authors discuss the positive effects of physical exercise programs in experimental models of epilepsy. Findings from animal studies show that exercise seems to modulate neuronal vulnerability to epileptic insults. The review also concludes that metabolic, electrophysiologic, and immunohistochemical evaluations have confirmed the positive influence of exercise on the epileptic patient.[144]

These finding seem to suggest that physical exercise should be considered and integrated into the therapeutic approach for reducing the intensity and frequency of seizures.

THERAPEUTIC APPROACH

Epileptic patients should be advised to avoid situations that could provoke further seizures or could pose dangers in the event that a seizure should occur. Also, they should be made aware of state laws regarding epilepsy and driving. Epileptic patients should avoid known initiators of seizure activity (e.g., bright flashing lights, sudden loud sounds). Therapy should continue at full dose until the patient has been seizure-free for at least 2 years. Dosage reduction should then be gradual over a period of several months. Epileptic patients who are not controlled with natural therapies require drug therapy.

Patients should eliminate pyridoxine antagonists (isoniazid, cycloserine, hydralazine, dopamine, penicillamine), oral contraceptives, alcohol, and hydrazine dyes (Food, Drug, and Cosmetic Act yellow no. 5).

Note: Status epilepticus, a prolonged seizure lasting longer than 30 minutes that is not likely to stop spontaneously, is a medical emergency that inevitably results in serious neurologic damage or death if untreated. Immediate hospitalization is required, preferably with ambulance or aid car transport, with the necessary equipment to maintain the patient's airway, assist in ventilation, and administer intravenous glucose and antiepileptic drugs.

Because endogenous depression is more prevalent in persons with epilepsy than in the general population,[145] monitoring for depressive illness is important in epileptic patients.

Diet

All sugar and other refined carbohydrates should be eliminated and protein levels should be moderated. Food allergens should be identified and eliminated. Small frequent meals are best. If a ketotic effect is desired, all carbohydrates should be strictly limited and fat intake increased. Furthermore, adequate intake of energy and protein, plus a higher proportion of omega-3 unsaturated to saturated dietary fats, should be assured. Finally, vitamin and mineral supplements should be used with ketotic diets (ketotic diets should be used only under professional supervision).

Lifestyle

Regular sleep patterns should be encouraged along with some form of physical exercise.

Nutritional Supplements

(The following are adult doses; reduce proportionately for children.)

- Vitamin B_6: 50 mg three times a day
- Folic acid: 0.4 to 4 mg/day
- Vitamin E: 400 IU/day
- Taurine: 500 mg three times a day
- Magnesium: 300 mg three times a day
- Manganese: 10 mg three times a day
- Selenium: 100 mcg/day
- Zinc: 25 mg/day
- Ubiquinone: 100 mg/day
- Melatonin: 3 mg a day in children, increase up to 20 mg or more in adults

Botanical Medicines

- Saiko-keishi-to: 300 mL before bedtime
- *G. biloba*: contraindicated at this time

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CHAPTER 164

Erythema Multiforme

Michael Traub, ND, DHANP, FABNO, and Michael T. Murray, ND

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DIAGNOSTIC SUMMARY

- Sudden onset of symmetrical erythematous, edematous, macular, papular, urticarial, bullous, or purpuric skin lesions
- Evolves into "target lesions" (lesions with clear centers and concentric erythematous rings)
- Characteristic first site: dorsum of the hand
- Characteristic distribution: extensor surfaces of extremities with relative sparing of head and trunk
- Although rare, oral manifestations ranging from tender superficial erythematous and hyperkeratotic plaques to painful, deep, hemorrhagic bullae and erosions
- Tendency to recur in spring and fall

GENERAL CONSIDERATIONS

The term *erythema multiforme* (EM) includes a wide range of clinical expressions, from exclusive oral erosions (oral EM) to mucocutaneous lesions ranging from mild (EM minor) to severe involvement of multiple mucosal membranes (EM major, Stevens-Johnson syndrome [SJS]) or with involvement of a large area of the total body surface (toxic epidermal necrolysis [TEN]). However, this terminology is not accepted worldwide, and often the various clinical categories show some overlapping features. Although significant differences exist among EM minor, EM major, SJS, and TEN with regard to severity and clinical expression, all variants share two common features: typical or less typical cutaneous target lesions and satellite-cell or more widespread necrosis of the epithelium. Clinically, EM major is characterized by typical or raised atypical targets located on the extremities and/or face. SJS is diagnosed when lesions are flat, atypical targets or purpuric maculae that are widespread or distributed on the trunk.[1]

Among the great number of suspected etiologic factors, the differentiating feature between EM and SJS/TEN is that herpes simplex virus or mycoplasmal infections are involved in roughly 90% of cases of EM minor, whereas SJS and TEN are caused in 80% of cases by systemic drugs, mainly by anticonvulsants, sulfonamides, nonsteroidal antiinflammatory drugs, and antibiotics. However, various vaccines (e.g., *Vaccinia*, tuberculosis, poliomyelitis, human papillomavirus, etc.), contactants, food allergies, and other infectious organisms have all induced EM minor. Evidence clearly points to hypersensitivity and immune system–mediated tissue damage caused by the release of highly reactive, polynuclear leukocyte–derived oxygen intermediates as the common factors in all variants of EM.[2]

HLA-DQ3 correlates closely with recurrent EM and may be a marker to distinguish herpes-associated EM from other skin diseases.[3] Biopsy can help predict disease progression from EM lesions to SJS or TEN.[4]

THERAPEUTIC CONSIDERATIONS

Potassium Iodide

Potassium iodide has historically been used to treat various erythematous disorders including the following:

- Erythema multiforme
- Erythema nodosum

- Nodular vasculitis
- Acute febrile neutrophilic dermatosis
- Subacute nodular migratory panniculitis

Clinical studies have documented dramatic success with potassium iodide.[5-7] The mechanism is apparently related to the suppression of the generation of oxygen intermediates such as hydrogen peroxide and hydroxyl radical by stimulated neutrophils.[8] Importantly, iodine therapy has occasionally been associated with various adverse skin reactions and gastrointestinal discomfort; it should never be used in pregnant women in the last trimester owing to its effect in suppressing the fetal thyroid.[9,10]

Zinc

Zinc sulfate (0.025% to 0.05%) has been used locally at the site of herpetic infection and to prevent the relapse of postherpetic EM.[11]

THERAPEUTIC APPROACH

A careful search should be made to determine the initiating factor. Underlying infections should be treated, all unnecessary medications stopped, and an antiinflammatory program initiated. In herpes-associated EM, antiviral treatment initiated after EM has erupted has shown no benefit. Symptomatic treatment—including local skin care, analgesics, and soothing mouthwashes—is important. Liquid antiseptics help prevent superinfection. A liquid diet may be necessary. Intravenous fluid replacement with electrolytes and nutrients should be started as early as possible. The use of systemic corticosteroids is controversial, some believing that it may increase the risk of complications.

Supplements

- Potassium iodide: 100 mg three times daily for 4 to 6 weeks, to be discontinued if there are adverse reactions
- Zinc sulfate: 0.025% to 0.05% solution applied locally to postherpetic lesions

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CHAPTER 165

Fibrocystic Breast Disease

Tori Hudson, ND

DIAGNOSTIC SUMMARY

- Common in reproductive-age women
- Pain or premenstrual breast pain and tenderness common, although condition often asymptomatic
- Characteristically cyclic and bilateral with multiple cysts of varying sizes, giving the breast a nodular consistency

GENERAL CONSIDERATIONS

Tender or lumpy breasts are among the most common reasons why women consult their health practitioners for assessment and treatment. The benign breast conditions that are present in almost all women of reproductive age to some degree should never have been labeled as disease. The widespread misconception that women with painful or lumpy breasts are at increased risk of breast cancer adds fuel to the fire for those already afraid of breast cancer. It would be much more useful to create descriptive categories of symptoms and conditions to replace the generic term *fibrocystic breast disease* (FBD). Nonetheless, we are left with a term that all health providers are familiar with, even though most agree that it would be better to describe and categorize these conditions more accurately.

Many women experience premenstrual pain or sensitivity. This may be attributed to a more prominent estrogen than progesterone effect on breast tissue at this time, when the effect of progesterone should normally be greater in the luteal phase. This does not necessarily mean that these women have lower or higher amounts of any particular hormone but may have an increased tissue sensitivity to estrogen with related fluid retention. Most women tolerate this discomfort perfectly well and can be merely reassured. Other women may need to employ lifestyle changes or use supplementation. Oral contraceptives, hormone replacement therapy, or both may similarly cause breast discomfort. These symptoms would be best described as physiologic cyclic pain and swelling.

Mastalgia, another descriptive category, refers to any breast pain severe enough to interfere with daily life and cause a woman to seek treatment. Women with cyclic mastalgia have this severity of pain about 15% of the time. Noncyclic severe pain is much rarer and may be due to infection, old trauma, or musculoskeletal conditions related to the chest wall.

Diffuse lumpiness may be either cyclic or noncyclic and may or may not include pain. Normal breasts can also include diffuse lumpiness due to glands, fat, and connective tissue. More prominent lumpiness and more numerous lumps set this apart from the normal state. Often this diffuse lumpiness is symmetrical and is an important finding in distinguishing a normal lump from a suspicious lump.

Even the majority of densities that are unilateral are benign. If the edge of the mass merges in one or more places with the surrounding breast tissue, it is considered nondominant. It is important to evaluate these masses and make a careful distinction between a dominant mass and a mass of concern. Evaluation may include fine-needle biopsy. The majority show some nonproliferative change, and about 20% show proliferative changes without atypical hyperplasia. None of these conditions places a woman at increased risk for breast cancer. Only the 5% who show atypical hyperplasia carry a significantly increased risk of breast cancer, especially when there is family history of a first-degree relative with breast cancer.[1]

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Dominant masses are noncyclic unilateral masses and distinct on all sides from the surrounding breast tissue. They persist over time and require thorough assessment except in the very young. They are either fibroadenomas or obvious cysts. Fibroadenomas are rubbery, smooth, benign fibrous tumors. They usually do not grow bigger. Cysts are softer and disappear when drained with needle aspiration. Fibroadenomas and cysts are not associated with an increased risk of breast cancer but must be distinguished from malignancies.

DIFFERENTIAL DIAGNOSIS

FBD cannot be definitively differentiated from breast cancer or fibroadenoma of the breast on clinical grounds alone. Pain, cyclic variations in size, high mobility, symmetry, and multiplicity of nodules are indicative of FBD. Noninvasive procedures such as mammography and ultrasonography can further aid differentiation. However, a definitive workup may include needle aspiration and fine-needle biopsy or excisional biopsy.

THERAPEUTIC CONSIDERATIONS

Discussion of premenstrual syndrome (see Chapter 202) may help to further elucidate factors that can influence FBD. The factors discussed here are not covered in depth in Chapter 202 and are particularly relevant to FBD.

Dietary Considerations

Methylxanthines

Epidemiologically,[2] experimentally,[3-5] and clinically[3-5] there is strong evidence supporting an association between methylxanthine consumption and FBD. Caffeine, theophylline, and theobromine are all known to inhibit the action of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate phosphodiesterase and to significantly elevate their levels in breast tissue.[3-5] In turn, increased levels of these cyclic nucleotides excessively stimulate protein-kinase activities and cause the overproduction of cellular products such as fibrous tissue and cyst fluid.

In one study, limiting methylxanthines (coffee, tea, cola, chocolate, and caffeinated medications) in the diet resulted in improvement in 97.5% of the 45 women who completely abstained, and in 75% of the 28 who limited their consumption. Those who continued with little change in their methylxanthine consumption showed little improvement.[3] According to this study, women may have varying thresholds of response to methylxanthines. However, three other studies have shown no association between methylxanthines and FBD.[6-8] Stress may also play an important role because fibrocystic breasts appear to be more responsive to epinephrine, the presence of which increases adenylate cyclase activity and hence cAMP production.

Fiber

A comparison between the diets of 354 women with benign proliferative epithelial disorders of the breast and those of 354 matched controls and 189 unmatched controls found an inverse association between dietary fiber and the risk of benign proliferative epithelial disorders of the breast.[9] An increased intake of dietary fiber may be associated with a reduced risk of both benign breast disease and breast cancer.

Soy

In an uncontrolled study, 64 premenopausal women consumed soy protein for 1 year. The women and their physicians reported a subjective reduction in both breast tenderness and FBD. Evaluation by breast-enhanced scintigraphy also showed that a nonstatistical reduction occurred in both the average and maximal breast tissue activity following 1 year of daily soy consumption. There was a statistically significant reduction ($P < 0.01$) in variability of tissue activity following 1 year of soy protein treatment.[10] These results are promising and included both objective and subjective findings consistent with a reduction in FBD.

Nutritional Supplements

Evening Primrose Oil

Several studies have examined EPO for both mastalgia and breast cysts. In one randomized controlled double-blind trial, 120 women were assigned to receive one of four treatments: (1) fish oil and control oil; (2) EPO and control oil; (3) fish oil and EPO; or (4) both controls.[11] Corn oil and corn oil with wheat germ oil were the control oils. The decrease in the number of days with pain was not significantly different between the groups. Pye et al, combined results from randomized trials and open studies that included 291 women with cyclic and noncyclic breast pain. Their report indicated a 45% response rate to EPO for cyclic mastalgia compared with 19% response rate in placebo groups. They also reported a 27% response rate to EPO in women with noncyclic mastalgia compared with a placebo response rate of 9%. Unfortunately, this publication did not provide sufficient information as to the details on the quality of the studies.[12] In another study, 73 women with breast pain randomly received 3 g/day of EPO or placebo. After 3 months, pain and tenderness were significantly reduced in both the women with cyclic breast pain and those with noncyclic pain. The women who took the placebo experienced no significant improvement.[13] A randomized trial of 36 women with severe cyclic or noncyclic mastalgia were randomly given 320 mg of gamma-linolenic acid/day from EPO or placebo for 4 months. After 4 months, no consistent clinical improvements were observed.[14]

One randomized controlled trial examined the effectiveness of EPO for recurrent breast cysts.[15] There was a slight but statistically significant reduction of breast cyst recurrence in women receiving EPO. Two hundred women with breast cysts were randomly assigned either six capsules per day of EPO or placebo for one year. Although there were fewer cysts in the EPO group (92 vs 113), this difference was not statistically significant.

Vitamin E

Alpha-tocopherol has been shown to relieve many PMS symptoms, particularly FBD, as evidenced by several double-blind clinical studies.[16,17] Two studies demonstrated that vitamin E is clinically useful in relieving pain and tenderness, whether cyclic or noncyclic.[18,19] The mode of action remains unclear. When larger numbers of women were studied, vitamin E did not fare so well, showing no significant effects either subjectively or objectively.[20,21] The results of the earlier studies were not duplicated until recently. In 2004, Bespalov et al studied the effects of supplementation with a combination of beta-carotene, vitamin E, vitamin C, and garlic powder in 66 women.[22] There was a reduction in the severity of mastalgia, premenstrual syndrome, infrequent menses, and menstrual cramping as well as a reduction in symptoms of fibromatosis in 75% of the women compared with 45% of women on placebo.

In 2009, there was a double-blind clinical trial of vitamin E supplementation in Iran that included 150 women.[23] Two groups of 75 women each were evaluated for severity and duration of

breast pain, which was measured according to a breast pain chart and a visual analog scale to gauge pain severity. Chewable tablets containing either vitamin E (200 mg) or placebo were given twice daily for 4 months. The severity and duration of pain were evaluated at the end of the second and fourth months, and the results at 2 months were dramatically better for the group receiving vitamin E than for those on placebo. Overall, such results appeared to be achievable in about 70% of the women. The improvement was seen as early as 2 months, and there was no further improvement at 4 months.

Vitamin A

Vitamin A has been only minimally studied for fibrocystic breasts. However, there are retinoid receptors in breast tissue, which can modulate breast changes. In a study of 12 women with fibrocystic breast disease, women were given 150,000 IU of vitamin A daily for 3 months. Five of the 9 patients who completed the study had full or partial remission of their FBD.[24] However, some patients developed mild side effects, leading 2 of the original 12 to withdraw because of headaches, and 1 patient required a reduction in dosage. Beta-carotene would appear to be a more appropriate source of retinol owing to its greatly decreased toxicity and similar activity in ovarian and inflammatory disorders (see Chapter 137). Nonetheless, some women will need supplemental vitamin A as a significant portion of the population has genomic variations that impair the conversion of beta-carotene to vitamin A (see Chapters 69 and 135).

Thyroid and Iodine

Experimental iodine deficiency in rats results in a mammary dysplasia histologically similar to human FBD.[23] In human patients, thyroid hormone replacement therapy in hypothyroid and some euthyroid patients may result in clinical improvement.[23,24] Research has shown that thyroid supplementation (0.1 mg/day of Synthroid) decreases mastodynia, serum prolactin levels, and breast nodules in supposedly euthyroid patients. These results suggest that subclinical hypothyroidism, iodine deficiency, or both may be etiologic factors in FBD.

Iodine (specifically iodine caseinate) may be an effective treatment for FBD.[25] It is theorized that an absence of iodine renders the epithelium more sensitive to estrogen stimulation. This hypersensitivity can produce secretions over the limit of absorption, thus distending the mammary ducts and producing small cysts and later fibrosis (hardening of the tissue owing to the deposition of fibrin, similar to the formation of scar tissue).

In studies in rats, it was shown that there is a hierarchical response to the type of iodine compound in correcting the abnormalities in mammary tissue due to iodine deprivation. Although iodides correct the cystic spaces and partially corrects the excessive cellular reproduction, iodine in its elemental form corrects the entire disease process. Thus, it appears that elemental iodine is the preferred form of iodine to enhance breast metabolism. Also, oral iodine supplementation is known to have significant antiinflammatory and antifibrotic effects in both acute and chronic experimental models.[26]

Human studies also indicate that elemental iodine may be more effective than iodides. Since 1975, three clinical trials have been performed in women with FBD[27]:

- An uncontrolled study with sodium iodide and protein-bound iodide
- A prospective controlled crossover study from iodide to molecular iodine
- A prospective controlled double-blind study with molecular iodine

Results from these studies indicate that although treatment with iodides was effective in about 70% of subjects, it was associated with a high rate of side effects (e.g., altered thyroid function in 4%, iodinism in 3%, and acne in 15%). Results with elemental iodine were about the same but were not associated with significant side effects. The most significant side effect with molecular iodine was a short-term increase in breast pain, which seemed to correspond to a softening of the breast and disappearance of fibrous tissue plaques on physical examination.

The dose of molecular iodine was 70 to 90 mg/kg body weight. This dose appears to be safe and effective in the treatment for FBD. The iodine supplements used in these studies (iodine caseinate and liquid iodine) are becoming available in the marketplace.

D
E
F

Herbal Supplements

Vitex Agnus-Castus (Chasteberry)

Chaste tree berry has been a very important plant for premenstrual syndrome (PMS) and premenstrual dysphoric disorder. The evidence for the use of chaste tree berry in the treatment of mastalgia has been reported in both randomized and non-randomized studies. A large open study (no control group) of 1634 women who experienced cyclic mastalgia as part of their premenstrual syndrome demonstrated that after 3 months of treatment, 80% of patients rated their response as good and 81% rated it as a very good treatment for their mastalgia.[28] In a prospective, multi-center trial using chaste tree in 50 patients with premenstrual cyclic mastalgia, 43 women were treated daily with chaste tree for three consecutive menstrual cycles.[29] By the end of the study period, cyclic mastalgia decreased significantly along with a smaller degree of improvement even 3 months after stopping the plant. Thirty-eight women rated the effectiveness as moderate to excellent, with 5 reporting no effect. In a randomized controlled trial, 97 women with cyclic mastalgia had twice the decrease in intensity of pain after one or two treatment cycles as compared with placebo.[30] The duration of pain also improved in the chaste tree group and half the women did not have severe pain at all during any time of the menstrual cycle and only 25% had severe pain for 4% of the days compared with severe mastalgia one fifth of the time before their use of chaste tree began. In a randomized trial of premenstrual dysphoric disorder, comparing chaste tree with an SSRI, 58% of patients being treated with chaste tree had an improvement in their cyclic mastalgia and 68% of patients had improvements in their psychological symptoms.[31] In a randomized controlled placebo controlled trial, 170 women were given chaste tree or placebo for three consecutive cycles. The improvement in breast pain was greater in the chaste tree group (52%) compared with the placebo group (24%).[32]

Other Considerations

Liver Function

Because FBD may be related to an increased sensitivity to estrogen and the liver is the primary site of estrogen clearance, any factor (e.g., cholestasis, "toxic liver syndrome," environmental pollution, or other hepatic compromise) that interferes with proper liver function may lead to an increased effect of estrogen on a particular estrogen-sensitive tissue. Adequate levels of lipotropic factors and B vitamins are necessary for estrogen conjugation.

Colon Function

Breast disease has been linked to the Western diet and bowel function. There is an association between epithelial dysplasia in

nipple aspirates of breast fluid and the frequency of bowel movements.[33] Women having fewer than three bowel movements per week have a risk of FBD 4.5 times greater than those having at least one a day.

This association is probably due to the bacterial flora in the large intestine transforming endogenous and exogenous sterols and fatty acids into various toxic metabolites, including polycyclic carcinogens and mutagens.[34] Fecal microorganisms are capable of synthesizing estrone, estradiol, and 17-methoxyestradiol as well as metabolizing estrogen sulfate and glucuronate conjugates,[35] resulting in the absorption of bacteria-derived estrogens and reabsorption of previously conjugated estrogen. Diet plays a major role in determining colonic microflora, transit time, and the concentration of absorbable metabolites.[35]

Women on vegetarian diets excrete two to three times more conjugated estrogens than those who are omnivorous, who also reabsorb more estrogens.[33] Furthermore, omnivorous women have 50% higher mean levels of unconjugated estrogens. Supplementation with *Lactobacillus acidophilus* has been shown to lower fecal β-glucuronidase.[36]

THERAPEUTIC APPROACH

Some women have noncyclic FBD and others have cyclic premenstrual breast tenderness and lumpiness, so the therapeutic approach outlined in Chapter 202 may be more appropriate for individual needs. The therapy recommended here also includes some of the key factors discussed in Chapter 202.

Diet

The diet should be primarily vegetarian, with large amounts of dietary fiber. All methylxanthines should be eliminated until symptoms are relieved. At that point methylxanthines can be reintroduced in small amounts. Reducing the fat content of the diet to 15% of total calories while increasing the consumption of complex carbohydrates has been shown to reduce the severity of premenstrual breast tenderness and swelling as well as the nodularity in some women.[37] Reducing the dietary fat intake to 20% of total calories results in significant decreases in circulating estrogens in women with benign breast disease.[38] Exogenous estrogens should be avoided, as they may exacerbate the condition (these include oral contraceptives, hormone replacement therapy, and estrogen-augmented animal products). The diet should emphasize whole unprocessed foods (whole grains, legumes, vegetables, fruits, nuts, and seeds). Patients should be encouraged to drink at least 48 oz of water daily.

Nutritional Supplements

- Lipotropic factors: 1000 mg of choline and 1000 mg of either methionine and/or cysteine a day. Alternatively, S-adenosylmethionine (SAMe) can be used at a dosage of 200 to 400 mg a day.
- Vitamin E: 400 to 800 IU/day of D-alpha tocopherol
- Beta-carotene: 50,000 to 300,000 IU/day
- Iodine (aqueous iodine): 3 to 6 mg/day (a prescription item)
- Evening primrose oil: 1500 mg twice a day

Botanical Medicines

Vitex (chaste berry): The usual dosage of chaste berry extract (often standardized to contain 0.5 percent agnuside) in tablet or capsule form is 175 to 225 mg per day. If using the liquid extract, the typical dosage is 2 to 4 mL (1/2 to 1 tsp) a day.

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CHAPTER 166

Fibromyalgia Syndrome

John C. Lowe, MA, DC

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DIAGNOSTIC SUMMARY

- Common: 2% to 13% of population; approximately 80% to 90% women
- Chronic widespread pain involving axial pain and pain on the left, right, upper, and lower parts of body[1]
- Abnormal tenderness at 11 or more of 18 specific anatomic tender point (TnP) sites[1] (Figure 166-1)

DIAGNOSIS

The 13 most common symptoms associated with the pain and tenderness of fibromyalgia syndrome (FMS) [2-4] are listed in Box 166-1.

Differential Diagnosis

The purpose of the 1990 American College of Rheumatology (ACR) criteria for FMS was to distinguish patients with a putative primary disorder designated FMS from those with similar symptoms due to other distinguishable medical disorders. The two major criteria for FMS are chronic (longer than 3 months) widespread pain and tenderness.[1] The criteria were established mainly for use in research that would eventually identify the underlying pathologic mechanism of the symptoms, but they have come to serve as diagnostic criteria in clinical practice.

Some theorists have argued that widespread pain and tenderness at predictable anatomic sites are features of many medical disorders.[5] Their argument is true only of hypothyroidism and cellular resistance to thyroid hormone, especially when the associated symptoms of FMS are also taken into account. When most patients with hypothyroidism or cellular resistance to thyroid hormone meet the ACR criteria for FMS and are effectively treated with thyroid hormone therapy, they no longer meet the FMS criteria.[6-15] This finding indicates that these patients' FMS symptoms and signs are a distinct clinical phenotype of inadequate thyroid hormone tissue regulation.[16] It also justifies a trial of thyroid hormone therapy to distinguish whether a patient's FMS symptoms and signs are features of hypothyroidism or cellular resistance to thyroid hormone.

The theorists' argument does not apply to other medical disorders, however, and is refuted by two lines of evidence.[17] First, studies have not established that chronic widespread pain and multiple TnPs are features of other medical disorders. Second, many patients with rheumatoid arthritis, osteoarthritis, Lyme disease, systemic lupus erythematosus, Chiari malformation, and spinal stenosis also meet the ACR criteria for FMS, but when these other disorders are effectively treated, the patients still meet the criteria for FMS.[18-20]

The argument is false, then, that chronic widespread pain and tenderness are features of many medical disorders. Nonetheless, the argument highlights the need to differentiate FMS from other disorders with similar symptoms that may lead the clinician to misdiagnose FMS. The main disorders the clinician should distinguish from FMS are arthritis, myopathy, polymyalgia rheumatica, diabetic polyneuropathy, ankylosing spondylitis, discopathy, cardiac or pleural pain,[21] multiple muscle myofascial pain syndromes,[22] and lupus erythematosus. A given patient may, of course, concurrently meet the criteria for FMS and one or more other disorders with overlapping symptoms. FMS can usually be distinguished from medical disorders other than hypothyroidism and cellular resistance to thyroid hormone by careful

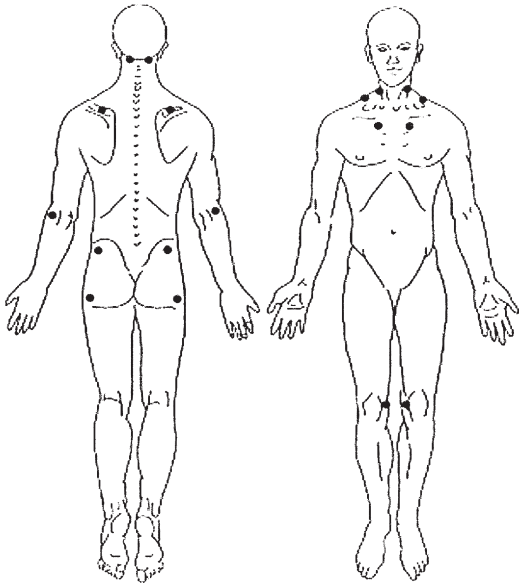


FIGURE 166-1 Locations of 18 anatomic tender point sites. (Copyright John C. Lowe.)

BOX 166-1 Most Common Associated Symptoms in Fibromyalgia Syndrome

- Fatigue
- Stiffness
- Headache
- Sleep disturbance
- Irritable bowel
- Depression
- Cognitive dysfunction
- Anxiety
- Coldness
- Paresthesias
- Sicca symptoms
- Exercise intolerance
- Dysmenorrhea

From references 6, 7, 11-13, 16, 110, 115, 116, and 173.

pathognomy. However, diagnostic scrutiny will show that the symptoms and signs of most FMS patients are indistinguishable from those of the subclass of hypothyroid and thyroid hormone–resistant patients for whom pain is a predominant symptom.

GENERAL CONSIDERATIONS

Current Focus of the Conventional Fibromyalgia Research Community

The serotonin deficiency hypothesis is the oldest proposed mechanism of FMS.[23-25] As a research-inspiring concept, it constituted the core theoretical underpinning of the rheumatology paradigm of FMS. This hypothesis proposed that a central nervous system (CNS) serotonin deficiency reduced the efficiency of the brainstem–spinal cord descending antinociceptive system, lowering the threshold for pain perception.[26] By 2000, the serotonin deficiency hypothesis had been effectively refuted[16] by three lines of evidence: First, the only site of low serotonin among FMS patients was their platelets.[26-28] Second, serotonin-increasing drugs were no more effective than placebos[29,30-34] and exacerbated some patients' FMS status.[35] And third, the low brain blood flow of FMS patients[36,37] contradicts a serotonin deficiency; serotonin is a potent vasoconstrictor,[38] and a low CNS level would produce cerebral vasodilation and increased blood flow.

This was further documented in the 2005 publication of the state of that paradigm.[39] The central theoretical viewpoint of the former paradigm had shifted from a serotonin deficiency to a generalized problem of augmented pain processing resulting in a hyperalgesic state,[39,40] which is plausibly explained by the extraordinarily high levels of substance P in patients with FMS.[41] But researchers espousing the former paradigm have failed to address the most plausible mechanism of the patients' high levels of substance P (see following section). Instead, their main efforts have been to develop pharmaceuticals to manage FMS pain. This has led to the approval of several drugs by the U.S. Food and Drug Administration for FMS and the recommendation that patients undergo education about FMS as well as psychotherapy and aerobic, strength, and flexibility training.[40]

Hypometabolism Hypothesis of Fibromyalgia Syndrome

The hypometabolism hypothesis posits that FMS is chronic hyperalgesia and other symptoms and signs of hypometabolism due to hypothyroidism, partial cellular resistance to thyroid hormone, or other metabolism-impeding factors. Among the other factors said to be responsible are pernicious diet, nutritional deficiencies, low physical fitness, and metabolism-impeding drugs. The term *hypometabolism* refers to the global impact on the patient of the underlying factors, most of which are catabolic and inhibitory, although some are anabolic or excitatory.[16]

Considerable evidence indicates that inadequate thyroid hormone regulation (ITHR) due to hypothyroidism or cellular resistance to thyroid hormone is the underlying mechanism of the two main features of FMS: chronic widespread pain and abnormal tenderness. ITHR of metabolic processes in cells of the brainstem–spinal cord descending antinociceptive system can result in chronically enhanced pain perception. Impairment of the antinociceptive system in FMS patients results in the following:

- Spontaneous or ongoing pain
- Tenderness (lowering of the pain threshold to mechanical stimuli)
- Hyperalgesia (increased responsiveness to noxious stimuli)[43,44]

ITHR can impair the antinociceptive system by two mechanisms. First, ITHR can severely increase production of substance P, which is extremely high in the cerebrospinal fluid (CSF) of tested FMS patients.[41] Substance P is released from the terminals of nociceptive neurons[42] and assists the summation of slow nociceptive signals.[45] This facilitation amplifies the transmission of nociceptive signals in the spinal cord.[46] Thyroid hormone normally inhibits the synthesis and secretion of substance P in many CNS cells. It does so by repressing the transcription of the preprotachykinin-A gene. Preprotachykinin-A is the precursor of substance P and its cognate substance P receptor.[47,48] Lowering thyroid hormone levels by thyroidectomy increased the substance P level in astrocytes[48]; anterior pituitary[49-51]; many brain nuclei[52]; and, most relevant to pain, the dorsal horns of the lumbar spinal cord. The increase in dorsal horn substance P was highly elevated (100%),[53,54] as in FMS patients.[41] Thyroid hormone treatment lowered the substance P level in the anterior pituitary,[50] brain nuclei,[55] and dorsal horns.[54] Excess thyroid hormone reduced substance P to subnormal levels.[51]

D
E
F

The second mechanism by which ITHR can reduce the effectiveness of the antinociceptive system is by reducing the synthesis and secretion of norepinephrine (NE) in cells of the brainstem locus ceruleus. Adequate NE is essential to normal function of the descending antinociceptive system.[56,57]

The antinociceptive pathways that descend from the brainstem to the dorsal horns contain two types of neurons: those that secrete serotonin and others that secrete NE.[20,56,58,59] Serotonin secretion by the neurons is tonically augmented by NE secretion. Normal serotonin secretion is therefore dependent on NE secretion.[54] The serotonin stimulates interneurons to secrete opiates.[56,58,60] These then inhibit transmission partly by blocking release of neurotransmitter substances such as glutamate and substance P from the afferent neurons.[61] They also block calcium influx and potassium efflux from the afferent terminals,[62] mainly those of types C and A delta fibers.[63] The decreased potassium efflux hyperpolarizes terminals, inhibiting the transmission of nociceptive signals to spinothalamic neurons that otherwise would transmit the signals to the brain.[64] Low NE secretion by descending neurons, however, may reduce the secretion of serotonin selectively at dorsal horn interneurons and secondarily reduce opiate secretion. As a result, the transmission of nociceptive signals in the CNS will increase, thus heightening pain perception.

That decreased NE production is involved in the heightened pain perception of FMS patients is indicated by low metabolites of both dopamine and NE in patients' CSF.[27] That inadequate T_3 regulation of locus ceruleus neurons accounts for the low NE production is suggested by the crucial role T_3 plays in the synthesis of both dopamine and NE. The locus ceruleus is the brain site with the heaviest concentration of T_3.[65-67] Thyroid hormone regulates the activity levels of two rate-limiting enzymes in dopamine and NE synthesis.[68] One enzyme, tyrosine hydroxylase, catalyzes the conversion of tyrosine to levodopa, which in turn is converted to dopamine.[69] Tyrosine hydroxylase activity in the noradrenergic neurons of the locus ceruleus is low in hypothyroidism.[70] Low activity of the enzyme and reduced conversion of levodopa to dopamine may be responsible for low dopamine levels in the striatum, hypothalamus, and superior cervical ganglia in hypothyroidism.[68] Thyroid hormone therapy increases the activity of tyrosine hydroxylase.[70] The second enzyme, dopamine-β-hydroxylase, catalyzes the conversion of dopamine to NE. Low activity of the enzyme in hypothyroidism can reduce NE levels.[68] Unfortunately, NE levels in the antinociceptive system and other tissues in thyroid disorders have not been studied extensively[71] enough to support this putative mechanism.

By raising substance P levels and possibly lowering NE levels in the spinal cord, ITHR can thus plausibly heighten FMS patients' pain perception. Patients' pain, however, is probably compounded by other factors. First, most FMS patients are physically inactive because of their pain,[72,73] although low motor drive from low dopamine levels[27] probably contributes to their inactivity. Their low physical activity level may further contribute to the inefficiency of the antinociceptive system.[74-76]

ITHR can also plausibly account for the other symptoms and objectively verified abnormalities of FMS: muscle and joint pain, paresthesias, cognitive dysfunction, depression, cold intolerance, exercise intolerance, weakness and fatigue, dry skin and mucous membranes, constipation, dysmenorrhea, and menorrhagia,[77,78] increased platelet α_2-adrenergic receptor density,[79,80] reduced brain blood flow,[81] reduced peripheral blood flow,[82] sleep disturbance,[83] deficient slow-wave sleep,[84] hypotension,[85] blunted sympathetic response to stress,[86] stiffness and swelling,[87] irritable bowel syndrome,[88] excessive urination,[83] high serum hyaluronic acid,[89] low procollagen III,[90] high ground substance proteoglycans,[91] low pyridinoline[92] and hydroxyproline,[93] glycolysis abnormalities,[94] low concentrations of high-energy phosphates in erythrocytes and muscle cells,[95,96] and low growth hormone and somatomedin C levels.[97] The cellular and genomic actions of thyroid hormone can explain the hormone's relationship to all of these factors.[16] Especially important is thyroid hormone's effect on the adrenergic system. If the hypometabolism hypothesis is verified at some point in the future, the definition of fibromyalgia will include an explanation of FMS as a condition of α-adrenergic dominance.

Experimental Support for the Hypometabolism Hypothesis of Fibromyalgia Syndrome

The hypothesis that ITHR is an underlying mechanism of FMS has considerable experimental support.[98] Many researchers have noted the virtually identical features of FMS, hypothyroidism, and the peripheral form of cellular resistance to thyroid hormone.[16,99-114]

Several research groups have used thyroid function testing to determine the incidence of thyroid disease among FMS patients. Each group has reported an incidence higher than in the general population.[99-109] A thorough analysis of all the available evidence indicates that approximately 90% of FMS patients have some form of thyroid disease, either primary or central hypothyroidism or cellular resistance to thyroid hormone.[115,116]

In two studies, 15 female FMS patients had low resting metabolic rates (RMRs) and basal axillary temperatures compared with 15 matched healthy controls. In both studies, the controls' mean RMR was within the reference range predicted by equations. However, in the first study, the mean RMR of FMS patients was 29.2% below normal based on their gender, age, height, and weight.[117] In the second study, FMS patients' mean RMR was 32.5% below normal.[118] In both studies, FMS patients' basal temperatures were significantly lower than those of controls. In the first study,[117] FMS patients' mean basal temperature was 96.95° F (36.08° C). In the second study,[118] the mean temperature of FMS patients was 96.38° F (35.77° C).

The only clinical trials in which patients have been fully relieved of FMS have involved orally administered thyroid hormone. It should be noted, however, that in each study patients also used other metabolism-regulating therapies (see later discussion on metabolism-regulating therapies other than thyroid hormone). Euthyroid and hypothyroid FMS patients fully recovered in five open but highly systematic trials,[6-10] three double-blind placebo-controlled crossover trials,[11-13] and a randomized double-blind placebo-controlled trial.[14] In another randomized double-blind trial, FMS patients had limited improvement with the use of transdermal T_3.[119] A 1- to 5-year follow-up study compared the status of control FMS patients with FMS patients who had either hypothyroidism or cellular resistance to thyroid hormone and underwent metabolic therapy, including the use of thyroid hormone. Although control patients' FMS status deteriorated, treated patients recovered and maintained their recovery throughout the follow-up period. Results of this study were the first to demonstrate the long-term effectiveness of an FMS treatment.[15]

Metabolism-Regulating Therapies Other Than Thyroid Hormone

Thyroid hormone therapy is necessary in most cases of FMS to ensure recovery, but it is not sufficient. For example, in a study of 77 euthyroid FMS patients,[6] those who declined to adopt a

wholesome diet, take nutritional supplements, and exercise to tolerance were among the 25% who failed to benefit from T_3 therapy. This result is consistent with years of clinical experience supporting the necessity for patients to use other metabolism-regulating therapies in addition to thyroid hormone. A common experience, for example, is a recovered patient stopping her use of B complex vitamins only to suffer a partial recurrence of FMS symptoms. The symptoms are again relieved when she resumes her use of the vitamins.

The most common other metabolism-regulating therapies that patients must use are a wholesome diet, nutritional supplementation, and exercise to tolerance. These therapies are necessary for most patients to recover fully. But except for the rare exception, they are not sufficient and must be used along with thyroid hormone therapy. This is shown by studies indicating that these therapies alone provide some improvement but that patients do not recover fully (they continue to meet the criteria for FMS). In addition to the metabolic therapies, most FMS patients also require some physical treatment for full relief of their FMS pain.

Wholesome Diet

Various diets and dietary supplements have been tested as FMS treatments. Mild-to-moderate improvements in FMS status have been reported for vegetarian diets[120,121]; elimination of the excitotoxins monosodium glutamate and aspartame[122]; *Chlorella pyrenoidosa* (a unicellular freshwater green alga rich in proteins, vitamins, and minerals)[123,124]; an uncooked vegan diet consisting of berries, fruits, vegetables and roots, nuts, and germinated seeds and sprouts[125]; and a strict, low-salt, uncooked vegan diet rich in lactobacteria.[126]

Nutritional Therapies

Long clinical experience shows that a wide array of nutritional supplements is necessary if FMS patients are to improve significantly or recover. As the sole treatment, however, supplements provide only mild improvement except for the rare patient.

Studies indicate that vitamins B_1, B_6, B_{12},[56,127-135] C,[136-140] and E, and beta-carotene[141] have antinociceptive properties. Other reports indicate that various nutritional supplements improve FMS status: the Myers' cocktail (intravenous formula of B vitamins, vitamin C, calcium, and magnesium)[142]; 5-hydroxytryptophan[143,144]; S-adenosylmethionine[145-148]; magnesium and malic acid[149,150]; combined aloe vera extracts, plant saccharides, freeze-dried fruits and vegetables, *Dioscorea,* and a vitamin/mineral complex[151]; collagen hydrolysat[152]; and a blend of ascorbigen and broccoli powder.[153]

Exercise to Tolerance

The results of studies of exercise in the treatment of FMS have been mixed: some have shown no improvement in FMS status[35,69,154,155-157] or only minimal improvement.[158-163] Cardiovascular exercise has provided the most improvement,[160-163] especially low-intensity endurance training.[163,164] Endurance exercise is important in reducing the physical limitations associated with FMS.[165] The importance of physical fitness and the high metabolic efficiency it provides[166,167] was shown by deficient slow-wave sleep, inducing FMS-like symptoms in sedentary and not aerobically fit students.[23] This finding suggests that low metabolic efficiency due to ITHR renders some individuals susceptible to FMS.[16]

Vigorous exercise tends to exacerbate patients' FMS symptoms.[72,73] As a result, some patients avoid exercise altogether and consequently are not physically fit.[165,168-170] The most plausible explanation for the exacerbations on vigorous exercise is the high-density of α_2-adrenergic receptors on FMS patients' platelets.[171] Platelet density of α_2-adrenergic receptors is a reliable indicator of the receptor density in the CNS.[172] Binding of catecholamines to a high density of the receptors on cells of most tissues inhibits energy metabolism. The inhibition of energy metabolism during vigorous exercise, mediated by the high density of the receptors, appears to worsen symptoms severely. During the early phase of treatment, then, exercise should be mild enough to avoid or minimize catecholamine secretion.[16] With effective thyroid hormone therapy, the density of α_2-adrenergic receptors decreases and the density of β-adrenergic receptors increases, enabling cells to respond appropriately to high levels of catecholamines. The shift away from α_2-adrenergic receptor dominance probably explains in part the FMS patient's ability to engage in vigorous physical activity after receiving thyroid hormone therapy.[6,7,8,11-13,15]

Physical Treatment

Extensive clinical experience and clinical trials[7,8,11-13] show that despite the use of integrated metabolic therapies, many patients require physical treatment to fully relieve their FMS pain.[173-176] Several studies have shown that spinal manipulation, soft tissue manipulation, and trigger point therapy provide palliative improvement in some FMS symptoms, especially pain.[177-180]

The most common lesions that exacerbate FMS symptoms are myofascial trigger points and spinal joint fixations.[16,174,181] However, any nociception-generating neuromusculoskeletal lesion may exacerbate FMS patients' pain, probably owing to their high levels of substance P.[40] Neuromusculoskeletal lesions can also disturb sleep.[182-184] This can, in turn, increase FMS symptoms.[23]

Summary

It appears, then, that for most FMS patients to improve or recover, integrated metabolic therapies that include the use of thyroid hormone are necessary and sufficient, whereas no single metabolic therapy is sufficient in itself. In addition, physical treatment may be necessary to eliminate most FMS patients' pain completely.

THERAPEUTIC CONSIDERATIONS

Laboratory Testing for Thyroid Status

Thyroid Function Tests

Before beginning an FMS patient's treatment, his or her thyroid status should be determined with thyroid function tests. Primary hypothyroidism (thyroid hormone deficiency due to subnormal function of the thyroid gland) in most patients can be determined with the standard thyroid panel:

- Free T_3, free T_4, and thyroid-stimulating hormone (TSH)

In untreated primary hypothyroidism, the TSH is elevated. The recently revised upper limit of the serum TSH reference range is 2.5 μIU/mL.[185]

Thyroid Antibodies

The most common cause of primary hypothyroidism is autoimmune thyroiditis. The presence of this disorder can be determined by the patient's titer of thyroglobulin and thyroid peroxidase (microsomal) antibodies. It is especially important to order tests of antibody levels in FMS patients. Many patients who have elevated thyroid antibodies have also had thyroid function test results within the reference ranges for many years.[187,188] But compared

with people without chronic, widespread musculoskeletal complaints, those with such complaints were found to have a significantly higher incidence of thyroid microsomal antibodies (16% vs. 7.3%, P <0.01). The prevalence of antibodies was also significantly higher in women than men (20.4% vs. 11.6%, P <0.02). However, thyroid function test results did not differ significantly between those with and without musculoskeletal complaints.[119] This study indicates that in patients with autoimmune thyroiditis, thyroid hormone levels too low to properly regulate the CNS antinociceptive system and properly inhibit the production of substance P can escape detection by thyroid function tests, including the TSH.

Thyroid Hormone Therapy Based on Initial Thyroid Status

FMS patients whose test results indicate hypothyroidism should begin therapy with a thyroid hormone preparation containing both T_4 and T_3. Many hypothyroid FMS patients do not benefit from T_4 alone no matter how high the dosage.[189] Most do benefit, however, from the use of T_4/T_3 preparations in a 4:1 ratio. The dosage range at which most patients improve or recover with T_4/T_3 preparations is that which was used throughout the twentieth century without harmful effects[190] before TSH assays came into widespread use in the early 1970s: 2 to 4 grains (76 mg T_4 and 18 mg T_3 to 152 mg T_4 and 36 mg T_3).[16,191]

The thyroid hormone therapy used in studies in which hypothyroid and euthyroid FMS patients recovered[6-14] was not conventional T_4-replacement therapy. Although T_4 was used in some studies,[9,10,14,15] it was T_4/T_3 preparations and T_3 alone used in a way that violated the mandates of T_4 replacement. Specifically, patients were permitted to use thyroid hormone despite laboratory test results indicating that they were euthyroid, and doses were not titrated according to TSH levels but by patients' clinical responses to particular doses.

Effective doses usually suppressed TSH levels. Despite this, patients did not have symptoms of thyrotoxicosis, nor did they have evidence of thyrotoxicosis according to electrocardiography, bone densitometry, or serum and urine biochemical test results.

FMS patients whose laboratory test results indicate euthyroidism should begin with T_3. In studies of the thyroid status of FMS patients at intake, approximately 33% were euthyroid according to thyroid function testing.[186,192] Of these patients, approximately 75% have partial peripheral cellular resistance to thyroid hormone according to four criteria[115,116]:

1. The patients are euthyroid (according to laboratory thyroid function test results) before beginning the use of T_3.
2. The patients recover from their hypothyroid-like FMS symptoms and signs with supraphysiologic doses of T_3.
3. The patients have high serum-free T_3 levels after beginning T_3 therapy.
4. The patients have no evidence of tissue thyrotoxicosis, according to the results of serial ECGs, serum and urine biochemical tests, and bone densitometry.

These patients usually benefit only from immediate-release T_3 (*not* sustained-release T_3) in a single daily dose.[16] They are likely to respond only to supraphysiologic doses of T_3. Effective T_3 dosages for most patients are between 75 and 125 mg. For some patients, however, safe and effective doses are far higher.[16]

Some FMS patients have both hypothyroidism and cellular resistance to thyroid hormone.[8] Most of these patients improve or recover only with T_3 therapy, typically supraphysiologic doses.

The Basis of Dosage Adjustments

After a patient's thyroid status has been determined and thyroid hormone therapy begun, dosage changes should be titrated according to symptom status and physiologic measures, not according to thyroid function test results. Thyroid function tests are of no value in finding the safest and most effective dosage for any particular patient.[193] There is no scientific justification for inferring the metabolic status of cells (other than the thyrotrophs of the anterior pituitary) from thyroid function test results. The belief that tissue metabolic status can be accurately inferred from TSH or thyroid hormone levels is a postulate, not a research-derived conclusion. This postulate was found to be false, at least for rats, by studies showing that the levels of T_3 and T_4 in the cells of different tissues cannot be accurately predicted from plasma levels of TSH, T_3, or T_4.[194,195] Moreover, some studies show that TSH levels correlate poorly with measures of the tissue effects of thyroid hormone, such as the speed of the relaxation phase of the Achilles reflex.[196] Conversely, other studies show that the patient's symptoms and signs are far more accurate and reliable indicators of tissue metabolic status than are the results of thyroid function tests.[193,197]

The RMR measured with indirect calorimetry is the most reliable measurement of oxidative metabolism, which is strongly regulated by thyroid hormone. In a study designed to find a correlation between patients' RMRs and their TSH levels, a significant correlation was obtained only by log transforming the TSH values.[198] The lack of a significant correlation without log transformation means that the TSH is not a useful tool for determining whether an individual patient's thyroid hormone dosage is providing him or her with sufficient oxidative metabolism. Preferably, clinicians will include indirect calorimetry in their clinical practices. However, this instrument is not necessary for finding patients' safe and effective dosages.

Rehabilitation Model: Data-Driven Clinical Decisions

The clinician should distinguish as clearly as possible all the various factors impairing the individual patient's metabolism. Next, the clinician should provide the patient with an individualized treatment regimen designed to correct, eliminate, or compensate for the causative factors. The treatment regimen that is most effective for guiding the FMS patient to recovery conforms to a rehabilitation model, which requires baseline and repeated monitoring of the patient's clinical status through objective assessment methods. Thus, clinical decisions, such as thyroid hormone dosage adjustments, are data-driven.

Objective Assessment of Patient Status

The FMS patient's recovery of normal metabolism, a symptom-free state, and full function occurs gradually over a range of 2 to 6 months. Because of the time involved, it is best for the clinician to quantify the patient's clinical status through objective measures at weekly or biweekly intervals. Scores from these measures should be posted as data points to line graphs after each evaluation. The patient's baseline score on each measure (taken before therapy is begun) is the initial data point on each graph.

Next, a line should be drawn through the data points to create a trend line that makes obvious, on visual inspection, changes in the patient's clinical status. The trend lines of the data points on the graphs thus help the clinician to assess the effectiveness of the patient's regimen at any point during treatment. In this way, the lines enable the clinician to make informed, data-driven decisions about any treatment changes needed to optimize clinical results.

The five line graphs in Figure 166-2 show the changes in FMS measures during metabolic rehabilitation of a euthyroid FMS patient reported by Honeyman-Lowe.[9] Typically, all measures change together in a direction of improvement, no improvement, or worse. The patient's subjective status usually corresponds closely to what the trend lines indicate.

During the course of the rehabilitation process, patients and clinicians often lose sight of the severity of the patient's clinical status before treatment. When patients occasionally experience a brief or mild exacerbation of symptoms, they are especially prone to forget the progress they have made. For some, this state of mind can lead to the false conclusion that they have made no progress at all. This false conclusion is quickly corrected, however, by a review of the patients' graphs, which show visually and objectively their real progress.

The five objective assessment methods that should be used at each patient evaluation are described as outlined below. The clinician should also perform a physical examination at each evaluation to further assess the patient's changing tissue metabolic status.

Pain Distribution Body Form

Four studies have shown that the most sensitive indicator for changes in FMS status is the pain distribution as a percentage of the body in pain.[11-13,162,199] This is convenient in that chronic widespread pain is one of the two major criteria for the assessment of FMS status.[1]

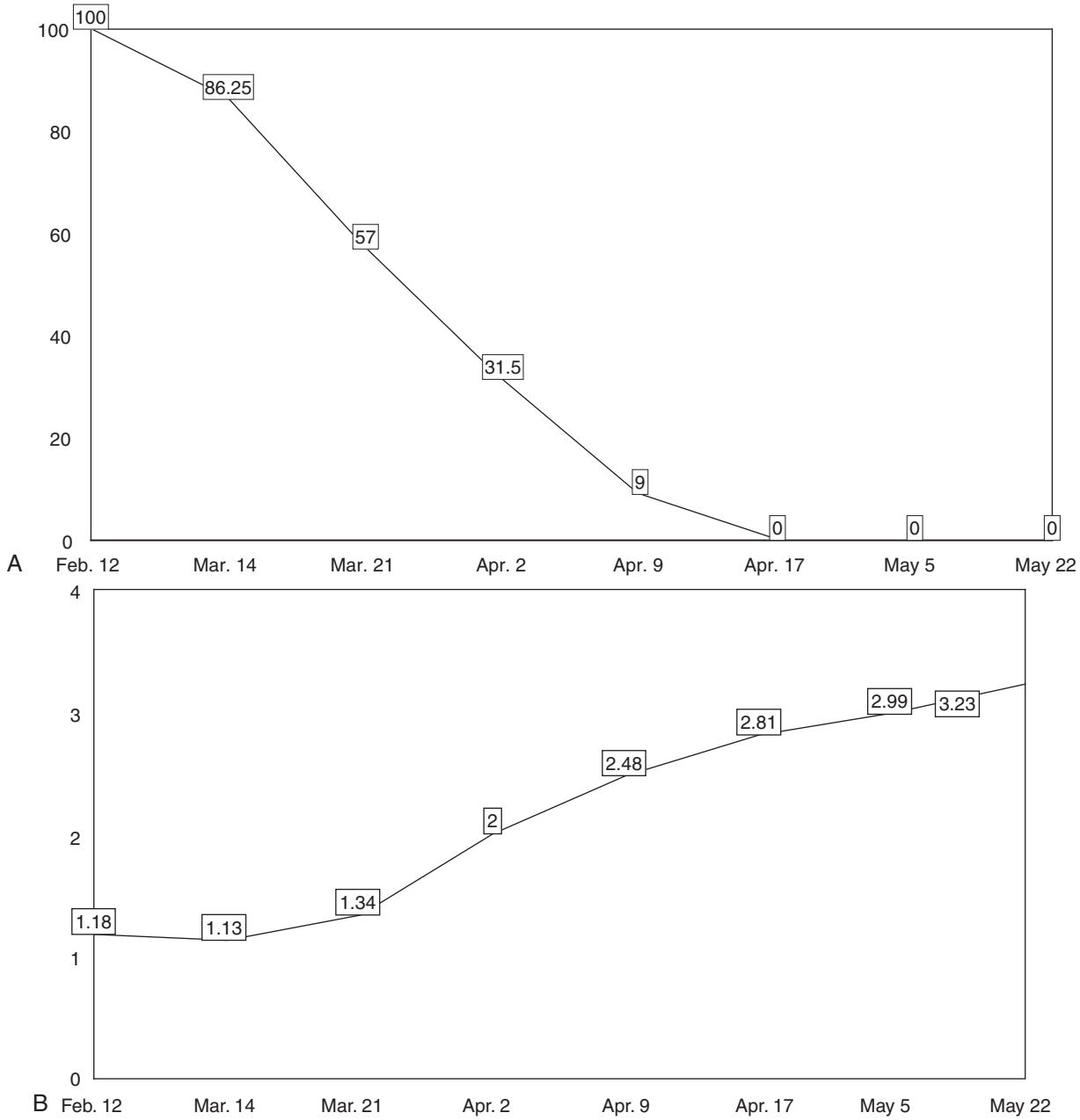


FIGURE 166-2, cont'd C, Decreases in mean intensity of fibromyalgia syndrome symptoms as calculated from the FibroQuest form. **D,** Decreasing scores on the Fibromyalgia Impact Questionnaire. **E,** Decreasing scores on Zung's Self-Rating Depression Scale.

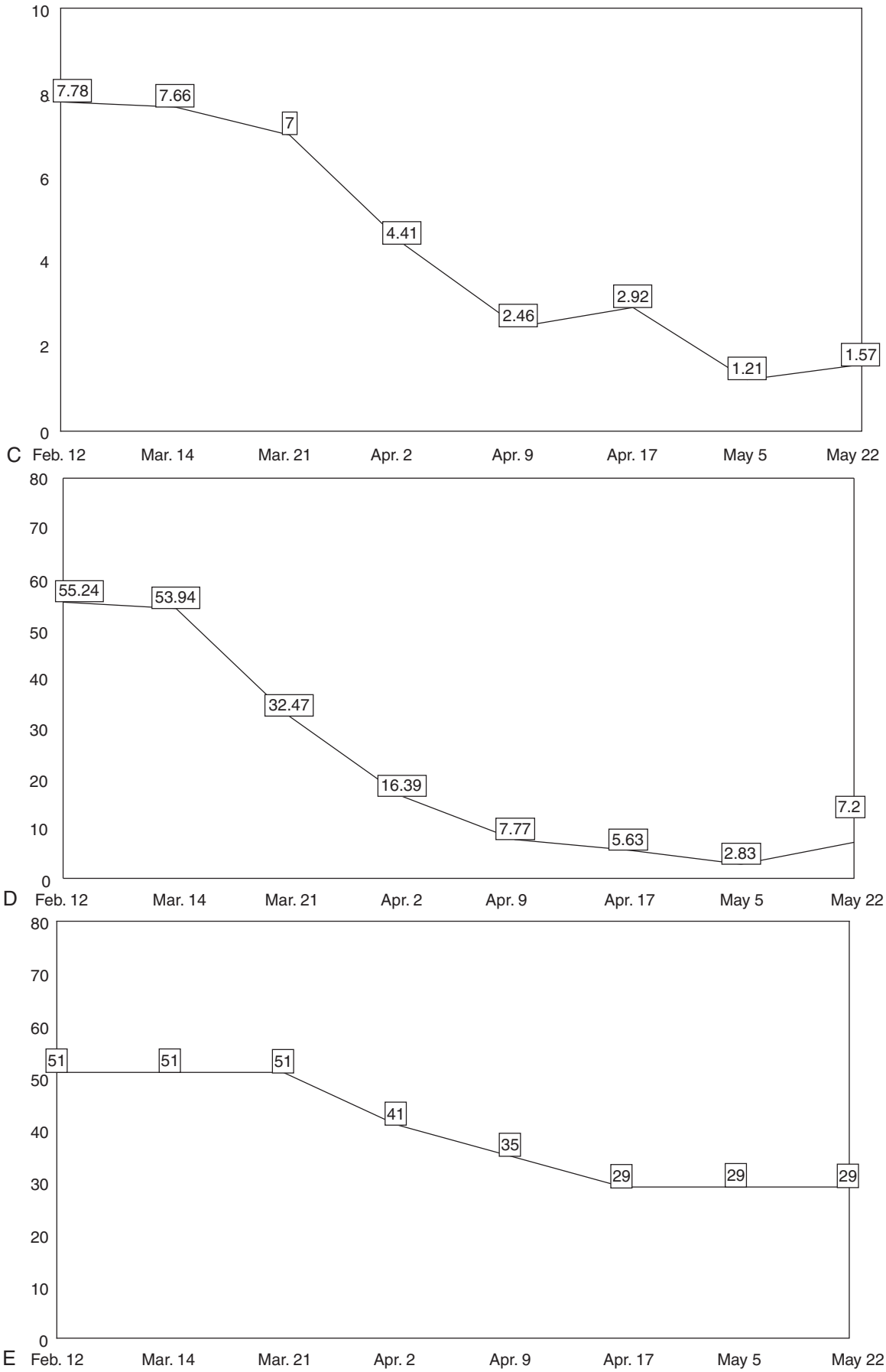


FIGURE 166-2 A, Pain distribution. Scores show the percentage of 36 body divisions containing pain at each evaluation (determined by the patient's pain drawing). At each evaluation, the percentage was posted to the graph. **B,** Increases in mean tender point pressure/pain threshold during metabolic rehabilitation.

Small changes in pain distribution are assessed by using a form containing drawings of the body. The patient precisely shades in where he or she has had aching, pain, soreness, or tenderness since the last evaluation. Next, a template is placed over the patient's shaded form, which shows the body form divided into 36 areas. Each of the 36 divisions has a percentage value.[16,11-13] To obtain the patient's pain distribution, the values of the shaded divisions are totaled. This percentage number is placed on a graph as a data point. The data points for each evaluation are connected by a line showing the trend of the pain distribution over time.

Mean Pressure/Pain Threshold of Tender Point Sites

The second major criterion for the assessment of FMS is the presence of tender point sites (TnPs).[1] A modified version of the TnP examination measures the pressure/pain threshold of TnPs with algometry (numeric values in kilograms per square centimeter). This provides more precise quantification than the 1990 ACR method and enables the clinician to make more objective, evidence-based decisions.[200] The mean of the threshold values is calculated and posted to a line graph.

FibroQuest Symptoms Survey

This assessment form consists of 100-mm visual analog scales (VASs), 1 for each of the 13 most common associated FMS symptoms.[2] These symptoms are also characteristic symptoms of hypothyroidism and the peripheral form of cellular resistance to thyroid hormone (see Box 166-1).[16] Readers can access and print this form free of charge from the author's website, www.drlowe.com/forms.htm.

The patient estimates the intensity of each symptom by marking the appropriate point on the scale (1-10). The values for each marked symptom are added, and this total symptom intensity is then divided by the number of symptoms the patient marked at intake (baseline). The mean score is then posted to a line graph.

Fibromyalgia Impact Questionnaire

The Fibromyalgia Impact Questionnaire (FIQ)[201] is a measure of the patient's functional status. The total score from the FIQ is posted as a data point to a line graph. The assessment of functional ability is highly pertinent to the care of FMS patients. For example, in a recent study of the functional abilities of 1735 female FMS patients ages 31 to 78, researchers concluded that the average patient had less ability in activities of daily living than the average community-dwelling woman in her eighties.[202]

Zung's Self-Rating Depression Scale

Depression is so common among FMS patients that an assessment specific for the presence and severity of depression is used in addition to the VAS scale for depression. Zung's is one such assessment tool.[203] The score from the depression scale is posted to a line graph.

Physical Examination

When the FMS patient's treatment includes thyroid hormone, the five FMS measures should be used in conjunction with physiologic tests that assess tissue responses to the hormone. The most convenient physiologic tests are the relaxation phase of the Achilles' reflex, basal pulse rate, and basal body temperature. A combination of physiologic measurements is a more reliable indicator of tissue metabolic status than are the results of laboratory thyroid function tests.

In the early twentieth century, indirect calorimeters came into use to measure patients' RMRs.[204] Based on the patient's measured oxygen consumption, the instrument calculates the patient's estimated 24-hour resting energy expenditure. Thyroid hormone potently and exquisitely regulates oxidative metabolism. Because of this, during the mid-twentieth century, indirect calorimeters were used as the most relevant instrument for the diagnosis of hypometabolism (subnormal oxidative metabolism) due to hypothyroidism and thyroid hormone resistance. In recent years, hand-held and other types of convenient-to-use, affordable, and accurate indirect calorimeters have become available for clinical use. Two studies have shown that FMS patients have abnormally low RMRs compared with matched controls.[117,118]

Integrated Metabolic Therapies Essential for All Fibromyalgia Syndrome Patients

The majority of FMS patients must control or eliminate at least four metabolism-impeding factors. First, for the approximately 90% of FMS patients who have some form of thyroid disease,[115,116] the proper preparation and dosage of thyroid hormone are necessary for the patient's recovery.

Second, most patients must also modify their diets so that they minimize the intake of arachidonic acid. A high intake of arachidonic acid can increase body levels of both the proinflammatory eicosanoids prostaglandin E2 and leukotriene B4,[205] which can contribute to chronic pain.[206] Patients must also reduce their intake of refined carbohydrate. ITHR of glycolysis, the citric acid cycle, and the electron transport chain results in low production of ATP and creatine phosphate. Dysglycemia and insulin resistance due to the intake of refined carbohydrates can worsen the low production of high-energy phosphates due to ITHR.[16]

Third, most patients must take a wide array of nutritional supplements. Various nutrients are synergistic to thyroid hormone in providing optimal intracellular metabolism, and patients must provide themselves with optimal amounts. For example, a deficiency of vitamin B_1 can render patients intolerant of even low dosages of thyroid hormone—dosages too low to be therapeutic.[207] In addition, supplemental thyroid hormone can increase the expenditure of vitamin B_1 in cells. If a patient has a marginal deficiency of the vitamin, supplemental thyroid hormone could induce a frank deficiency. This can result in a beriberi-type of cardiomyopathy.[207]

Fourth, most patients must also exercise to tolerance. Biochemical treatments such as thyroid hormone, optimal diet, and nutritional supplements provide the patient with increased metabolic capacity. Sufficiently vigorous physical activity, however, is necessary for optimizing metabolism in most tissues and for priming the descending nociceptive inhibitory system of the CNS.

Additional Metabolic Therapies Necessary for Some Patients

Adrenocortical Hypofunction

Some patients must be treated for adrenocortical hypofunction. Low cortisol levels can produce some symptoms that are the same as those associated with FMS. These include weakness, fatigue, exagerated responses to stress, exercise intolerance, hypotension, and low nociception threshold. Low cortisol levels can also render the patient intolerant of a dosage of thyroid hormone high enough to be fully therapeutic. The reason is that a minimally effective dosage of thyroid hormone is likely to accelerate the hepatic clearance of cortisol.[208] This typically exacerbates the symptoms of cortisol deficiency symptoms.

Metabolism-Impairing Medications

Several classes of medications may be significant in the development or perpetuation of FMS symptoms. Because of this, some patients must cease taking some metabolism-impairing medications and they must convert from the maintenance to as-needed use of others.

Beta blockers impair metabolism directly by reducing the density of β-adrenergic receptors on cell membranes and rendering α_2-adrenergic receptors predominant in the regulation of cell function, exactly as hypothyroidism does. In some patients, this shift in adrenoceptor isoform balance creates a general mental and physical inhibitory state that may be indistinguishable from hypothyroidism or the associated symptoms of FMS.[209] The shift in adrenergic receptor isoform may also impair the function of the CNS's descending antinociceptive system, resulting in the pain and tenderness characteristic of FMS.

Narcotics, tranquilizers, and muscle relaxants are commonly prescribed as FMS treatments. Patients should be weaned from these as soon as possible because they can render patients disinclined to engage in vigorous physical activity. As the patient's physical fitness level declines, anergia and pain perception increase.

Some antidepressants (also commonly prescribed for FMS) and decongestants can cause tachycardia when they are used simultaneously with exogenous thyroid hormone. Because of this, patients using these drugs must reduce the dosages or stop their use in order to be able to take a dosage of thyroid hormone high enough to be therapeutic.

THERAPEUTIC APPROACH

Assessment of Fibromyalgia Syndrome Status

The patient's FMS status should be evaluated before treatment is begun and at intervals throughout the course of treatment. Reevaluations are best performed weekly to biweekly and before each increase in thyroid hormone dosage. If patients have taken measurements at home, such as the basal temperature, they should provide the clinicians with a record of these measurements. (An individualized self-monitoring form for patients is available at www.drlowe.com.forms.htm) A physical examination and five FMS measures should be used at each evaluation:

- Pain distribution as the percentage of 36 body divisions containing pain, according to a body drawing
- Mean TnP score in kg/cm^2 measured by algometry
- Symptom intensity estimate according to visual analog scales (FibroQuest Symptoms Survey)
- Functional status according to the Fibromyalgia Impact Questionnaire
- Depression according to the Zung's Self-Rating Depression Scale

Scores for each assessment instrument should be posted to a line graph so that the trend of the scores is obvious on visual inspection. Changes in the patient's individualized treatment regimen should be based on the trend of scores on the line graphs combined with the physical examination and the clinician's and patient's subjective assessments. This process is continued (usually for 2 to 6 months) until the scores on the line graphs are representative of normal, the patient no longer meets the ACR criteria for FMS, and the patient is symptom free and fully functional.

Patient Safety

All patients must have an electrocardiogram before beginning metabolic rehabilitation and, if appropriate, at intervals throughout the treatment process. Although dysrhythmic conditions are usually not obstacles to metabolic treatment, it is essential to be aware of them before treatment with thyroid hormone.

Patients should be educated extensively on the possible signs and symptoms of thyrotoxicosis and its management should overstimulation occur. When a patient's history indicates, he or she should be tested for possible adrenocortical hypofunction. If testing reveals decreased cortisol production, the patient should be treated with physiologic doses of cortisol at least temporarily before the use of thyroid hormone is initiated.

Thyroid Hormone Therapy

If the FMS patient is hypothyroid, he or she should begin treatment with 1 grain (60 mg) of desiccated thyroid or a synthetic T4/T3 preparation with a 4:1 ratio. The dosage should be increased by 1 grain at approximately 3- to 4-week intervals until an optimal dosage has been reached.

If the patient is euthyroid, he or she should begin treatment with immediate-release T3, usually with a starting dosage of 50 mcg. The dosage is increased at weekly to biweekly intervals by 12.5 mcg. Dosage increases should continue until the patient is symptom-free, no longer meets the ACR criteria for FMS, is fully functional, and has reference range physiologic measures such as the basal body temperature and basal pulse rate.

Wholesome Diet

If they have not done so already, patients should adopt a diet that both stabilizes blood sugar regulation and insulin levels and reduces pain perception. Such a diet involves lean meats—especially poultry, fish, fruits, vegetables, and a minimal intake of whole grains. It also minimizes the intake of foods high in arachidonic acid (which increases the production of the proinflammatory eicosanoids prostaglandin E2 and leukotriene B4[193]) and additive excitotoxins such as monosodium glutamate and aspartame. The author recommends that patients use organic foods and purified drinking water to decrease the quantity of chemical contaminants ingested.

Nutritional Supplements

Patients should take at minimum the following nutrients in the approximate dosages given:

High potency multiple vitamin and mineral
Vitamin B_{12}: 3000 to 5000 mcg a day of methylcobalamin
Vitamin C: 500 mg to 1 g three times a day
Vitamin E: 800 to 1600 IU a day
Carotenoids (mixed): 15 mg a day
Calcium: 2000 mg a day in divided dosages
Magnesium (preferably as aspartate, citrate, malate, or glycinate): 1000 mg a day in divided dosages
Fish oils: 1000 to 2000 mg EPA+DHA a day

Exercise to Tolerance

Exercise is essential to help normalize metabolism. We recommend that patients engage in forms of exercise that they enjoy and gradually increase the intensity as their symptoms diminish. Weight-bearing exercise is encouraged as it supports bone health. Aerobic exercise is essential to strengthen the cardiovascular and pulmonary systems. Toning activities build lean muscle mass, which in turn improves metabolism. A combination of these forms of exercise is best. Many patients who have become severely deconditioned owing to their FMS symptoms find warm-water exercise an ideal way to begin.

Physical Treatment

Myofascial therapy to eliminate trigger points in muscles and spinal manipulation to regain flexibility of the spine and other joints are essential for completely eliminating some patients' FMS pain. Both trigger points and spinal lesions can be perpetuated by self-sustaining skeletal muscle contractures. The contractures may result from deficient intramuscular high-energy phosphate production due to ITHR.[20,22,195] Both forms of treatment may raise the nociceptive threshold and increase mobility.

If an examination indicates the need, orthotics should be prescribed to relieve pain-inducing chronic postural muscle tension. The therapeutic aim is to reduce nociceptive input of somatic origin to the CNS.

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CHAPTER 167

Gallstones

Michael T. Murray, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- May be asymptomatic or cause biliary colic with irregular pain-free intervals of days or months
- Real-time ultrasonography provides a definitive diagnosis

GENERAL CONSIDERATIONS

Gallstones are another example of a "Western diet"–induced disease. In the United States, autopsy studies have shown that gallstones exist in approximately 20% of women and 8% of men older than age 40. Conservative estimates suggest that about 20 million Americans (10% of the U.S. population) and 5% to 22% of the population in the Western world have gallstones.[1] Each year 1 million more develop gallstones. More than 300,000 gallbladders are removed each year in the United States owing to the presence of gallstones.[2-5] Gallstones are also considered a significant risk factor for gallbladder cancer.[6,7]

The bile components include bile salts, bilirubin, cholesterol, phospholipids, fatty acids, water, electrolytes, and other organic and inorganic substances.[8] Table 167-1 shows the characteristics of the major bile components. Gallstones arise when a normally solubilized component of bile becomes supersaturated and precipitates. Gallstones can be divided into four major categories:

- Pure cholesterol
- Pure pigment (calcium bilirubinate)
- Mixed—containing cholesterol and its derivatives along with varying amounts of bile salts, bile pigments, and inorganic salts of calcium
- Stones composed entirely of minerals

Pure stones, either cholesterol or calcium bilirubinate, are extremely rare in the United States, where recent studies indicate that approximately 80% of the stones are of the mixed variety. The remaining 20% of the stones are composed entirely of minerals, principally calcium salts, although some stones contain oxides of silicon and aluminum.[2-4]

PATHOGENESIS

The formation of gallstones has been divided into three steps:

- Bile supersaturation
- Nucleation and initiation of stone formation
- Enlargement of the gallstone by accretion

Cholesterol and Mixed Stones

The requisite step in cholesterol and mixed stone formation is cholesterol supersaturation of bile within the gallbladder. Bile solubility, as well as bile supersaturation, is based on the relative molar concentrations of cholesterol, bile acids, phosphatidylcholine (lecithin), and water. Because free cholesterol is water insoluble, it must be incorporated into a lecithin-bile salt micelle (Figure 167-1). Using triangular coordinates, it is possible to demonstrate the solubility of cholesterol in bile (Figure 167-2).

As illustrated in the figures, either an increase in cholesterol secretion or a decrease in bile acid or lecithin secretion will lead the bile to become supersaturated. Once the bile is supersaturated, stone formation is initiated by such factors as biliary

TABLE 167-1 **Characteristics of the Major Bile Components**

COMPONENT	PERCENTAGE OF BILE	WATER SOLUBILITY	PHYSIOCHEMICAL PROPERTIES
Cholesterol	5	Very poor	Will precipitate from aqueous solutions
Bile salts	69-90	Soluble; have polar and nonpolar regions	Capable of solubilizing cholesterol and phospholipid in aqueous phase
Phospholipid	2-25	Poor	Fits between bile salt molecules, thus increasing their capacity to solubilize cholesterol

Modified from Rubenstein E, Federman DD. Scientific American medicine. New York: Scientific American, 1986;4:VI-1–VI-10.

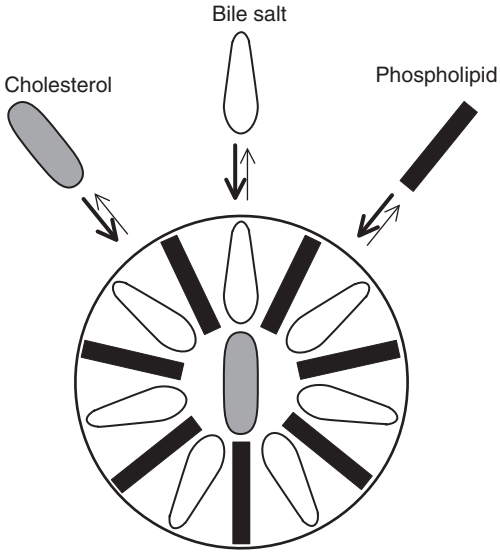


FIGURE 167-1 Mixed micelle.

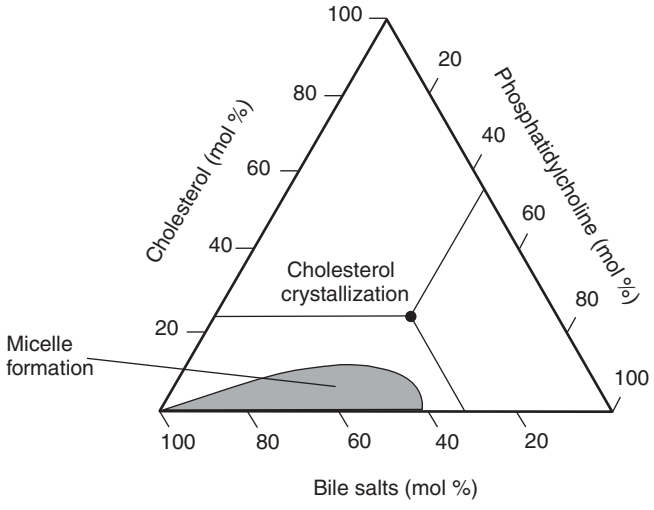


FIGURE 167-2 Cholesterol solubility in bile.

stasis, infection, and increased mucin secretion by the gallbladder epithelium. Once the stone begins to form, its radius increases at an average rate of 2.6 mm/year, eventually reaching a size of a few millimeters to more than a centimeter. Symptoms typically occur an average of 8 years after formation begins. Cholelithiasis is present in 95% of patients with cholecystitis.[8]

Risk Factors for Cholesterol and Mixed Stones

The major risk factors for the development of cholesterol and mixed gallstones include the following[2-4]:

- Diet
- Gender
- Race
- Obesity
- High caloric intake
- Estrogens
- Gastrointestinal diseases (especially Crohn's disease and cystic fibrosis)
- Drugs
- Age

The role of a low-fiber, high-fat diet in the development of gallstones, as well as other dietary factors, is discussed later. The other factors are briefly discussed here.

Gender

The frequency of gallstones is two to four times greater in women than in men. Women are thought to be predisposed to gallstones because of either increased cholesterol synthesis or suppression of bile acids by estrogens. Pregnancy, use of oral contraceptives or other causes of elevated estrogen levels, and tamoxifen use greatly increase the incidence of gallstones.

Genetic and Ethnic

The prevalence of gallstones appears to have some genetic aspects. Gallstones are most common in Native American women over age 30. Nearly 70% of this group have gallstones. In contrast, only 10% of black women over 30 have gallstones. The difference in the prevalence rate between ethnic and genetic groups reflects the extent of cholesterol saturation of the bile. The extent to which dietary factors affect this value probably outweighs genetic factors.[9]

Obesity

Obese subjects are at risk for developing gallstones both by being overweight and when initially losing weight.[10] Obesity causes an increased activity of HMG-CoA reductase with increased secretion of cholesterol in the bile as a result of increased cholesterol synthesis. Therefore, obesity is associated with a significantly increased incidence of gallstones due to biliary cholesterol saturation.

Important to note is that during active weight reduction, changes in body fat and diet can actually promote gallstone problems. During the first stages of weight loss, biliary cholesterol saturation initially increases.[4] The secretion of all biliary lipids is reduced during weight loss, but the secretion of bile acids decreases more than that of cholesterol. Once the weight is stabilized, bile acid output returns to normal levels while the cholesterol output remains low. The net effect is a significant reduction in cholesterol saturation. In prescribing diet therapies for obese patients with a high risk of gallstones, it should be recognized that prolonged dietary fat reduction can also promote biliary stasis,[1] thus contributing to cholesterol saturation. Studies show that at least 10 g of fat per day is necessary in order to assure proper gallbladder emptying.[11]

Gastrointestinal Tract Diseases

Malabsorption of bile acids from the terminal ileum disturbs the enterohepatic circulation, thereby reducing the bile acid pool and the rate of secretion of bile. Diseases associated with this phenomenon include Crohn's disease and cystic fibrosis.

Drugs

Tamoxifen treatment in postmenopausal breast cancer patients greatly increases gallstones. One retrospective cohort study of 703 women demonstrated that after 5 years, the incidence of stone formation in the tamoxifen-treated patients was 37.4%, whereas it was 2% in patients who did not receive tamoxifen.[12] Most gallstones became apparent after 3 years.

In addition to oral contraceptives and other estrogens, as discussed earlier, drugs that increase the risk of gallstones include the cephalosporin ceftriaxone, octreotide, HMG-CoA reductase inhibitors,[1] and possibly other lipid-lowering drugs.

Age

Gallstones have been reported from fetal age to extreme old age, but the average patient is 40 to 50 years old. Decline in the activity of cholesterol 7-α-hydroxylase with age[1] leads to an increase in biliary cholesterol hypersecretion[13] and thus cholesterol saturation, with accelerated formation of gallstones.

Risk Factors for Pigmented Gallstones

Risk factors for pigmented gallstones are not related to diet as much as they are to geography, sun exposure, and severe diseases. Pigmented gallstones are more common in Asia because of the higher incidence of parasitic infections of the liver and gallbladder by various organisms including the liver fluke *Clonorchis sinensis.* Bacteria and protozoa can cause stasis or act as nucleating agents. In the United States, pigmented stones are usually caused by chronic hemolysis or alcoholic cirrhosis of the liver.

THERAPEUTIC CONSIDERATIONS

Gallstones are easier to prevent than to reverse. Primary treatment, therefore, involves reducing the controllable risk factors discussed earlier. Once gallstones have formed, therapeutic intervention involves avoiding aggravating foods and employing measures that increase the solubility of cholesterol in bile. If symptoms persist or worsen, cholecystectomy should be considered.

A number of dietary factors are important in the prevention and treatment of gallstones. Foremost is the elimination of foods that can produce symptoms. Also important are increasing dietary fiber, eliminating food allergies, and reducing the intake of refined carbohydrates and animal protein. There is a protective effect of vegetables and fruits against gallbladder cancer, and red meat (beef and mutton) was found to be associated with an increased risk of gallbladder carcinogenesis.[14] Because gallstones are a risk factor for gallbladder cancer,[6,7,14] appropriate nonlithogenic dietary practices will protect against both cancer and the development of gallstones.

Other treatment measures involve the use of nutritional lipotropic compounds, herbal choleretics, and other natural compounds in an attempt to increase the solubility of bile.

Biliary cholesterol concentration and serum cholesterol levels do not seem to correlate.[15] Although some authors have reported an inverse correlation between high-density-lipoprotein cholesterol and bile saturation and a direct correlation between low-density-lipoprotein cholesterol and bile saturation,[16,17] more detailed research does not appear to support these correlations.[15] There does, however, seem to be an association between increased levels of serum triglycerides and bile saturation.[18]

Asymptomatic Gallstones

The natural history of silent or asymptomatic gallstones supports the contention that elective cholecystectomy is not warranted. Although there is a cumulative chance of developing symptoms—10% at 5 years, 15% at 10 years, and 18% at 15 years—a patient should never experience discomfort if controllable risk factors are eliminated or reduced.[3]

Diet

Dietary Fiber

The hypothesis that the main cause of gallstones is the consumption of fiber-depleted refined foods has considerable research support.[4,5] As mentioned earlier, in population studies, gallstones are associated with the Western diet. Such a diet, high in refined carbohydrates and fat and low in fiber, leads to a reduction in the synthesis of bile acids by the liver and a lower bile acid concentration in the gallbladder.

Another way in which fiber may prevent gallstone formation is by reducing the absorption of deoxycholic acid.[4,5] This compound is produced from bile acids by bacteria in the intestine. Deoxycholic acid greatly lessens the solubility of cholesterol in bile.

Dietary fiber has been shown both to decrease the formation of deoxycholic acid and to bind deoxycholic acid and promote its excretion in the feces. This greatly increases the solubility of cholesterol in the bile. A diet high in fiber, especially those fibers capable of binding to deoxycholic acid (i.e., predominantly the water-soluble fibers found in vegetables and fruits, pectin, oat bran, and guar gum), is extremely important in both the prevention and reversal of most gallstones.[5]

Interestingly, diets rich in legumes with high concentrations of water-soluble fibers are associated with an increased risk for gallstones.[9] Chileans, Pima Indians, and other North American Indians have the highest prevalence rates for cholesterol gallstones, and all consume a diet rich in legumes. Evidently, legume intake increases biliary cholesterol saturation as a result of legumes' saponin content.[9] A study conducted in The Netherlands showed just the opposite, because legume intake was shown to offer significant protection against gallstones.[62] Until this issue is clarified, it might be best to restrict legume intake in individuals with existing gallstones.

Vegetarian Diet

A vegetarian diet has been shown to protect against gallstone formation.[5,19] A recent study in England compared a large group of healthy nonvegetarian women with a group of vegetarian women. Ultrasound diagnosis showed that gallstones occurred significantly less frequently in the vegetarian group.

Although this may simply be a result of the increased fiber content of the vegetarian diet, other factors may be equally important. Animal proteins, such as casein from dairy products, have been shown to increase the formation of gallstones in animals, whereas vegetable proteins such as soy were shown to be preventive against gallstone formation.[4,5,20]

Food Allergies

Since 1948, J.C. Breneman, author of *Basics of Food Allergy,* has used a successful therapeutic regimen to prevent gallbladder attacks: allergy elimination diets. The idea that food allergies cause gallbladder pain has some support in the scientific literature.[21-24]

A 1968 study revealed that 100% of a group of patients were free from symptoms while they were on a basic elimination diet (beef, rye, soybean, rice, cherry, peach, apricot, beet, and spinach).[21] Foods inducing symptoms, in decreasing order of their occurrence, were as follows:

- Egg
- Pork
- Onion
- Fowl
- Milk
- Coffee
- Citrus
- Corn
- Beans
- Nuts

The addition of eggs to the diet caused gallbladder attacks in 93% of the patients.

Several mechanisms have been proposed to explain the association of food allergy and gallbladder attacks. Breneman believes that the ingestion of allergy-causing substances causes swelling of the bile ducts, resulting in impairment of bile flow from the gallbladder.

Buckwheat

Buckwheat is a well-known alternative for those avoiding wheat for hypoallergenic purposes. When they gave three groups of eight hamsters a buckwheat-, soy-, or casein-based diet, a Japanese research group demonstrated that buckwheat can significantly decrease gallstone formation and reduce the concentration of cholesterol in the gallbladder, plasma, and liver of hamsters compared with the casein diet.[25] Even though soy is a known potent gallstone attenuator itself,[26] these researchers found that the positive effects of buckwheat were far stronger than those of soy. Gallstones were clearly visible in all eight hamsters fed the casein diet, whereas two of seven hamsters fed the soy diet (29%) and none of the buckwheat-fed animals had gallstones. Studies in rats have also corroborated these findings.[27] The authors suggest that buckwheat can enhance bile acid synthesis and fecal excretion of steroidal compounds. Buckwheat may be useful to treat patients with both high cholesterol and gallstones and may reduce colon cancer cell proliferation.[28] The authors also postulated that higher levels of arginine and glycine may play a role in buckwheat's protective function.

Sugar

A 4-year study evaluated 111 cases of biliary tract cancer and compared them with 480 controls for various dietary parameters, including sugar intake. The major finding was an increased risk associated with the intake of sugars, either monosaccharides or disaccharides, independent of other energy sources. Sugar may be a risk factor for biliary tract cancer based on the relationship among sugars, blood lipids, and gallstone formation. The author also noted an association between the intake of sugar and gallstones. Diets high in refined carbohydrates have been found to be associated with increased cholesterol saturation of the bile.[29,30] A 25-year follow-up study of 860 men, 54 of whom developed symptomatic gallstones, also found a positive association between sugar consumption and gallstones.[31]

Caloric Restriction

In a case-controlled study in which 200 patients with gallstones were compared with 98 controls, total caloric and carbohydrate intake and serum triglyceride levels were higher in the gallstone patients. Dietary intake of refined carbohydrates was higher in the female patients with gallstones, whereas male patients with gallstones had an increased fat intake.[32] In another study, 76 patients whose gallstones were detected by ultrasound were matched to control subjects without cholethiasis. It was found that high caloric intake of greater than 2500 kcal/day and those diets rich in carbohydrates and saturated fats significantly increased gallstone risk.[33] One intriguing note to this study was the finding that alcohol consumption of 20 to 40 g/day was protective.

However, caloric restriction must be instituted carefully, as rapid weight loss[34] and fasting[35] increase the risk of gallstones (see earlier section on obesity). For example, in 179 obese patients, 9% of whom had preexisting gallstones, a low-calorie (605 kcal) diet resulted in 11% of the patients developing gallstones either during or within 6 months of completing the diet.[34] Another study of a 925-kcal diet found that 12.8% of the 47 female patients displayed gallstones at week 17 as determined by sonography. Those who developed gallstones had significantly higher baseline triglyceride and total cholesterol levels than those who did not. They also had a significantly greater rate of weight loss.[36]

Coffee

Although coffee can promote symptoms of gallstones, it may also inhibit their formation. In one study, 400 mL of regular coffee and 165 mL of regular and decaffeinated coffee were assessed for their effect on cholecystokinin secretion. Regular coffee at both dosages and decaffeinated coffee caused significant gallbladder contractions as compared with the control sodium chloride in six healthy regular coffee drinkers.[37] Another study of 80,898 female nurses between the ages of 34 and 59 years found that drinking four cups of caffeinated coffee per day was associated with a 28% lowered risk of developing symptoms of gallstones. Even one to three cups seemed to have some protective effect.[38]

It may be that women who began to drink coffee regularly before or during early gallstone formation were able to either inhibit development or clear any small stones due to the enhanced gallbladder contractions from multiple daily coffee doses. In women who already have large stones present, increased contractions from coffee may exacerbate their condition and cause untoward symptoms.

Nutritional Supplements

Lecithin (Phosphatidylcholine)

As the main cholesterol solubilizer in bile, lecithin in low concentrations may be a causative factor for many individuals with gallstones. For example, a pure bile salt micelle requires 50 molecules to enclose a single molecule of cholesterol, whereas a mixed bile salt/phospholipid micelle requires only seven molecules.[8] Studies have shown that the ingestion of lecithin can have the direct effect of solubilizing cholesterol.[39] As little as 100 mg of lecithin taken three times a day will increase the concentration of lecithin in the bile, whereas larger doses (up to 10 g) produce even greater increases.[40,41] This is significant, because an increased lecithin content of bile usually increases the solubility of cholesterol. However, no significant effects on gallstone dissolution have been obtained using lecithin supplementation alone.

Nutrient Deficiencies

Deficiencies of either vitamin E or C have been shown to cause gallstones in experimental studies in animals.[42,43]

Olive Oil

A popular lay remedy for gallstones is the olive oil "liver flush." There are several variations. A typical one involves drinking 1 cup of unrefined olive oil with the juice of two lemons in the morning for several days.

Many people tell tales of passing huge stones while on the liver flush. However, what they think are gallstones are simply soft, saponified complexes of minerals, olive oil, and lemon juice produced within the gastrointestinal tract.[44]

The olive oil liver flush is undesirable for patients with gallstones for several reasons. First, consuming a large quantity of any oil results in contraction of the gallbladder, which may increase the likelihood that a stone will block the bile duct. This may result in cholecystitis, requiring immediate surgery to prevent death. Second, oleic acid, the main component of olive oil, has been shown to increase the development of gallstones in rabbits and rats by increasing the content of cholesterol in the gallbladder.[45,46] Although this effect has not yet been observed in humans, the animal research suggests that it is unwise to use an olive oil liver flush as a treatment of gallbladder disease.[47] This recommendation is not meant to obviate the use of the liver flush as a viable method of liver detoxification. Rather, it is a caution against its use in patients with gallstones.

Fish Oils

Although human studies appear not to be available at this time, some provocative animal studies exist. For example, one study compared a diet high in lard with a diet high in fish oils in 21 male African green monkeys. One group was fed 0.8 mg cholesterol per kilocalorie and 42% of the calories as fat, with one half of the fat calories derived from lard, while the other group was fed a similar diet with an isocaloric substitution of menhaden oil instead of the lard. After 2 to 3 years, necropsies were performed and it was found that 67% of the animals fed the lard diet had cholesterol gallstones compared with 22% of the animals fed the fish oil. The cholesterol saturation index of the gallbladder bile was also higher in the lard-fed group, although there was no difference in bile acids. There was a significantly greater rate of biliary phospholipid secretion in the fish oil–fed animals compared with the lard-fed animals.[48]

A more recent study found similar effects in a prairie dog model using a diet more typical of human habits: 12 animals consumed a standard control diet, while 16 consumed a lithogenic 1.2% cholesterol diet. Half the animals in each group were supplemented with 200 mg/kg/day of omega-3 fatty acids from eicosapentaenoic and docosahexaenoic acids. After 14 days, those fed the diet with added fish oil showed an inhibition of gallstone formation accompanied by a significant decrease in biliary calcium and total protein concentration. This antilithogenic effect may be due to an enhancement in the stability of biliary phospholipid-cholesterol vesicles.[49]

Lipotropic Factors and Botanical Choleretics

The naturopathic approach to the treatment of gallstones has typically involved the use of lipotropic and choleretic formulas. Lipotropic factors are by definition substances that hasten the removal or decrease the deposit of fat in the liver through their interaction with fat metabolism. Compounds commonly employed as lipotropic agents include choline, methionine, betaine, folic acid, and vitamin B_{12}.

Often these nutritional factors are used with herbal cholagogues and choleretics. Cholagogues stimulate gallbladder contraction to promote bile flow, whereas choleretics increase bile secretion by the liver.

Many herbal choleretics have a favorable effect on the solubility of bile. Choleretics that are appropriate to use in the treatment of gallstones include *Taraxacum officinale*, silymarin from *Silybum marianum*, *Cynara scolymus*, and *Curcuma longa*. In addition, *Peumus boldo* contains alkaloids such as boldine that are useful in the treatment of gallstones.

One study in rats given a diet that promoted gallstones demonstrated that the animals supplemented with 0.5% dietary curcumin for 10 weeks had only a 26% incidence of gallstone formation compared with a 100% incidence in the group fed the lithogenic diet alone.[50] This effect was found to be dose-dependent.

Chemical Dissolution of Gallstones

Several successful nonsurgical alternatives for the treatment of gallstones now exist. These entail using a complex of plant terpenes alone or, preferably, in combination with oral bile acids. As the formation of the stone depends on either increased accumulation of cholesterol or reduced levels of bile acids or lecithin, decreasing gallbladder cholesterol levels or increasing bile acid or lecithin levels should result in dissolution of the stone. Chemical dissolution is especially indicated in the treatment of gallstones in the elderly, who cannot withstand the stress of surgery, and in other cases where surgery is contraindicated.

Bile Acids

Use of bile acids, like ursodeoxycholic acid and tauroursodeoxycholic acid, are effective in dissolving small, uncalcified cholesterol gallstones. About 15% of all patients with cholesterol gallstones meet these criteria. Treatment with bile acids will lead to complete dissolution in about 90% of cases after 6 months of therapy. Once dissolved it is important to follow the recommendations for gallstone prevention in order to reduce the risk for recurrence. Bile acid preparations are available by prescription only and represent a safe and effective nonsurgical alternative for many people with gallstones.[50,51] The typical dosage is 12 mg per kg body weight daily.

Terpenes

Gallstone dissolution by a natural terpene combination of menthol, menthone, pinene, borneol, cineol, and camphene has been demonstrated in several studies.[52-56] This nonsurgical approach to gallstone removal offers an effective alternative to surgery and has been demonstrated to be safe even when it has been implemented for prolonged periods of time (up to 4 years).

Combined Therapy

Although terpenes are effective alone, the best results appear to be achieved when plant terpene complexes are used in combination with bile acid therapy.[57-59] This combined approach offers better results than either bile acids or plant terpenes used alone.[58,59] Furthermore, because a lower dose of bile acid can be used, there is a significant reduction in the risk of complications or side effects and in the cost of bile acid therapy. Because menthol is the major component of this formula, peppermint oil, especially enteric-coated capsules, may offer similar results.

Lifestyle

Sunbathing

Because almost all cholesterol gallstones contain a central pigmented nucleus with radial or lamellar pigmented bands alternating with layers of crystalline cholesterol, one researcher speculated that activation of the pigmentary system by ultraviolet light might lead to increased concentrations of indole metabolites in the bile, triggering their polymerization. In a case-controlled study of 206 white-skinned individuals, a positive attitude toward sunbathing was associated with twice the risk of cholelithiasis as

a negative attitude. When the effect of sunbathing attitude was considered for individual skin pigmentation types, the association was found to be almost entirely restricted to those who always burn after long sunbathing. In this group, the relative risk was a remarkable 25.6% for a positive attitude toward sunbathing versus a negative one.[60]

Social Stress

Using a fish model, one research experiment examined the effect of stress on the gallbladder function. In this work, fish were subjected to prolonged cohabitation with dominant individuals. It was found that this chronic social stress could increase bile retention, increase gallbladder hypertrophy, and inhibit gallbladder emptying.[61] This study suggests that chronic stress may be a predictor of gallbladder dysfunction and eventual gallstone formation.

THERAPEUTIC APPROACH

As is typical of most diseases, gallstones are much easier to prevent than to reverse. The risk factors and causes of gallstones are well known, and in most cases a healthy diet rich in fiber, with a limitation of excess calories and saturated fats, is adequate prevention.

Once gallstones have developed, measures to avoid gallbladder attacks and increase the solubility of the bile are necessary. To limit the incidence of symptoms, the foods to which an individual is intolerant or allergic must be determined (see Chapter 15) and, along with fatty foods, avoided. The solubility of the bile can be increased by following the dietary guidelines and using the nutritional and herbal supplements recommended here.

Diet

Patients should increase their intake of vegetables, fruits, dietary fiber (especially the gel-forming or mucilaginous fibers such as flaxseed, oat bran, guar gum, and pectin), and buckwheat. They should reduce their consumption of saturated fats, refined carbohydrates, cholesterol, sugar, and animal proteins. All fried foods should be avoided.

An allergy elimination diet can be used to reduce gallbladder attacks.

Water

Consumption of six to eight glasses of water is necessary each day to maintain the water content of bile.

Nutritional Supplements

- Vitamin C: 1 to 3 g/day
- Vitamin E: 200 to 400 IU/day
- Phosphatidylcholine: 500 mg/day
- Choline: 1 g/day
- L-Methionine: 1 g/day
- Fiber supplement (guar gum, pectin, psyllium, or oat bran): minimum of 5 g/day

Botanical Medicines

Choose one or more of the following:

- Dandelion (*Taraxacum officinale)* (three times/day)
 - Dried root: 4 g
 - Fluid extract (1:1): 4 to 8 mL
 - Solid extract (4:1): 250 to 500 mg
- *Pneumus boldo* (three times/day)
 - Dried leaves (or by infusion): 250 to 500 mg
 - Tincture (1:10): 2 to 4 mL
 - Fluid extract (1:1): 0.5 to 1 mL
- Milk thistle *(Silybum marianum)*
 - Sufficient dosage according to form to yield 70 to 210 mg of silymarin three times/day
- Artichoke *(Cynara scolymus)*
 - Extract (15% cynarin): 500 mg three times/day
- Curcumin: 300 mg three times/day

Gallstone-Dissolving Formula

- Menthol: 30 mg
- Menthone: 5 mg
- Pinene: 15 mg
- Borneol: 5 mg
- Camphene: 5 mg
- Cineol: 2 mg
- Citral: 5 mg
- Phosphatidylcholine: 50 mg
- Medium-chain triglycerides: 125 mg
- Chenodeoxycholic acid: 750 mg

The dosage for this formula is to take it three times daily if used in combination with meals.

Note: Peppermint oil in an enteric-coated capsule can be used instead at a dosage of 1 to 2 capsules (0.2 mL per capsule) three times daily between meals.

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CHAPTER 168

Glaucoma: Acute (Angle Closure) and Chronic (Open Angle)

Michael T. Murray, ND

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DIAGNOSTIC SUMMARY

Acute Glaucoma

- Increased intraocular pressure, usually unilateral
- Severe throbbing pain in eye with markedly blurred vision
- Pupil moderately dilated and fixed
- Absence of pupillary light response
- Nausea and vomiting common

Chronic Glaucoma

- Persistent elevation of intraocular pressure associated with pathologic cupping of optic discs
- Asymptomatic in the early stages
- Gradual loss of peripheral vision, resulting in tunnel vision
- Insidious onset in older individuals

Normotensive Glaucoma

- Normal intraocular pressure with no pathologic cupping of optic discs
- Asymptomatic in the early stages
- Gradual loss of peripheral vision, resulting in tunnel vision
- Insidious onset in older individuals, more common in women than men
- Low blood pressure a common underlying feature

GENERAL CONSIDERATIONS

Glaucoma refers to increased intraocular pressure (IOP) as a result of an imbalance between production and outflow of the aqueous humor. Obstruction to outflow is the main factor responsible for this imbalance in closed-angle glaucoma. Acute glaucoma can occur only with the closure of a preexisting narrow anterior chamber angle, while in chronic open-angle glaucoma the anterior chamber appears normal.

In the United States, approximately 3 million people have glaucoma, which is undetected in 25% of them.[1] The chronic open-angle type, for which there appears to be no consistent anatomic basis, accounts for 70% to 75% of these cases. Histologically, however, there is a strong correlation between the content and composition of collagen and the glaucomatous eye.[2]

Collagen is the most abundant protein in the body, including the eye. In the eye it provides tensile strength and integrity to the tissues (e.g., cornea, sclera, lamina cribrosa, trabecular meshwork, vitreous). Inborn errors of collagen metabolism (e.g., osteogenesis imperfecta, Ehlers-Danlos syndrome, Marfan syndrome) are often associated with ocular complications: glaucoma, myopia, retinal detachment, ectopia lentis, and blue sclera.[3] Morphologic changes in the lamina cribrosa (the scleral area that is pierced by the optic nerve fibers and blood vessels), trabecular meshwork (the connective tissue network through which aqueous humor must pass to reach the canal of Schlemm), and papillary blood vessels in the eye have all been observed in glaucomatous eyes.[2,4-6] These changes may result in elevated IOP readings or, perhaps more significantly, lead to the progression of peripheral visual loss. Changes in collagen structure would explain the following[2,4-6]:

TABLE 168-1 **Differential Diagnosis of the Inflamed Eye**

	ACUTE CONJUNCTIVITIS	ACUTE IRITIS	ACUTE GLAUCOMA	CORNEAL TRAUMA OR INFECTION
Incidence	Very common	Common	Uncommon	Common
Discharge	Moderate to copious	None	None	Watery or purulent
Vision	No effect	Slightly blurred	Markedly blurred	Usually blurred
Pain	None	Moderate	Severe	Moderate to severe
Conjunctival injection	Diffuse, mostly fornices	Circumcorneal	Diffuse	Diffuse
Cornea	Clear	Usually clear	Steamy	Clarity may change
Pupillary size	Normal	Small	Dilated and fixed	Normal
Pupillary light response	Normal	Poor	None	Normal
Intraocular pressure	Normal	Normal	Elevated	Normal
Anterior chamber		Normal depth	Very shallow	Normal depth
Iris	Normal	Dull, swollen	Congested and bulging	Normal unless infected
Smear	Causative organisms	No organisms	No organisms	Causative organisms if there is infection

Modified from Distelhorst JS, Hughes GM. Open-angle glaucoma. Am Fam Physician 2003;67:1937-1944.

- Similar peripheral vision loss in patients with normal and elevated IOP
- Cupping of the optic disc even at low IOP levels
- No apparent anatomic reason for decreased aqueous outflow

In some cases glaucoma develops in people with normal IOP. Referred to as low-tension glaucoma or normotensive glaucoma, this form accounts for approximately 25% to 30% of all cases of glaucoma in the United States. Because elevated IOP is not a factor in normal-tension glaucoma, other factors must be responsible for the optic nerve damage. Suggested causes include:

- Reduced blood flow
- Early nerve cell death
- Nerve irritation
- Excess glutamate production
- Autoimmune disease

Normotensive glaucoma is more common in women than in men and affects adults averaging 60 years of age. A common risk factor for normotensive glaucoma is low blood pressure.

DIAGNOSIS

Patients with open-angle glaucoma initially have no symptoms, which is why this disease can be so insidious. Physical examination may reveal slight cupping of the optic disc and narrowing of the visual fields. Tonometry is key to confirmation of the diagnosis.

The primary challenge with acute glaucoma is early recognition, because delay in referral for surgical intervention increases the risk of blindness. Table 168-1 provides an overview of the differential diagnosis of the inflamed eye.

THERAPEUTIC CONSIDERATIONS

Treatment and prevention of both acute and chronic glaucoma depend on the reduction of IOP and improvement of collagen metabolism, particularly in the optic disc and trabecular meshwork.

The optic disc is composed of the lamina cribrosa, optic nerve fibers, and blood vessels. The lamina cribrosa is a meshlike network rich in collagen through which the optic nerves and blood vessels must pass. The morphologic changes in the collagen of the eye (i.e., lamina cribrosa, papillary vessels, and trabecular meshwork) precede pressure changes. Therefore, primary prevention of breakdown of the ground substance and collagen framework is important here, as it is in other conditions involving collagen abnormalities (i.e., atherosclerosis, rheumatoid arthritis, and periodontal disease).

Corticosteroids

The importance of collagen destruction in the etiology of glaucoma is apparent in corticosteroid-induced glaucoma.[2] Corticosteroid use should be discouraged in the glaucoma patient, as it is known to inhibit the biosynthesis of collagen and glycosaminoglycans, thereby worsening the patient's glaucoma.[2]

Supplements and Diet

Vitamin C

Of foremost importance in achieving collagen integrity are optimal tissue concentrations of ascorbic acid (AA). Furthermore, AA has been demonstrated to lower IOP levels in many clinical studies.[7-11] A daily dose of 0.5 g/kg, whether in single or divided doses, reduces the IOP by an average of 16 mm Hg.[11] Near normal tension levels were achieved in some patients unresponsive to acetazolamide (a carbonic anhydrase inhibitor) and 2% pilocarpine (a miotic agent).[11]

The hypotonic action of AA on the eye is long-lasting if supplementation is continued, and intravenous administration results in an even greater initial reduction in IOP.[7,9-11] The patient must be monitored to determine the appropriate individual dose, because some patients respond to as little as 2 g/day, whereas others will respond only to extremely high doses (e.g., 35 g/day).[7-11] Abdominal discomfort as a side effect of high doses is common but usually resolves after 3 to 4 days.[11]

The proposed mechanisms by which AA lowers IOP include the following:

- Increased blood osmolarity
- Diminished production of aqueous fluid by the ciliary epithelium
- Improved outflow of aqueous fluid

In light of recent research, however, the role of AA in collagen formation may be the key to its antiglaucomatous action.

Flavonoids

To further aid normal collagen metabolism, flavonoids should be supplemented, particularly the anthocyanosides (the blue-red pigments found in berries) and proanthocyanosides. These compounds elicit an AA-sparing effect, improve capillary integrity, and stabilize

the collagen matrix by preventing free radical damage, inhibiting enzymatic cleavage of the collagen matrix, and cross-linking with collagen fibers directly to form a more stable collagen matrix.[12-14] *Vaccinium myrtillus* (European bilberry) extract is particularly rich in these flavonoid and anthocyanidin compounds and has been used in Europe with good results in reducing myopia, improving nocturnal vision, and reversing diabetic retinopathy.[15] Mirtogenol, a combination of bilberry anthocyanoside extract (160 mg Mirtoselect) and pine bark extract (80 mg Pycnogenol) was studied in 38 asymptomatic subjects with intraocular hypertension. Patients were given either Mirtogenol (20 subjects) or were not treated (18 subjects). After 2 months of supplementation with Mirtogenol, the mean IOP decreased from a baseline of 25.2 to 22.2 mm Hg. After 3 months of treatment with Mirtogenol, the IOP was significantly lowered compared with that of untreated controls (P <0.05) to 22 mm Hg. No further improvement was found after 6 months. Of the 20 patients taking Mirtogenol, 19 had a decreased IOP after 3 months. Only marginal effects on the IOP were found in the 18 control subjects. No side effects were observed. Ocular blood flow (central retinal, ophthalmic, and posterior ciliary arteries) improved both in the systolic and diastolic components as measured by ultrasound. After 3 months of treatment, the improvement in ocular blood flow was significant as compared with both baseline and the control group.[16] Rutin has also been demonstrated to lower IOP when used as an adjunct in patients unresponsive to miotics alone.[17]

In patients with normotensive glaucoma (NTG), *Ginkgo biloba* extract (GBE) may be helpful, based on the results of two double blind studies. In the first study, which comprised healthy human volunteers, GBE (120 mg daily) significantly increased end-diastolic velocity in the ophthalmic artery (23% change), with no change in the placebo group. GBE did not alter arterial blood pressure, heart rate, or IOP.[18] In the second study, patients with NTG received either 40 mg GBE or placebo three times daily for 4 weeks, followed by a washout period of 8 weeks, then 4 weeks of the opposite treatment. After GBE treatment, a significant improvement in visual field indices was recorded, showing that GBE improves preexisting visual field damage in some patients with NTG.[19]

Allergy

The successful treatment of chronic glaucoma by antiallergy measures has been reported in the literature.[20] In one study, many of the 113 patients demonstrated an immediate rise in intraocular pressure of up to 20 mm Hg (in addition to other typical allergic symptoms) when challenged with the appropriate allergen, whether food borne or environmental. The author speculated that the known allergic responses of altered vascular permeability and vasospasm could result in the congestion and edema characteristic of glaucoma.

Magnesium

Because channel-blocking drugs benefit some glaucoma patients, a group of researchers at the University Eye Clinic in Basel, Switzerland, decided to evaluate the effect of supplemental magnesium, which has been referred to as "nature's physiologic calcium-channel blocker." The trial included 10 glaucoma patients (6 with primary open-angle glaucoma and 4 with normal-tension glaucoma). All patients had a digital cold-induced vasospasm. Magnesium was given at a dose of 121.5 mg twice daily for 1 month. After 4 weeks of treatment, the visual fields improved, as noted by a decrease in the mean defect and square root of loss variance scores. All three nail fold–capillaroscopic parameters improved, as well as digital temperature. These results demonstrate that magnesium supplementation improves the peripheral circulation and seems to have a beneficial effect on the visual field in patients with glaucoma.[21]

To evaluate the effect of oral magnesium therapy on ocular blood flow and visual field perimetry indices in patients with normotensive glaucoma (NTG), 15 patients with NTG (the study group) received 300 mg of oral magnesium (citrate) for 1 month, while 15 patients with NTG (the control group) received no treatment. In the study group, significant improvements were noted in visual field measurements (e.g., mean deviation improved from –3.7 at baseline to -2.5 and pattern standard deviation improved from 3.6 baseline to 2.8). There was no change in ocular blood flow, so the exact mechanism of magnesium's effect is not known.[22]

Chromium

A case-controlled study of 400 consecutive eye patients, 52 of whom had ocular hypertension glaucoma, or both, found that primary open-angle glaucoma was strongly associated with a deficiency of erythrocyte chromium, habitual daily intake of ascorbic acid, and elevations of erythrocyte vanadium, which is chromium's principal antagonist.

Ascorbic acid and chromium potentiate insulin receptors, which help to sustain strong focusing activity in the ciliary muscle. Deficiencies of either ascorbic acid or chromium were associated with elevated intraocular pressure, which tends to stretch the normal eye, thereby reducing focusing power.[23]

Fish Oil

In an interesting speculative study, rabbits were fed food soaked with cod liver oil, resulting in a drop in IOP from 25 to 11 mm Hg. Intramuscular injections of cod liver oil produced a dose-dependent reduction in IOP. When the animals were taken off cod liver oil, their IOP returned to baseline. Control animals given liquid lard or safflower oil experienced no change in IOP.[24] Preliminary studies in humans with docosahexaenoic acid have had encouraging results.[25]

Caffeine

Many physicians instruct patients with glaucoma to avoid coffee, although clinical data supporting this practice are insufficient. To estimate the effect of coffee drinking on IOP, the results of the consumption of regular coffee (180 mg caffeine in 200 mL of coffee) and decaffeinated coffee (3.6 mg caffeine in 200 mL of coffee) were compared in patients with normotensive glaucoma or ocular hypertension in a double-blind crossover study. IOP was monitored in both groups at 30, 60, and 90 minutes after coffee ingestion. In patients with normotensive glaucoma who drank regular coffee, the mean changes in IOP at 30, 60, and 90 minutes were 0.9, 3.6, and 2.3 mm Hg, respectively; in those who drank decaffeinated coffee, they were 0.75, 0.70, and 0.4 mm Hg, respectively. The corresponding values in patients with ocular hypertension were as follows: after regular coffee, 1.1, 3.4, and 3 mm Hg; and after decaffeinated coffee, 0.6, 0.9, and 0.5 mm Hg, respectively. This study showed clearly that subjects who drank regular coffee demonstrated a greater elevation in IOP, which may be clinically significant.[26]

Other Recommendations

Exercise

Exercise can lead to an immediate and prolonged reduction in IOP. Within 5 minutes of starting exercise, IOP initially increases and then gradually decreases to its lowest level 60 minutes following exercise. The drop in IOP is approximately 23% in normal individuals, while people with glaucoma usually experience a greater drop and longer duration of postexercise recovery than do those with normal eyes.[27] Specifically, the drop in IOP for

glaucoma patients following walking/jogging and running was 7.2% and 12.7%, respectively, more than the decrease in IOP experienced by persons normal eyes. Similarly, the mean duration of the IOP-lowering effect following running was approximately 84 minutes in glaucomatous eyes and 63 minutes in normal eyes. The mechanism of acute lowering of IOP is independent of systemic blood pressure and level of sympathetic stimulation but may be partly due to increased serum osmolarity.

Exercise appears to be effective in lowering IOP in sedentary subjects engaging in moderate to heavy exercise but is somewhat less effective in physically fit subjects.[28] However, individuals who are more physically fit tend to have lower IOP. If one stops exercising, the effect wears off in 3 weeks. Although exercise may not be effective in lowering IOP in everyone, it can lead to significant improvements in many. One study found that IOP was lowered by at least 2 mm Hg by exercise in 34% of subjects; however, 57% had no change in IOP, while 9% had an IOP elevation.[29]

Helicobacter pylori

Several studies have found an association between *Helicobacter pylori* infection and open-angle glaucoma.[30] A particularly interesting 2-year study found that successful eradication of *H. pylori* resulted in decreased IOP.[31] See Chapter 198 for a discussion of the treatment of *H. pylori*.

THERAPEUTIC APPROACH

Acute closed-angle glaucoma is an ocular emergency; such patients should be referred immediately to an ophthalmologist. Unless adequately treated within 12 to 48 hours, the patient will become permanently blind within 2 to 5 days. An asymptomatic eye with a narrow anterior chamber angle may convert spontaneously to angle-closure glaucoma. The process can be precipitated by anything that dilates the pupil, such as atropine and epinephrine-like drugs. Typical signs and symptoms include extreme pain, blurring of vision, conjunctivitis, and a fixed, dilated pupil.[1]

Agents that dilate the pupils must be strictly avoided in any patient suspected of having glaucoma.

Supplements

- Vitamin C: 0.1 to 0.5 g/kg per day in divided doses
- Bioflavonoids (mixed): 1000 mg/day
- Magnesium: 300 mg/day
- Chromium: 100 mcg/day

Botanical Medicine

For the prevention and treatment of chronic open-angle glaucoma. Either bilberry extract or a proanthocyanoside extract alone or in combination, as follows:

- *V. myrtillus* extract (25% anthocyanidin content): 160 to 240 mg a day
- Pine bark extract (Pycnogenol) or grape seed extract (95% proanthocyanidin content): 150 to 300 mg a day

For normotensive glaucoma:

- *Ginkgo biloba* extract: 120 to 320 mg a day

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CHAPTER 169

Gout

Michael T. Murray, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- Acute onset, frequently nocturnal, with typically monoarticular joint pain, involving the metatarsophalangeal joint of the big toe in about 50% of cases
- Elevated serum uric acid level
- Asymptomatic periods between acute attacks
- Identification of urate crystals in joint fluid
- Aggregated deposits of monosodium urate monohydrate (tophi) chiefly in and around the joints of the extremities but also in subcutaneous tissue, bone, cartilage, and other tissues
- Uric acid kidney stones
- Familial disease; 95% males

GENERAL CONSIDERATIONS

Gout is a common type of arthritis caused by an increased concentration of uric acid (the final breakdown product of purine metabolism) in biological fluids. In gout, uric acid crystals (monosodium urate) are deposited in joints, tendons, kidneys, and other tissues, where they cause considerable inflammation and damage.[1] Gout is a condition characterized biochemically by increased serum uric acid levels, leukotriene levels, and neutrophil accumulation. Gout may lead to debilitation owing to the tophaceous deposits around the joints and tendons; renal involvement may result in kidney failure due to either parenchymal disease or urinary tract obstruction.

Gout is associated with affluence and is often called the "rich man's disease." Throughout history, the sufferer of gout has been depicted as a portly, middle-aged man sitting in a comfortable chair with one foot resting painfully on a soft cushion as he consumes great quantities of meat and wine. In fact, the traditional picture does have some basis in reality, as meats, particularly organ meats, are high-purine foods, whereas alcohol inhibits uric acid secretion by the kidneys. Furthermore, even today, gout is primarily a disease of adult men; more than 95% of sufferers of gout are men older than age 30. The incidence of diagnosed gout cases has been estimated at 2.13% of the 2009 U.S. population, although 10% to 20% of the adult population has hyperuricemia. Gout is a strong predictor of the metabolic syndrome and an increased risk for type 2 diabetes.[1-4]

Causes of Gout

Gout is classified into two major categories: primary and secondary. Primary gout accounts for about 90% of all cases, whereas secondary gout accounts for only 10%. Primary gout is usually idiopathic (i.e., the underlying metabolic defect is unknown). However, there are several genetic defects in which the exact cause of the elevated uric acid is known.[1] The synthesis and degradation of purines are summarized in Figure 169-1.

The term *secondary gout* refers to those cases in which the elevated uric acid level is secondary to some other disorder such as excessive breakdown of cells or some form of renal disease. Diuretic therapy for hypertension and low-dose aspirin therapy are also important causes of secondary gout because they cause decreased uric acid excretion.

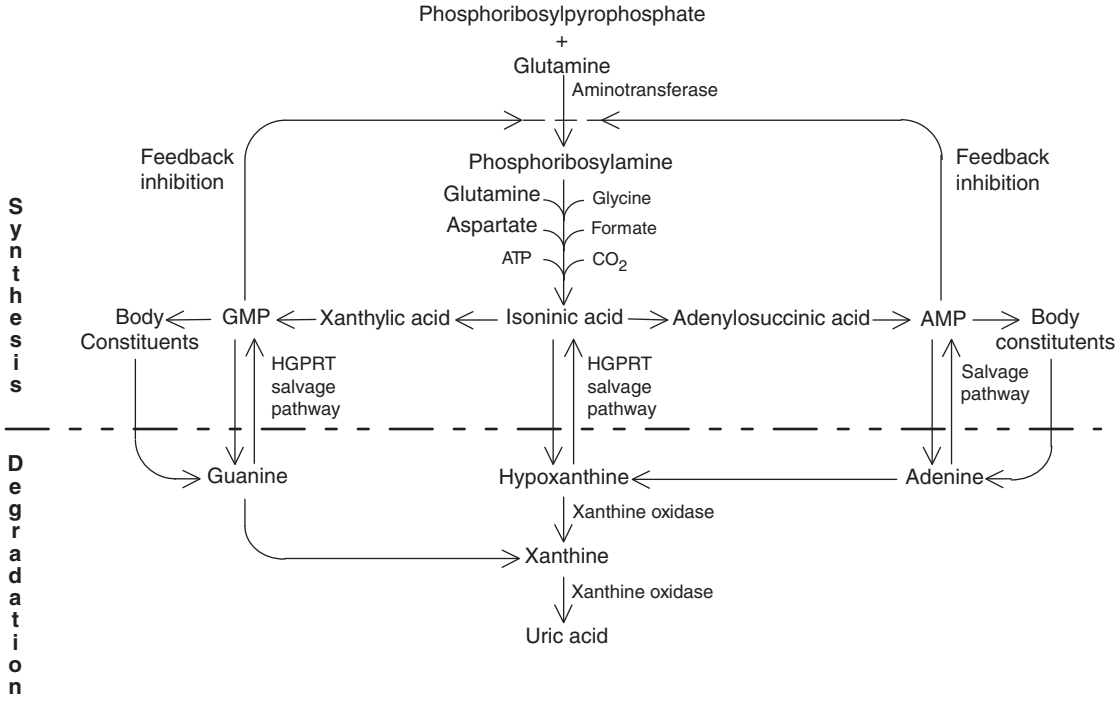


FIGURE 169-1 Purine synthesis and degradation. (From Nutrition Foundation. Nutrition reviews' present knowledge in nutrition, ed 5. Washington, DC: Nutrition Foundation, 1984:740-756.)

BOX 169-1 **Causes of Hyperuricemia**

Metabolic
- Increased production of purine (primary)
- Idiopathic
- Specific enzyme defects (e.g., Lesch-Nyhan syndrome, glycogen storage disease)
- Decreased enzyme activity (e.g., hypoxanthine-guanine phosphoribosyltransferase is decreased in 1% to 2% of adults with gout)
- Increased enzyme activity (e.g., phosphoribosylpyrophosphate synthetase)
- Increased production of purine (secondary)
 - Increased turnover of purines
 - Myeloproliferative disorders
 - Lymphoproliferative disorders
 - Carcinoma and sarcoma (disseminated)
 - Chronic hemolytic anemia
 - Cytotoxic drugs
 - Psoriasis
- Increased de novo synthesis (e.g., glucose-6-phosphatase deficiency)
- Increased catabolism of purines
 - Fructose ingestion or infusion
 - Exercise

Renal
- Decreased renal clearance of uric acid (primary)
 - Intrinsic kidney disease
- Decreased renal clearance of uric acid (secondary)
- Functional impairment of tubular secretion
 - Drug-induced (e.g., thiazides, probenecid, salicylates, ethambutol, pyrazinamide)
- Hyperlacticemia (e.g., lactic acidosis, alcoholism, toxemia of pregnancy, chronic beryllium disease)
- Hyperketoacidemia (e.g., diabetic ketoacidosis, fasting, starvation)
- Diabetes insipidus
- Bartter syndrome
- Chronic lead intoxication
- Glucose-6-phosphatase deficiency

The increased serum uric acid level observed in primary idiopathic gout can be divided into three categories:
- Increased synthesis of uric acid, found in a majority of individuals
- Reduced ability to excrete uric acid, typical of a smaller group (about 30%)
- Overproduction of uric acid, as well as underexcretion of uric acid—a small minority

Although the exact metabolic defect in gout is unknown in the majority of cases, gout is one of the most controllable metabolic diseases. Box 169-1 summarizes the causes of gout.

About 200 to 600 mg of uric acid are excreted daily in the urine of an adult male. This is two thirds of the amount produced, the rest being excreted in the bile and other gastrointestinal tract secretions. The dietary component of uric acid is usually 10% to 20%, but in an individual with significant hyperuricemia, 1 mg/100 mL may be added to the serum concentration of uric acid through the diet, enough to increase precipitation into the tissues if the individual is near the saturation threshold.

Almost all of the plasma urate is filtered at the glomerulus: only the small amount bound to protein is not filtered. Renal excretion is peculiar in that about 80% of the filtered uric acid is reabsorbed in the proximal tubule of the nephron. Actually, the distal tubule secretes most of the uric acid found in the urine. Distal to this site, some postsecondary reabsorption occurs. These events are summarized in Figure 169-2.

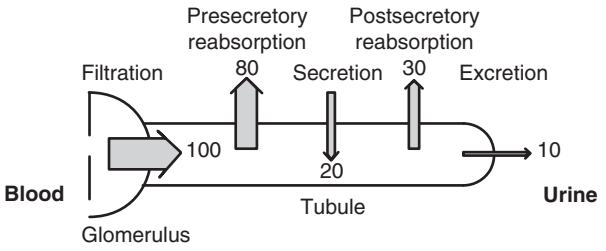


FIGURE 169-2 Normal uric acid excretion.

TABLE 169-1 **Prevalence of Gouty Arthritis by Maximum Urate Level**

SERUM URATE (MG/100 ML)	MEN (%)	WOMEN (%)
<6	0.6	0.08
6-6.9	1.9	3.3
7-7.9	16.7	17.4
8-8.9	25	0
9+	90	0

Data from Faller J, Fox IH. Ethanol-induced hyperuricemia: evidence for increased urate production by activation of adenine nucleotide turnover. N Engl J Med 1982;307:1598-1602.

Uric acid is a highly insoluble molecule; at pH 7.4 and body temperature, the serum is saturated at 6.4 to 7 mg/100 mL. Although higher concentrations do not necessarily result in urate deposition (some unknown factor in serum appears to inhibit urate precipitation), the chance of an acute attack is greater than 90% when the level is above 9 mg/100 mL (Table 169-1). Lower temperatures decrease the saturation point of uric acid, which may explain why urate deposits tend to form in areas such as the pinna of the ear, where the temperature is lower than the mean body temperature (Table 169-2). Uric acid is insoluble below pH 6 and can precipitate as the urine is concentrated in the collecting ducts and passed to the renal pelvis.

Signs and Symptoms

The first attack of gout is characterized by intense pain, usually involving only one joint. The first joint of the big toe is affected in nearly one half of the first attacks and is at some time involved in more than 90% of individuals with gout. If the attack progresses, fever and chills will appear. The first attacks usually occur at night and are generally preceded by a specific event such as dietary excess, alcohol ingestion, trauma, certain drugs, or surgery.

The classic description of gout was offered in 1683 by Sydenham, an English physician who suffered from gout. Little has changed in the clinical picture of gout in more than 300 years. Sydenham's classic description is as follows:

> *The victim goes to bed and sleeps in good health. About two o'clock in the morning he is awakened by a severe pain in the great toe; more rarely in the heel, ankle, or instep. The pain is like that of a dislocation, and yet parts feel as if cold water were poured over them. Then follows chills and shivers, and a little fever. The pain which at first was moderate, becomes more intense. With its intensity the chills and fever increase. After a time this comes to a height, accommodating itself to the bones and ligaments of the tarsus and metatarsus. Now it is a violent stretching and tearing of the ligaments—now it is a gnawing pain and now a pressure and tightening. So exquisite and lively meanwhile is the feeling of the part affected, that it cannot bear the weight of bedclothes nor the jar of a person walking in the room. The night is passed in torture, sleeplessness, turning the part affected, and perpetual change of posture; the tossing about of the body being as incessant as the pain of the tortured joint, and being worse as the fit comes on. Hence the vain effort by change of posture, both in the body and the limb affected, to obtain an abatement of pain.*

TABLE 169-2 **Solubility of Urate Ion as a Function of Temperature in 140 mM Na+**

TEMPERATURE (°C)	MAXIMUM SOLUBILITY (mg/100 mL)
37	6.8
35	6
30	4.5
25	3.3
20	2.5
15	1.8
10	1.2

Data from Faller J, Fox IH. Ethanol-induced hyperuricemia: evidence for increased urate production by activation of adenine nucleotide turnover. N Engl J Med 1982;307:1598-1602.

Subsequent attacks are common, with the majority of such individuals having another attack within 1 year. However, nearly 7% never have a second attack. Chronic gout rarely is an issue owing to the advent of dietary therapy and drugs that lower uric acid levels. When it does occur, chronic gout is due to poor compliance or inadequate response to treatment, or it may arise in patients with high flare frequency, tophi, and the inability to maintain serum urate levels below 6 mg/dL.[2] Some degree of kidney dysfunction occurs in nearly 90% of subjects with gout, and there is a higher risk of kidney stones.

THERAPEUTIC CONSIDERATIONS

The current standard medical treatment of acute gout is administration of colchicine, the antiinflammatory drug originally isolated from the plant *Colchicum autumnale* (autumn crocus, meadow saffron). Colchicine has no effect on uric acid levels; rather, it stops the inflammatory process by inhibiting neutrophil migration into areas of inflammation.

More than 75% of patients with gout show a major improvement in symptoms within the first 12 hours after receiving colchicine. However, up to 80% of patients are unable to tolerate an optimal dose because of gastrointestinal side effects, which may precede or coincide with clinical improvement.

Colchicine may also cause bone marrow depression, hair loss, liver damage, depression, seizures, respiratory depression, and even death. Other antiinflammatory agents are also used in acute gout, including various nonsteroidal antiinflammatory drugs, indomethacin, phenylbutazone, naproxen, and fenoprofen.

Once the acute episode has resolved, a number of measures are taken to reduce the likelihood of recurrence:

- Drugs like allopurinol or febuxostat to keep uric acid levels within a normal range
- Controlled weight loss in obese individuals
- Avoidance of known precipitating factors such as heavy alcohol consumption or a diet rich in purines or refined carbohydrates

- Low doses of colchicine to prevent further acute attacks

Several dietary factors are known to cause gout: consumption of alcohol, especially beer and hard liquor; foods high in purine content (e.g., organ meats, meat, yeast, poultry); fats; refined carbohydrates, especially high-fructose corn syrup; and overconsumption of calories.[5] Individuals with gout are typically obese; they are prone to hypertension, the metabolic syndrome, and diabetes and are at a greater risk for cardiovascular disease. Obesity is probably the most important dietary factor. Thiazide and loop diuretics are also associated with a higher risk of incident gout and higher rate of gout flares.[5]

In concept, the naturopathic approach for chronic gout does not differ substantially from the standard medical approach. However, naturopaths focus on dietary and herbal measures to keep uric acid levels within the normal range rather than on the use of drugs. In the conventional medical treatment of gout, drugs that inhibit xanthine oxidase are often too much relied upon. Allopurinol, a structural isomer of hypoxanthine (a naturally occurring purine in the body), has been the mainstay treatment for decades. However, in February 2009, the U.S. Food and Drug Administration approved febuxostat (Uloric), another xanthine oxidase inhibitor; it is a more effective treatment for lowering and maintaining serum urate levels.[6] Febuxostat is beginning to supplant allopurinol in the conventional management of gout. Uricosuric agents (probenecid, sulfinpyrazone, and benzbromarone) are used as second-line therapy for patients with underexcretion of uric acid.

Lead Toxicity

An additional item of concern relates to lead toxicity. A secondary type of gout, sometimes called saturnine gout, can result from lead toxicity. Historically, saturnine gout was due to the consumption of alcoholic beverages stored in containers with lead in them. An unexpected and fairly common source of lead appears to be leaded crystal, because port wine elutes lead when stored in a crystal decanter.[6] Lead concentration increases with storage time, reaching toxic levels after several months. Even a few minutes in a crystal glass results in a measurable increase in the level of lead in the wine. Lead promotes hyperuricemia as a result of decreasing renal urate excretion.

Dietary Considerations

The dietary treatment of gout involves the following guidelines:

- Elimination of alcohol intake
- Low purine intake
- Achievement of ideal body weight
- Liberal consumption of complex carbohydrates
- Low fat intake
- Low protein intake
- Liberal fluid intake

Alcohol

Alcohol increases uric acid production by accelerating purine nucleotide degradation; it also reduces uric acid excretion by increasing lactate production (a result of ethanol oxidation), which impairs kidney function. The net effect is a significant increase in serum uric acid levels. This explains why alcohol consumption is often a precipitating factor in acute attacks of gout. In many individuals, elimination of alcohol is all that is necessary to reduce uric acid levels and prevent gouty arthritis.

Low-Purine Alkaline-Ash Diet

A low-purine diet has been the mainstay of the dietary therapy of gout for many years. However, with the advent of potent drugs that lower uric acid levels, many physicians lower serum urate levels without subjecting the patient to the inconvenience and deprivation associated with a purine-free diet. However, dietary restriction of purines is recommended to reduce metabolic stress. Foods with high purine levels should be entirely omitted. These include organ meats, meats, shellfish, yeast (brewer's and baker's), herring, sardines, mackerel, and anchovies. Foods with moderate levels of protein should be curtailed as well. These include dried legumes, spinach, asparagus, fish, poultry, and mushrooms.

An alkaline-ash diet is recommended in the dietary treatment of gout, because a more alkaline pH increases uric acid solubility. An alkaline-ash diet was shown to increase uric acid excretion from 302 mg/day at pH 5.9 to 413 mg/day at pH 6.5.[8]

Weight Reduction

Excess weight is associated with an increased rate of gout. Weight reduction in obese individuals significantly reduces levels of serum uric acid levels.[9] Weight reduction should involve the use of a low glycemic diet designed to improve insulin sensitivity. Such a diet also helps to manage the elevated cholesterol and triglycerides that are common in obesity.

Carbohydrates, Fats, and Protein

Refined carbohydrates and saturated fats should be kept to a minimum, as the former increase uric acid production, whereas the latter increase uric acid retention. In addition, one of the key dietary goals in the treatment of gout appears to be the enhancement of insulin sensitivity.[9]

Protein intake should not be excessive (i.e., >0.8 g/kg per day), because it has been shown that uric acid synthesis may be accelerated in both normal and gouty patients by a high protein intake.[5] Adequate protein is necessary (0.8 g/kg daily); however, amino acids decrease the resorption of uric acid in the renal tubules, thus increasing uric acid excretion and reducing serum uric acid concentrations.[7]

Fluid Intake

Liberal fluid intake keeps the urine dilute and promotes the excretion of uric acid. Furthermore, dilution of the urine reduces the risk of kidney stones.

Nutritional Supplements

Eicosapentaenoic Acid

Eicosapentaenoic acid (EPA) supplementation may prove useful in the treatment of gout. EPA limits the production of the proinflammatory leukotrienes, the mediators of much of the inflammation and tissue damage observed in gout.

Folic Acid

Folic acid has been shown to inhibit xanthine oxidase, the enzyme responsible for producing uric acid.[10] Research has demonstrated that a derivative of folic acid is an even greater inhibitor of xanthine oxidase than allopurinol, suggesting that folic acid at pharmacologic doses may be an effective treatment for gout.[11] Positive results in the treatment of gout have been reported, but the data are incomplete and uncontrolled.[12]

Quercetin

The bioflavonoid quercetin has demonstrated several effects in experimental studies, indicating its possible benefit to individuals with gout.[13-15] Quercetin may offer significant protection by inhibiting the following:

- Xanthine oxidase in a similar fashion to the drug allopurinol

- Leukotriene synthesis and release
- Neutrophil accumulation and enzyme release

For more information on the pharmacology of quercetin, see Chapter 92.

Vitamin C

Megadoses of vitamin C are probably contraindicated in individuals with gout, because vitamin C may increase uric acid levels in a small number of individuals.[16]

Niacin

High doses of niacin (i.e., above 50 mg/day) are probably contraindicated in the treatment of gout, because niacin competes with uric acid for excretion.[17]

Botanical Medicines

Cherries

Consuming one-half pound of fresh or canned cherries per day has been shown to be effective in lowering uric acid levels and preventing attacks of gout.[18] To assess the physiologic effects of cherry consumption, one study measured plasma urate, antioxidant, and inflammatory markers in 10 healthy women who consumed two servings (280 g) of cherries after an overnight fast.[19] Blood and urine samples were taken before the cherry dose and at 1.5, 3, and 5 hours afterward. Plasma urate decreased 5 hours after the cherry consumption by an average of 30 mmol/L. This reduction correlated with an increase in urine urate excretion. Plasma C-reactive protein and nitric oxide concentrations decreased slightly after the 3-hour mark.

Cherries, hawthorn berries, blueberries, and other dark red and blue berries are rich sources of anthocyanidins and proanthocyanidins. These compounds are flavonoid molecules, which give these fruits their deep red-blue color, and are remarkable in their ability to prevent collagen destruction. Anthocyanidins and other flavonoids affect collagen metabolism in many ways:

- They have the unique ability to actually cross-link collagen fibers, resulting in reinforcement of the natural cross-linking of collagen that forms the collagen matrix of connective tissue (e.g., ground substance, cartilage, tendon).
- They prevent free radical damage through their potent antioxidant and free radical scavenging action.
- They inhibit enzymatic cleavage of collagen by enzymes secreted by leukocytes during inflammation.
- They prevent the release and synthesis of compounds that promote inflammation, such as histamine, serine proteases, prostaglandins, and leukotrienes.

THERAPEUTIC APPROACH

As stated earlier, the naturopathic approach to the prevention and treatment of gout does not differ substantially from the standard medical approach. The basic approach involves the following:

- Dietary and herbal measures that maintain uric acid levels within the normal range
- Controlled weight loss in obese individuals
- Avoidance of known precipitating factors (such as heavy alcohol consumption and a high-purine diet)
- The use of nutritional substances to prevent further acute attacks
- The use of herbal and nutritional substances to inhibit the inflammatory process

Diet

Patients should be advised to eliminate alcohol intake, maintain a low-purine diet, increase consumption of complex carbohydrates, decrease consumption of simple carbohydrates, maintain a low-fat intake, optimize protein intake (0.8 g/kg daily), and consume liberal quantities of fluid. Urinary 24-hour uric acid levels can be used to monitor compliance with a purine-free diet (maintained below 0.8 g/day).

In addition, liberal amounts (250 to 500 g/day) of cherries, blueberries, and other anthocyanoside-rich (i.e., red-blue) berries (or extracts), should be consumed.

Nutritional Supplements

- Fish oils: 3000 mg EPA+DHA per day
- Folic acid: 10 to 40 mg/day

Botanical Medicines

- Choose one of the following:
- Cherry fruit extract (10:1): 500 to 1000 mg three times a day
- Grape seed extract (>95% procyanidolic oligomers): 100 to 300 mg/day
- Pine bark extract (>90% procyanidolic oligomers): 100 to 300 mg/day
- Anthocyanoside extracts (e.g., *Vaccinium myrtillus*): equivalent to 80 mg anthocyanoside content a day
- Quercetin: 200 to 400 mg three times a day between meals (Note: Consider EMIQ at a dosage of 100 to 200 mg/day, see Chapter 92 for more information).

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CHAPTER 170

Hair Loss in Women

Michael T. Murray, ND

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INTRODUCTION

In clinical practice, one of the most common complaints from female patients is excessive hair loss. In most cases it is not severe alopecia; rather, it is the perception that hair loss is occurring at an increasing rate. Often these complaints are dismissed, because minor hair loss is difficult to quantify and it is certainly not a life-threatening disorder. However, the patient wants an answer as to why it is happening, so it is important to address it. Physicians should also be careful not to underestimate the emotional impact of hair loss for some patients.

BASIC PHYSIOLOGY OF THE HAIR CYCLE

Between 100,000 and 350,000 hair follicles occupy the human scalp, but not all of these hairs undergo cyclic phases of growth and rest. During the growth (anagen) phase, there is active genetic expression of protein synthesis. As the hair matures, it enters into a resting stage (telogen). Then the hair bulb migrates outward and eventually is sloughed. It is during this migratory phase that the stage is set for new hair to fill the remaining papilla after the original hair is lost. Age, pathology, and a wide variety of nutritional and hormonal factors influence the duration of the hair cycle. Generally speaking, hair loss is a normal part of aging. By the age of 40 or so, the rate of hair growth slows down. New hairs do not grow in as quickly as old ones fall out.

The hair-pull test can help to determine the relative formation of new hair. It involves taking a few strands between the thumb and forefinger and pulling on them gently. Anagen hairs should remain rooted in place, whereas hairs in telogen should come out easily. By knowing approximately how many hairs were pulled and the number that came out, the percentage of hair follicles in a telogen state can be determined. Thus, if 20 hairs were pulled and 2 came out, the frequency of telogen hair follicles is 10%. As a very rough guide, a 10% telogen frequency is excellent, up to 25% is typical, and over 35% is problematic. If after the pull test there are still hairs in the balding areas it is regarded as a positive test.

DIFFERENTIAL DIAGNOSIS

Hair loss can be broadly divided into two types: focal and diffuse (Table 170-1). Diffuse hair loss is most often due to *telogen effluvium*—an umbrella term denoting nonscarring alopecia characterized by diffuse hair shedding, often with an acute onset, caused by a metabolic or hormonal stress or by medications. Generally, recovery occurs when the precipitating factors are dealt with. Women can also experience male- or female-pattern hair loss (previously called androgenic alopecia). Focal hair loss is most often secondary to an underlying disorder that may cause nonscarring or scarring alopecia. Nonscarring focal alopecia is usually caused by tinea capitis or alopecia areata, although patchy hair loss may also be caused by traction alopecia or trichotillomania. Scarring alopecia is rare and has a number of causes, most often discoid lupus erythematosus.[14]

CAUSES OF HAIR LOSS IN WOMEN AND THERAPEUTIC CONSIDERATIONS

Five common causes of hair loss in women are discussed below in greater detail: (1) high levels of androgens, (2) drugs, (3) nutritional deficiencies, (4) hypothyroidism, and (5) the presence of antigliadin antibodies.

TABLE 170-1 **Differential Diagnosis of Hair Loss**

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TABLE 170-2 **Classes of Drugs That Can Cause Hair Loss**

CLASS	EXAMPLES
Antibiotics	Gentamicin, chloramphenicol
Anticoagulants	Warfarin, heparin
Antidepressants	Fluoxetine, desipramine, lithium
Antiepileptic drugs	Valproic acid, phenytoin
Cardiovascular drugs	Angiotensin converting enzyme inhibitors, beta blockers
Chemotherapy drugs	Doxorubicin, vincristine, etoposide
Endocrine drugs	Bromocriptine, clomiphene, danazol
Gout medications	Colchicine, allopurinol
Lipid-lowering drugs	Gemfibrozil, fenofibrate
Nonsteroidal antiinflammatory drugs	Ibuprofen, indomethacin, naproxen
Ulcer medications	Cimetidine, ranitidine

Van Neste DJJ, Rushton H. Hair problems in women. *Clin Dermatol,* 1997;15:113-125.

Androgenic Female-Pattern Hair Loss

Women can suffer from androgen-related hair loss, just like men.[1-4] The female pattern, however, is more diffuse than the characteristic male pattern, so it was originally referred to as "diffuse androgen-dependent alopecia"; now, however, it is referred to as either female- or male-pattern hair loss.[1] It is a relatively common condition. In fact, one report states that it affects approximately 30% of women before the age of 50.[1] Although genetic factors are clearly significant, androgen excess, insulin resistance, the polycystic ovary syndrome, and low antioxidant (i.e., reduced glutathione) status are also associated with female-pattern hair loss.[2-10] Three possible recommendations to help slow down this genetically predisposed process are as follows: (1) improve blood glucose regulation through dietary, lifestyle, and supplementary measures (see Chapter 176); (2) increase antioxidant intake; (3) consider saw palmetto extract; and (4) consider hormone replacement therapy.

Reactive oxygen species have been shown to play a central role (along with testosterone) in male-pattern baldness. Higher levels of these damaging compounds are found in the hair follicles of men (and presumably women) with male-pattern baldness.[6] This appears to be due to lower levels of glutathione. The use of glutathione-sparing antioxidants like vitamin C and flavonoids seems appropriate.

Saw palmetto extract is a popular recommendation for benign prostatic hyperplasia (BPH). It is effective in BPH as a result of several mechanisms of action, including an ability to inhibit the formation and transport of dihydrotestosterone (DHT). This potent androgen is formed from testosterone by the action of the enzyme 5-α-reductase. The activity of this enzyme is increased in BPH, as well as in both male- and female-pattern baldness.[7] Saw palmetto extract may offer some benefit in androgen-related alopecia by reducing the formation of DHT. This is the same mechanism as that of the drug finasteride (Propecia), which is often used in the treatment of female-pattern hair loss.[10] Saw palmetto extract also inhibits the transport of DHT to nuclear receptor sites and therefore may prove even more useful. The dosage for the extract standardized to contain 85% to 95% fatty acids and sterols is 320 mg/day.

Drug-Induced Hair Loss

A long list of drugs can cause hair loss, but it should not be assumed that simply because a woman is complaining of hair loss and taking one of these drugs that the drug is the single cause. Of course some drugs, most notably chemotherapy agents like fluorouracil, are obviously causative because they are such powerful inhibitors of hair growth. When medically appropriate, natural alternatives to the suspected drug or drugs should be employed (Table 170-2).

Nutritional Deficiency

A deficiency of any number of nutrients can lead to significant hair loss. Zinc, vitamin A, essential fatty acids, and iron should be ruled out first. The patient's nails should be examined for the characteristic white lines indicating poor wound healing of the nail bed even with the most minor of trauma, which may be a sign of a low zinc level. The backs of the arms should be examined for hyperkeratosis, a common sign of vitamin A deficiency. The skin of the elbows and general health of the skin should also be evaluated, looking for the dry skin associated with a deficiency of essential fatty acids. To determine iron status, a serum ferritin evaluation is recommended.

In evaluating serum ferritin levels, it is important to know that many reference laboratories report low ferritin levels (e.g., 10-30 mg/L) to be within the normal range. If the serum ferritin is less than 30 mg/L, iron replacement is indicated. When serum ferritin levels fall below this, hair growth and regeneration are impaired, as the body seeks to conserve the remaining iron.[11] There is a very strong association between low body iron stores and diffuse hair loss in women when the serum ferritin level is at or below 30 mg/L.[12,13]

Women with noticeable generalized hair loss typically suffer from deficiencies of all of these nutrients. The treatment of hair

loss secondary to nutritional deficiency is straightforward—the dietary intake of these nutrients must be increased and supplements used appropriately. One caveat is that many of these women turn out to be hypochlorhydric. In these cases, hydrochloric acid supplementation at meals may be all that is necessary. A general recommendation for women with hair loss related to nutritional status is to take a high-potency multivitamin/multimineral formula that contains iron along with 1 tablespoon of flaxseed oil per day. If their serum ferritin levels are below 30 mg/L, such women can consume iron-rich foods and supplement with additional iron, either 30 mg of iron bound to succinate, fumarate, or other chelate twice daily between meals. If this recommendation results in abdominal discomfort, 30 mg taken with meals three times daily can be suggested. After 2 months, serum ferritin levels should be reassessed. Improvements in serum ferritin often correlate with improved health of the hair and the halting of excessive hair loss.

Hypothyroidism

It is well known that hair loss is one of the cardinal signs of hypothyroidism. Using blood levels of thyroid hormones as the criterion, an estimated 1% to 4% of the adult population has moderate to severe hypothyroidism and another 10% to 12% have mild hypothyroidism.[15] The prevalence of hypothyroidism in American women is estimated to be as high as 20%, even among practitioners of conventional medicine.

Antigliadin Antibodies

The protein gluten and its polypeptide derivative, gliadin, are found primarily in wheat, barley, and rye. It appears that antibodies to gliadin can elicit cross-reacting antibodies that attack the hair follicles, leading to alopecia areata—an autoimmune disease characterized by areas of virtually complete hair loss.[16]

BOX 170-1 Key Diagnostic Features of Celiac Disease

- Bulky, pale, frothy, foul-smelling, greasy stools with increased fecal fat
- Weight loss and signs of multivitamin and mineral deficiencies
- Increased levels of serum gliadin antibodies
- Diagnosis confirmed by jejunal biopsy

Celiac disease, also known as nontropical sprue, gluten-sensitive enteropathy, or celiac sprue, is characterized by malabsorption and an abnormal small intestinal structure that reverts to normal on removal of dietary gluten. Evidence is growing that many people with gluten intolerance do not have overt gastrointestinal symptoms. Instead, they may demonstrate gluten intolerance insidiously as hair loss. Rather than testing for antigliadin antibodies in patients with general hair loss or alopecia areata, the test for human antitissue transglutaminase antibodies (IgA anti-tTG) is recommended, because it is more sensitive than the test for antigliadin antibodies (see Chapter 155). This recommendation is especially important in the presence of any gastrointestinal symptoms pointing to celiac disease (Box 170-1).

CONCLUSION

Hair loss in women should not be dismissed. Although some hair loss is a natural part of the aging process, complaints of excessive or accelerated hair loss should be investigated and treated appropriately. Clinical studies have investigated the psychological impact of increasing hair loss in women and found that it is a significant source of anxiety, fear, and depression.[1,4] Conversely, increasing the health of the hair results in an improvement in the general health, especially the mental health, of these patients.

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CHAPTER 171

Hepatitis

Melissa Palmer, MD, and Peter B. Bongiorno, ND, LAc

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GENERAL CONSIDERATIONS

Hepatitis refers to inflammation (-itis) of the liver (hepar-). Inflammation lasting less than 6 months is known as acute hepatitis, whereas that lasting longer than 6 months is called chronic hepatitis. In people with acute hepatitis who do not progress to chronic disease, all of the symptoms, signs, and blood test abnormalities return to normal without permanent or long-term sequelae. People who progress from acute to chronic hepatitis are at risk of progressing to cirrhosis and its complications, such as portal hypertension and hepatocellular carcinoma (HCC). Hepatitis is a term that encompasses many inflammatory causes, such as autoimmune liver disease, obesity, alcoholic liver disease, and some medications and herbs. Only hepatitis caused by a virus (viral hepatitis) is potentially infectious to others. This chapter focuses on viral hepatitis A, B, and C.

Hepatitis A is caused by a virus of the Picornaviridae family and is transmitted via the fecal–oral (enteric) route by person-to-person contact. Prior to its identification in 1973, hepatitis A was known as infectious hepatitis. It is the most common cause of acute viral hepatitis in the United States, with approximately one third of adults having evidence of prior exposure, as do almost all people living in areas of poor sanitation. Although infection with the hepatitis A virus (HAV) does not lead to chronic disease, it accounts for an estimated 100 deaths each year in the United States.

Hepatitis B is caused by a virus of the Hepadnaviridae family and is transmitted via the parenteral route through blood or blood products, through sexual contact, or from mother–child transmission during pregnancy and childbirth. Prior to its identification in 1963, it was known as serum hepatitis. Approximately 350 to 400 million people worldwide, including 1.25 million people in the United States, are chronically infected with the hepatitis B virus (HBV), defined through blood work as a positive hepatitis B surface antigen (HBsAg) and a positive hepatitis B core antibody (HBcAb). Chronic HBV infection is the most common cause of cirrhosis and liver cancer worldwide.[1]

Hepatitis C is caused by a virus of the Flaviviridae family and is transmitted via the percutaneous route through blood-to-blood contact. Intravenous drug users, anyone who received a blood or a blood-product transfusion prior to 1992, individuals born to a mother infected with the hepatitis C virus (HCV), and those who may be at increased risk for exposure to infected blood, such as health care or public safety workers, are at increased risk of infection. Unlike the case with HBV, sexual contact is an inefficient means of HCV transmission. Prior to its identification in 1989, it was known as non-A non-B hepatitis. An estimated 130 million people worldwide, 5 million of whom are in the United States, have been exposed to HCV, and approximately 350,000 to 500,000 people per year die of HCV-related liver disease.[2,3]

Symptoms and Signs

Acute viral hepatitis may be totally asymptomatic, or may be an extremely debilitating disease manifesting with jaundice, flulike symptoms, decreased appetite, abdominal pain, nausea, diarrhea, vomiting, and fatigue. Typically, the more severely ill and jaundiced a person is during the acute phase of hepatitis, the better his or her chances of not progressing into chronic hepatitis. The probability of developing chronic disease is approximately 1% to 5% in HBV- infected adults and

approximately 90% to 95% in HBV-infected infants. Hepatitis A never leads to chronic disease. Hepatitis C progresses to chronicity in 55% to 85% of infected individuals, with females and children being less likely to progress to chronic diseases than male adults.[4,5] The symptoms of chronic hepatitis vary from virtually nonexistent to relentless fatigue as well as signs and symptoms of decompensated cirrhosis, such as ascites, variceal bleeding, and hepatic encephalopathy.

DIAGNOSTIC CONSIDERATIONS

A diagnosis of hepatitis is made via a combination of a thorough history and physical examination, laboratory tests including serial liver function tests (aspartate aminotransferase [AST] and alanine aminotransferase [ALT], which are known together as transaminases), and hepatitis-specific serologies in addition to imaging studies. Because these evaluations typically do not accurately correlate with the extent of damage done to the liver, a liver biopsy is often necessary to determine the grade (degree of inflammation) and stage (degree of fibrosis) of the disease as well as the need for therapy.

Prevention

All people with chronic liver disease or chronic hepatitis of any etiology should receive immunizations for hepatitis A and B if they have not already been exposed to these viruses. The hepatitis A vaccination was first approved by the FDA in 1995. The development of the hepatitis B vaccine represents one of the most important advances in medicine. This is the first and only vaccine in history that can simultaneously prevent liver cancer, cirrhosis, and a sexually transmitted disease, hepatitis B. The FDA approved the hepatitis B vaccine in 1981, and the improved version has been available since 1986.

It is considered safe to administer the hepatitis B vaccine to pregnant women if needed. Infants born to HBsAg-positive mothers should receive both the hepatitis B vaccination and the hepatitis B immune globulin (HBIG) within 12 hours of birth. See Box 171-1 for a list of those at increased risk for hepatitis B and who therefore should receive the hepatitis B vaccination.

There is currently no vaccine available to prevent HCV. One of the major barriers to the development of this vaccine involves the complex HCV population of mutant strains, known as quasispecies, that can exist in a person infected with hepatitis C.

The hepatitis A virus can be killed by boiling infected foods for at least three minutes and by disinfecting surfaces with bleach. It is best to avoid eating raw or partially cooked mollusks (clams, oysters, mussels, and scallops), as these fish often live in HAV-contaminated rivers and seas. When traveling to areas of the world known to have a high incidence of hepatitis A, it is especially important to eat well-cooked foods and to drink only bottled water. Sanitizing diaper-changing tables is also important, as hepatitis A–infected infants are typically a silent source for the spread of hepatitis A infection. Meticulous handwashing is of great importance after using the bathroom, before eating a meal, and before preparing food for others.

The avoidance of unprotected sex will greatly reduce the likelihood of infection with HBV. Employing a barrier such as a condom, dental dam, female condom, and finger cot will decrease the risk of transmission and acquisition of HBV. Although the risk of sexual transmission of HCV is rare, protected sex is recommended if a person engages in anal sex, has multiple sex partners, has frequent prostate infections, has open cuts or sores on the genitalia, or is menstruating. People with hepatitis B or C should avoid sharing anything that may contain even the tiniest amount of their blood, including toothbrushes, razors, and nail clippers.

BOX 171-1 Groups Recommended to Receive the Hepatitis B Vaccination

- All newborns with HBsAg-positive mothers
- At-risk children age 11 or 12 who did not receive the vaccine at birth
- People of any age who have more than one sex partner within a 6-month period
- People with a sexually transmitted disease
- Immigrants from geographic areas in which HBV is endemic—Asia, sub-Saharan Africa, Middle East, Amazon basin
- Children born in the United States to a person from an HBV-endemic area
- Adopted children from HBV-endemic areas
- Men who have sex with men
- Intravenous drug users and their sex partners
- People with blood-clotting-factor disorders
- Those who have intimate or household contact with a person who is an HBV carrier (HBsAg-positive).
- People who work in health care
- Public safety workers who may come into contact with blood
- People receiving hemodialysis
- People who live or work in an institution for the developmentally disabled
- Prison inmates
- Alaskan Natives and Pacific Islanders

In order to further reduce the likelihood of spreading hepatitis B and C, people who are using injection drugs should never share needles with others or inject themselves with a used needle. A drop of blood so minuscule that it cannot be seen by the human eye may contain hundreds or even thousands of HBV and/or HCV particles. Even meticulous cleaning may not totally eradicate the virus from a needle. If a person needs unused needles but cannot obtain them, he or she should seek out a needle-exchange program. Alternatively, needle use can be limited to autodestruct syringes. These needles are not reusable. They are designed to self-destruct after one use so that they cannot be reused or shared with others. Of course the best advice for a person who continues to use illicit drugs is to discontinue this activity immediately and seek help at a drug rehabilitation center. Also, anyone who intends to get a tattoo or have a body part pierced should deal only with establishments that are clean and that adhere to meticulous sterilization practices.

THERAPEUTIC CONSIDERATIONS

Conventional Therapies

The goals of treatment of chronic hepatitis are to achieve sustained viral suppression or total elimination of the virus from the body; to slow or prevent progression to cirrhosis, hepatic decompensation, and HCC; and to prevent transmission to others. Chronic hepatitis B is not curable. Conventional treatment options for hepatitis B include either nucleoside/nucleotide analogues (NAs) or pegylated interferon. Interferons (IFNs) are a family of proteins made naturally by the body that have antiviral, antiproliferative, and immunomodulatory properties. IFN and pegylated IFN have been shown to be effective in reducing HBV

BOX 171-2 Factors Impacting Hepatitis C SVR Rates

Host Factors
- Ethnicity
- BMI
- Age
- Insulin resistance/DM
- Gender
- Alcohol use
- Nutritional factors

Viral Factors
- Genotype
- Viral load
- Interleukin-28B polymorphism

Disease Factors
- Degree of fibrosis
- HCV/HIV coinfection

Adherence Factors
- Patient education
- Response-guided therapy
- Management of AEs
- Alternative RBV formulations
- Support team – medical and personal

replication and inducing disease remission. However, the efficacy of IFN is limited to a narrow population of HBV patients. In addition, its numerous side effects, difficult subcutaneous route of administration, cost, and associated high relapse rate after medication is discontinued have hampered its use for patients with chronic HBV. There are currently five FDA-approved NAs for the treatment of chronic HBV. NAs are quite effective for suppressing HBV replication, induction of disease remission, and the improvement of long-term outcomes. However, the length of time during which patients are treated is not predefined; and is determined by specific parameters that may differ from one patient to another, and treatment may be indefinite for some. Furthermore, long-term use of NAs can be complicated by the selection of antiviral-resistant mutations.

In contrast to hepatitis B, hepatitis C is a curable disease in many patients. This is referred to as a sustained virologic response rate (SVR) and ranges between approximately 20% to 90% (i.e., it is a measure of virus suppression). Length and success of HCV treatment are dependent upon a variety of factors (see Box 171-2). Pegylated interferon (PI) administered subcutaneously once a week, along with oral ribavirin (RBV) pills daily for 24 to 48 weeks, is the current standard of care (SOC) treatment for patients with chronic hepatitis C genotypes 2 and 3, and was the SOC for patients with genotype 1 (G1), the most common and most difficult to cure genotype worldwide. In May 2011, a major advance in the field of hepatology occurred. With the addition of a protease inhibitor, either telaprevir (*Incivek,* manufactured by Vertex) or boceprevir, (*Victrelis,* manufactured by Merck), to SOC treatment, SVRs jumped from approximately 42% to as high as 86% for many G1 patients. And, between 44% and 60% of treatment naïve G1 patients are now capable of being cured in just 24 to 28 weeks as opposed to 48 weeks. However, numerous adverse events (AEs), complex treatment regimens, exorbitant costs, and the potential for the development of drug-resistance, may decrease their therapeutic usefulness. This underscores the need for clinicians to be aware of the effects of natural and integrative therapies on the progression of HCV, and of the potential benefits of these therapies either with or without SOC treatment for chronic hepatitis C.

Several nutrients and herbs, discussed later, have been shown to inhibit viral reproduction, improve immune system function, and stimulate regeneration of the damaged liver cells.

Lifestyle Recommendations

Sleep

Experimental studies have demonstrated that sleep deprivation results in poorer immune function, such as reduced natural killer cell activity, suppressed interleukin-2 production, and increased levels of circulating proinflammatory cytokines.[6,7] A recent study showed that survival was inversely associated with sleep disturbance among 156 patients with cirrhosis. The study's authors suggested that tailored behavioral interventions might help to improve overall health-related quality of life and could potentially improve patient outcomes.[8] Sleep problems have been reported in patients with chronic hepatitis C, with about 60% to 65% of individuals reporting such complaints. Subjects administered IFN-α demonstrated increased waking after sleep onset, decreased sleep efficiency, and reduced stage 3 and/or 4 sleep.[9] Evidence also suggests that impairments in sleep quality exist independent of antiviral therapy with IFN-α and prior to the advanced stages of liver disease.[10] Sleep deprivation has also been found to attenuate antibody response to hepatitis A immunization.[11] In terms of sleep duration, individuals with less than 7 hours of regular sleep are approximately three times more likely to develop a cold when exposed to nasally introduced rhinovirus than those with 8 hours or more of sleep.[12] It may therefore be prudent to encourage proper sleep habits and a duration of 8 hours or more in order to optimize immune and antiviral benefits in the hepatitis patient as well.

Exercise

The benefits of exercise for people with liver disease are numerous. Studies of patients with hepatitis C incorporating exercise as part of their therapy with SOC show that they can safely participate in an exercise program, create clear changes in the way they perceive their bodies and its capacities, as well as improve their self-confidence, all of which can lead to far-reaching changes in the way this disease and the constraints of treatment are perceived.[13] Because fatigue is probably the most common as well as one of the most bothersome symptoms affecting people with chronic hepatitis, exercise can provide a boost of energy and also improve cardiovascular function. Exercise leads to a reduction in total body fat, which is important to all people with liver disease. When total body fat is reduced, the fat content of the liver is also reduced, often resulting in a significant reduction in elevated liver enzymes.[13] Thus, it is recommended that all patients with chronic hepatitis incorporate an exercise program combining weight training and aerobics into their daily routine as tolerated once they have been medically cleared by their physicians.

Diet

Nutritional treatment decisions for those with acute viral hepatitis should be symptom directed. In general, the focus should be on replacing fluids through consumption of vegetable broths, diluted vegetable juices (diluted with 50% water), and herbal teas in order to avoid dehydration, especially if diarrhea is present. Alcohol should be completely avoided because it can trigger a relapse of acute hepatitis.

Nutritional treatments for chronic viral hepatitis have been shown to have a significant impact on disease progression (e.g., obesity, alcohol consumption, and iron overload) and can worsen the disease, whereas the consumption of caffeine may be helpful. A diet low in saturated fats, simple carbohydrates (e.g., sugar, white flour, fruit juice, honey), oxidized fatty acids (fried oils), sodium, and animal products may be beneficial in patients with decompensated cirrhosis complicated by ascites (fluid retention) and/or hepatic encephalopathy (HE) (brain fog). A diet focused on plant foods (i.e., a high-fiber diet) has been shown to increase the elimination of bile acids, drugs, and toxic bile substances in some patients with decompensated cirrhosis complicated by HE. Alcohol should be completely avoided.

Fruit and Hepatitis C

Blueberries have been found to inhibit the replication of HCV,[14] and rats fed diets high in blueberries were protected from developing acute hepatitis.[15] This effect may be due to the antioxidant properties of the flavonoid proanthocyanidin that is a component of blueberry leaves.

Naringenin, a flavanoid contained in grapefruit and other citrus fruits, has been found to have antiinflammatory, antioxidant, and lipid-lowering properties and may act as a promoter of carbohydrate metabolism. Naringenin has been found to lower very low density lipoprotein cholesterol. It is suspected that the hepatitis C virus may "hitch a ride" on cholesterol—a theory that has held up in test tube experiments. Studies have demonstrated that naringenin can inhibit or reduce steatosis, (the deposition of fat in the liver),[16] in addition to inhibiting HCV viral replication.[17] It is important to remember that grapefruit contains furanocoumarins and flavonoids, which can inhibit components of the cytochrome P450 drug metabolism pathway leading to toxic levels of many medications.[18,19]

Caffeine and Hepatitis C

The mechanism by which caffeine exerts its hepatoprotective effect is under investigation. Data from two population-based studies found that people consuming more than 2 cups of coffee a day were less likely to have elevated serum liver enzymes and were less likely to have chronic liver disease when compared with those who did not drink coffee.[20,21] The protective effect of coffee drinking on the development of cirrhosis and its complications, including HCC, has also been shown.[22-25]

Higher coffee consumption was associated with less hepatic steatosis, a lower ratio of serum aspartate (AST)/alanine aminotransferase (ALT), and lower α-fetoprotein levels in patients with hepatitis C. Patients who drank more than 2 to 3 cups of coffee a day had a lower incidence of disease progression and less fibrosis on histologic evaluation compared with HCV patients who drank less coffee.[22,26] Similar results were not seen in patients who got caffeine from other sources or who consumed decaffeinated coffee. Caffeine may also reduce the fatigue associated with HCV and/or chronic liver disease. Although the exact coffee intake necessary to obtain benefits is unclear, it appears reasonable for patients with hepatitis C to drink 2 to 4 cups of regular coffee daily.

Whey Protein

A product of the milk curding process, whey may boost immune function, protect against free-radical damage, and improve cellular glutathione levels. A preliminary trial found that 24 g of whey protein daily reduced serum ALT levels and increased plasma glutathione levels in people with hepatitis B but not those with hepatitis C.[27]

Nutrient Therapeutics

Vitamins C and E

Patients with hepatitis C treated with pegylated interferon and ribavirin were found to have higher SVRs and to be less likely to experience ribavirin-associated anemia when they supplemented this antiviral treatment with vitamins C and E.[28,29] It should be kept in mind that vitamin C increases iron absorption and many patients with hepatitis C already have elevated iron stores.

Vitamin E levels have been shown to be low in both serum[30] and liver tissue[31] in people with hepatitis as well as in those who later develop liver cancer from chronic hepatitis. In one preliminary trial of adults with hepatitis C, administering 1200 IU/day of vitamin E for 8 weeks appeared to reduce liver damage.[32] In another study, 544 IU of vitamin E/day for 24 weeks improved the response to interferon/antioxidant therapy, although the results did not reach statistical significance.[33]

Zinc and Hepatitis C

Zinc is essential to the normal functioning of the immune system and may protect the liver from chemical damage. Some researchers believe that zinc may protect the body from viruses, including the common cold. Blood zinc levels have been shown to inversely correlate with progression of chronic hepatitis C, and zinc deficiency is often present in patients with hepatitis C who also have HCC and/or cirrhosis. Oral zinc supplementation (150 mg/day) may slow HCV progression and reduce the incidence of HCC in these patients.[35,36] In addition, zinc supplementation may improve the response to interferon treatment in patients with chronic hepatitis C.[37,38] One study using 17 mg of zinc twice daily (in the form of a zinc complex of L-carnosine) enhanced the response to interferon therapy in patients with chronic hepatitis C.[39] However, it is not clear whether this benefit was due primarily to the zinc or the carnosine. Although daily doses up to 100 mg of zinc may boost the immune system and improve the response to interferon, an excess of this amount may be immunosuppressive. It should also be kept in mind that excessive zinc consumption may lead to nausea, vomiting, and diarrhea, all possible side effects of HCV antiviral SOC therapy.

Vitamin D and Hepatitis C

Patients with chronic hepatitis C often have lower serum levels of 25 hydroxy (OH) vitamin D than individuals without hepatitis C and approximately one third of these patients are severely vitamin D–deficient.[40] Decreased 25 (OH) vitamin D serum levels have been independently correlated with both the severity of inflammation and fibrosis on histologic evaluation, as well as with a reduced incidence of sustained virologic responses (SVRs) to therapy with SOC pegylated interferon (PI) plus ribavirin (RBV).[41] Additional preliminary findings have suggested that supplementation with vitamin D (1000-4000 IU/day) with the goal of achieving a serum level greater than 32 ng/mL may improve SVRs in some HCV patients treated with SOC antiviral therapy. These results suggest that the immunomodulatory properties of vitamin D may act in synergy with this antiviral therapy. Further evaluation revealed that tissue expression of cytochrome P450 25-hydroxylating liver enzymes CYP27A1 paralleled with vitamin D levels and inversely correlated with hepatic necroinflammatory activity. Although further study is expected, because population-based studies have concluded that up to 75% of Americans are deficient in vitamin D,[42] it seems reasonable for all patients with hepatitis C to add vitamin D to their antiviral regimens.

Selenium

Selenium is a trace element required for the activity of the enzyme glutathione peroxidase, an oxidant mediator essential to human health. Its deficiency is associated with various pathologies, including immune dysfunction, cancer, and liver necrosis. Whole blood and plasma selenium levels in 59 patients with chronic liver pathologies including alcoholic and viral liver cirrhosis were found to be significantly lower than in healthy controls.[43] Another study of hepatocellular carcinoma cell lines reveals that liver cancer cells are able to acquire a selective survival advantage that is prominent under conditions of selenium deficiency and oxidative stress.[44] Oxidative stress is a well-known feature in late-stage cirrhotic liver disease, and subsequent study has found it to occur much earlier than had previously been thought.[45] Yu and colleagues found that selenium deficiency correlated with the development of HCC in patients with chronic hepatitis B[46] and that patients supplemented with 200 mcg of selenium daily were less likely to develop HCC as compared with nonsupplemented individuals.[47] Given this information and the safety of selenium when used in doses below 1000 mcg, it is reasonable to employ selenium in a hepatitis protocol.

S-Adenosyl Methionine (SAMe) and Hepatitis C

SAMe functions as a methyl group donor. In a mouse model SAMe has been shown to enhance interferon's antiviral properties.[99] In a small pilot study performed on G1 HCV nonresponders to pegylated interferon plus ribavirin, it was demonstrated that those patients who were retreated with the same regimen but supplemented with 400 mg SAMe tablets per day, displayed both improved early viral kinetics and interferon signaling. This led to enhanced interferon responsiveness and resulted in a higher percentage of patients achieving SVR.[100]

Liver Extracts

The oral administration of liver extracts has been used in the treatment of many chronic liver diseases since 1896. Numerous investigations into the therapeutic efficacy of liver extracts have demonstrated that these extracts promote hepatic regeneration and are quite effective in the treatment of chronic liver disease, including chronic active hepatitis.[48-50] For example, in one double-blind study, 556 patients with chronic hepatitis were given either 70 mg of a liver extract or a placebo three times daily.[50] At the end of 3 months, the group receiving the liver extract had far lower liver enzyme (aminotransaminase) levels, suggesting that liver extract may have an antiinflammatory effect on the liver. This study must be interpreted with caution, because the cause of chronic hepatitis was not clearly stated.

Thymus Extracts

The effectiveness of orally administered bovine thymus in viral hepatitis is reflective of broad-spectrum immune system enhancement presumably mediated by improved thymus gland activity. Several double-blind studies in both acute and chronic hepatitis B have shown that thymus extracts may be effective. In these studies, a therapeutic effect was noted by accelerated decreases of liver enzymes (transaminases), elimination of the virus, and a higher rate of seroconversion to anti-HBe.[51,52] (see Chapter 56 for additional information on the thymus gland).

Botanical Medicines

Although long-term clinical trials have yet to confirm the efficacy of plant medicines,[53] several have been investigated for their effects in viral hepatitis. The two with the most positive results are licorice *(Glycyrrhiza glabra)* and silymarin (the flavonoid complex from milk thistle, *Silybum marianum*).

Glycyrrhiza Glabra (Licorice Root)

Glycyrrhizin is the component of licorice root most responsible for its benefits. Glycyrrhizin has been shown to reduce serum alanine transaminase and aspartate transaminase values. Glycyrrhizin inhibits immune-mediated cytotoxicity against hepatocytes and also antagonizes nuclear factor (NF)-κ B, a transcription factor that activates genes encoding inflammatory cytokines.[39]

Licorice is suggested to exert many pharmacologic actions beneficial in the treatment of acute and chronic hepatitis, including the following:

- Antihepatotoxic effects
- Immune-modulating actions
- Antiviral effects
- Choleretic effects

Licorice has been shown to stimulate the production of the body's natural supply of interferon. This may account for its popularity in Japan, where it is sometimes used in the treatment of chronic viral hepatitis.[54-59] When used intravenously, licorice has been demonstrated to lower liver enzymes,[60] and studies have suggested a possible beneficial effect in treating hepatitis C and in decreasing the risk of HCV-associated HCC.[61,62] A product called Stronger Neominophagen C (SNMC) consists of 200 mg of glycyrrhizin, 100 mg of cysteine, and 2000 mg of glycine in 100 mL of physiologic saline. When it is administered intravenously, liver enzymes were decreased in approximately 40% of patients[54-58]; however, the HCV load was not reduced. Furthermore, the beneficial effect of SNMC on the reduction of liver enzymes was short-lived: after discontinuation of this supplement, ALT elevations returned. A similar outcome was found by others.[60]

In a study of 453 Japanese patients diagnosed with chronic hepatitis C, 84 were treated with SNMC at a dosage of 100 mL/day for 8 weeks, followed by treatments two to seven times weekly for periods up to 16 years. The rates of cumulative HCC and cirrhosis in year 10 were 7% and 12%, respectively; in year 15, they were 12% and 21%, respectively. And in a cohort of HCV patients who were unresponsive to interferon therapy, intravenous glycyrrhizin decreased the risk of progression to HCC.[63] Unfortunately the beneficial results of glycyrrhizin in hepatitis are not consistent. When lower doses of oral glycyrrhizin were used, significant reductions in ALT levels were not observed. Many have concluded that although licorice may reduce ALT elevations, long-term beneficial effects on HCV-associated fibrosis have not been shown.[64]

The main adverse effect of licorice administration is the production of its aldosterone-like effects; thus, licorice should probably not be used in patients with a history of ascites, hypertension, or renal failure or who are currently using of digitalis preparations.

Silybum Marianum (Milk Thistle)

The origins of the effects of milk thistle on the liver can be traced back to ancient Roman times when Pliny the Elder (AD 23-79) referred to the milky juice of this plant as being excellent for "carrying off bile." John Gerard, a sixteenth-century British herbalist, recommended milk thistle for "expelling melancholy," a symptom attributed to liver disease during that era. In Germany, during the nineteenth century, doctors commonly treated jaundice and other liver diseases with an extract from milk thistle seeds. In 1949, German researchers found that milk thistle appeared to protect the livers of animals exposed to high doses of carbon tetrachloride, a potent hepatotoxin.

In 1968, it was found that the active ingredient in milk thistle is located in the seed and that it consists of three components: silybin, silydianin, and silychristin, collectively referred to as the silymarin, a flavonoid. Silymarin is currently used in Europe to treat all types of liver disorders. In the United States, because of the lack of FDA regulation, the actual percentage of biologically active silymarin in a given preparation of milk thistle is unknown.

Silymarin inhibits hepatic damage by doing the following:

- Acting as a direct antioxidant and free radical scavenger
- Increasing the intracellular content of glutathione and superoxide dismutase
- Inhibiting the formation of leukotrienes
- Stimulating hepatocyte regeneration

Silymarin has been used to treat both acute and chronic hepatitis of varying etiologies. In a study conducted in patients with acute viral hepatitis, 29 patients treated with silymarin showed greater improvements in serum levels of bilirubin and liver enzymes compared with the placebo group.[65]

Other investigators specifically evaluating the antiviral effect of silymarin on patients with hepatitis C concluded that improvements in some symptoms occurred when silymarin was administered orally but that it failed to exert an antiviral effect or result in significant reductions in ALT or improvements in ultrasound abnormalities related to hepatitis C.[66,67]

In humans, flavonoids have a low bioavailability owing to extensive first-pass metabolism; thus, plasma levels needed to exert an antiviral effect may not be possible. Discrepant results reported by various investigators may be due to lack of homogeneity among doses and routes of administration.

A newer form of silymarin that binds it to phosphatidylcholine (referred to as silymarin phytosome) may provide greater benefit. A growing body of research indicates that phosphatidylcholine-bound silymarin is better absorbed and produces better clinical results than the unbound variety.[68-73] These benefits were demonstrated in a study involving 232 patients with chronic hepatitis (viral, alcoholic, or chemically induced) treated with silymarin phytosome at either 120 mg twice a day or 120 mg three times a day for up to 120 days.[73] Liver function returned to normal faster in patients given silymarin phytosome compared with both the commercially available silymarin and placebo.

Intravenous silibinin is capable of the greatest suppression of hepatitis C viral replication. The first study that provided clear evidence of the antiviral effects of silymarin in humans with hepatitis C was published in 2008 by Ferenci and colleagues.[74] These investigators found that such patients who were nonresponders to SOC treatment were able to achieve undetectable HCV RNA levels after intravenous administration of silibinin for 15 days. Although these results proved to be temporary, the antiviral effect of intravenous silibinin was permanent for one patient with hepatitis C who received this treatment for 2 weeks after liver transplantation. This suggests that silibinin may be capable of preventing graft reinfection with HCV.[75] Further studies are needed to confirm these promising results.

Phyllanthus Amarus

P. amarus is an Asian herb with a long history of use in liver disorders. A preliminary report in 1988 demonstrated that 59% of patients with hepatitis B had lost the hepatitis B surface antigen when tested 15 to 20 days after treatment with a preparation of *P. amarus* (200 mg of the dried, powdered, sterilized plant in capsules three times a day).[76] In this double-blind study, only 4% (1 of 23) placebo-treated controls tested negative. Although this report was met with a great deal of excitement,[77] these results have not been confirmed by other researchers,[77-80] indicating that either the type of extract used was not effective or that *Phyllanthus* itself is not effective.

Combination Approach with Antioxidant and Botanical Therapy

A report by Berkson describes three patients with advanced cirrhosis, portal hypertension, and esophageal varices secondary to chronic hepatitis C infection who were effectively treated with a low-cost combination program.[81] Although these patients were originally given extremely poor prognoses, all "recovered quickly," showed improved liver enzymes, and were able to resume their normal daily activities. One patient revealed a substantial improvement in her condition within only 2 weeks. The other patients progressed to health within 4 to 7 months.

Berkson's regimen was composed of oral supplementation of α-lipoic acid (600 mg/day in two divided doses), selenium (as selenomethionine at 400 mcg/day in two divided doses), and silymarin (900 mg/day in three divided doses). The subjects were also asked to take a B-complex vitamin, eat a diet high in fruits and vegetables, consume 4 oz or less of meat per meal, and drink eight glasses of water per day. They also took between 1000 and 6000 mg of vitamin C daily and 400 IU/day of vitamin E. They were encouraged to walk 1 mile three times a week. Only the α-lipoic acid/selenium/silymarin portion of the protocol was verified, and it is not known how strictly the other nutritional and lifestyle suggestions were followed.

Although this protocol is documented in only three cases, it makes reasonable sense from a naturopathic standpoint given the excellent safety record, reasonable cost, and known efficacy of the individual treatment options and is certainly worth trying, especially in patients failing to respond to conventional therapies. It is hoped that stringent clinical trials of this type of multiantioxidant/lifestyle combination protocol will be conducted in the near future.

Acupuncture and Chinese Medicine Herbs

The Chinese medicine diagnosis for hepatitis often includes consideration of damp heat in the liver and spleen channels. Acupuncture points and herbal formulas are often directed at clearing heat and damp to cool and drain these channels. Often efforts are made to also nourish liver blood and tone the liver and spleen.

In a study of 60 patients with hepatitis B, 30 were given acupuncture once a day for 30 minutes for 4 to 6 weeks while the other 30, the control group, continued their conventional medication. Those in the treatment group had significantly shorter recovery times, greater symptom improvement, and lower interleukin-8 levels.[82] Studies have also investigated the use of acupuncture to improve secondary and comorbid symptoms such as depression and myalgias. One 6-week trial categorized 28 patients: group one comprised 13 patients with high depression and myalgia scores; group two was made up of 11 patients with low depression but high myalgia scores; and group three consisted of 4 patients with high depression but low myalgia scores. When compared with baseline levels, significant improvement was shown in end-treatment depression and myalgia scores.[75] Although no positive outcomes regarding improved viral load using acupuncture have been shown, acupuncture may help other symptoms, improve immune balance, and lower comorbidities in patients with hepatitis. More study is needed, but given the possible benefit and low risk, acupuncture may be a reasonable therapy.

Because the standard operating procedure for acupuncture mandates the use of clean-needle technique, the risk of hepatitis

from acupuncture is considered extremely low.[83] Acupuncture may help to improve symptoms and hepatic function. A patient should look for a practitioner who uses only disposable needles as opposed to resterilized needles.

Sho-saiko-to or "Xiao Chai Hu Tang"

Sho-saiko-to (named Xiao Chai Hu Tang in Chinese) is a botanical formulation containing seven herbs traditionally used to treat liver and gastrointestinal disorders.[84] This formula has been shown in animal models to prevent liver injury and promote liver regeneration by inhibiting oxidative stress on lipid peroxidation in hepatocytes and hepatic stellate cells[85,86] and, in human trials, to prevent the progression of cirrhosis to HCC.[87] One prospective study of 260 patients also found that it increased the survival of those with chronic viral hepatitis by reducing progression to HCC.[88]

Clinical studies are ongoing at Sloan Kettering to determine whether Sho-saiko-to can increase survival in patients with liver cancer. Of note, this treatment is contraindicated with interferon drug therapy because there is an increased risk of pneumonitis,[89] and Sho-saiko-to has been reported to cause acute hepatitis.[90] Thus, until further studies prove otherwise, its use in patients with liver disease is not recommended.

Hepatotoxic Supplements

Used mostly for hyperlipidemia, niacin may be contraindicated in patients with compromised liver function. Known to cause flushing, headache, and stomachache in some people, doses above 20 mg[91] and/or sustained-release forms at doses of 2 g/day or higher[92,93] may contribute to liver toxicity and should be avoided in patients with hepatitis. Used for mood and glycemic regulation, a specific form of niacin called niacinamide seems not to induce abnormalities and is considered a safer option,[94] but it should be avoided in hepatitis when other options are available.

Vitamin A belongs to a group of compounds known as retinoids. About 80% to 90% of total-body stores of retinoids are found in hepatic stellate cells.

Excessive consumption of vitamin A (acute doses of over 100, 000 IU or chronic doses of 25,000 to 100,000 IU daily for over a year) may cause hypervitaminosis A, which can lead to cirrhosis and its complications.[95] Vitamin A's potential to cause liver toxicity is enhanced by alcohol consumption, by an excessive intake of other fat-soluble vitamins, and by a vitamin C deficiency.

Iron has been demonstrated to generate reactive oxygen species leading to point mutations, chromosomal damage, and inactivation of tumor suppressor genes such a p53; therefore it is a direct hepatotoxin. Unless a patient is found to be iron deficient, iron supplementation should be avoided, because iron has been shown to speed the progression and worsen the course of many liver diseases. This is especially true for alcoholic liver disease, as alcohol and excess iron have been shown to have an additive harmful effect on the liver.

Hepatotoxic Botanicals

Given the pharmacologic nature of plant medicines, it is important to remember that some commonly used botanicals may be hepatotoxic and should be avoided in patients with hepatitis. Perhaps the most researched is *Symphytum officinale* (comfrey). These effects are most likely due to various hepatotoxic pyrrolizidine alkaloids (PAs) such as lasiocarpine and symphytine and their related N-oxides.[96] Although used most often as a topical vulnerary remedy, *Symphytum* PAs may still be absorbed through the skin and should be avoided in patients with liver disease. *Piper methysticum* (kava kava) has also been implicated in hepatic liver damage.[97] A number of these reported cases of kava toxicity seemed to involve poor documentation, preexisting conditions, kava overdose, or concomitant polypharmacy. Although considered safe at normal doses for people without liver disease,[98] those with hepatic conditions should avoid kava kava as a precaution.

THERAPEUTIC APPROACH

During the contagious phase (2 to 3 weeks before symptoms appear to 3 weeks after), careful hygiene and avoiding close contact with others is important. In particular, once a diagnosis has been made, work in a day care center, restaurant, or other similar employment is not recommended. Chronic hepatitis requires a multifactorial integrative approach that will include lifestyle and dietary measures as well as possibly a combination of nutrients, botanicals, and conventional pharmaceuticals as needed on an individual basis.

Lifestyle

In the acute phase, bed rest is important, with slow resumption of activities as health improves. Strenuous exertion should be avoided with exercise recommended at the level of intensity safest for each patient. This level may vary from person to person. Smoking and drinking alcohol should be avoided. Eight hours of sleep is recommended.

Diet

A whole foods, high-fiber diet is recommended. Low saturated fats and oxidized fatty acids (fried oils) and minimal simple carbohydrates such as sugar, white flour, and fruit juices is recommended. Consumption of vegetable broths, diluted vegetable juices (diluted with 50% water), and herbal teas, is helpful to avoid dehydration, especially in the presence of diarrhea. Foods such as flavonoid-rich blueberry, coffee, and grapefruit (provided that there are no interactions with medication) may be beneficial to the patient with chronic hepatitis.

Nutritional Supplements

Vitamin C: to bowel tolerance (10 to 50 g/day) in acute cases; 1000 mg three times/day in chronic cases. Caution in cases of iron overload when taken with iron sources.

Vitamin D: 1000 to 4000 IU a day

Vitamin E: 1200 IU a day

Selenium: 200 mcg a day

Whey protein: for hepatitis B at 24 g a day

Liver extracts: 70 mg three times a day

Thymus extracts: equivalent to 120 mg pure polypeptides with molecular weights of less than 10,000 or roughly 750 mg of the crude polypeptide fraction a day

Botanical Medicines

Glycyrrhiza glabra (licorice): Powdered root: 1 to 2 g three times daily, fluid extract (1:1): 2 to 4 mL (1 to 2 g) three times daily, solid (dry powdered) extract (5% glycyrrhetinic acid content): 250 to 500 mg three times daily. Intravenous administration may be the most effective form. Note: chronic licorice administration may call for an increased intake of potassium-rich foods. Silybum marianum (milk thistle). The standard dose of milk

thistle (70 to 210 mg three times daily) is based on its silymarin content. For this reason, standardized extracts are preferred. The best results are achieved at higher dosages (i.e., 150 to 300 mg three times daily). The dosage for silybin bound to phosphatidylcholine is 120 mg two to three times daily between meals. Intravenous silibinin may be the most effective form.

Berkson Combination Antioxidant Approach

See the earlier section on antioxidant/botanical therapy for this specific protocol.

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CHAPTER 172

Herpes Simplex

Michael Traub, ND, DHANP, FABNO, and Michael T. Murray, ND

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DIAGNOSTIC SUMMARY

- Acute or recurrent viral infection of the skin or mucous membranes characterized by the appearance of grouped vesicles on an erythematous base frequently occurring about the mouth (herpes gingivostomatitis), lips (herpes labialis), genitals (herpes genitalis), and conjunctiva and cornea (herpes keratoconjunctivitis)
- Incubation period of 2 to 12 days, average 6 to 7
- Positive culture, vesicle scraping stained with Giemsa stain, or serologic test (type-specific glycoprotein testing for both herpes simplex viruses 1 and 2)
- Regional lymph nodes sometimes tender and swollen
- Outbreak may follow minor infections, trauma, hormonal fluctuations, stress (emotional, dietary, and environmental), and sun exposure
- Viral shedding, leading to possible transmission, during primary infection, recurrences, and (asymptomatically) between recurrences

GENERAL CONSIDERATIONS

More than 70 viruses compose the Herpesviradae family. Of these, four are important in human disease: herpes simplex virus (HSV), varicella zoster virus, Epstein-Barr virus, and cytomegalovirus. Serologic methods have distinguished two types of HSV, which have been designated HSV-1 and HSV-2. HSV-1 is frequently acquired in early childhood, with evidence of serologic infection approaching 90% in adults. More than one-third of the world's population has recurrent HSV. Although 80% of seropositive individuals do not have clinically apparent recurrences, they still shed virus asymptomatically. Current estimates indicate that 20% to 40% of people in the United States have recurrent HSV infections.[1] Previously, HSV-1 was primarily isolated from extragenital sites, while genital infections were caused primarily by HSV-2. By the year 2000, however, HSV-1 had replaced HSV-2 as the primary cause of genital lesions, likely due to orogenital contact.[2] A retrospective review of genital HSV isolates collected in a university student health service showed that HSV-1 accounted for 78% of all genital isolates in this population by 2001, compared with 31% of isolates in 1993.[3] Individuals who are exposed to HSV and have asymptomatic primary infections may experience an initial clinical episode of genital herpes months to years after becoming infected.

Herpes outbreaks on the hands and fingers (herpes whitlow) is increasingly recognized, probably owing to digital–genital contact. Cigarette smoking is a risk factor because a nicotine by-product concentrates in genital secretions and suppresses T-cell function.

Recurrence Rate

HSV-1 genital lesions have a recurrence rate of 14%, whereas the HSV-2 recurrence rate is 60%. Men seem more susceptible to recurrences. After resolution of the primary infection, HSV probably becomes a dormant inhabitant within sensory or autonomic trigeminal or lumbosacral ganglia or both. Recurrences develop at or near the sites of primary infection and may be precipitated by many different stimuli:

- Sunburn
- Sexual activity
- Menses
- Stress
- Food allergy

- Drugs
- Certain foods

The risk of clinical herpes infection after sexual contact with an individual who has active lesions is estimated to be 75%.

Immunologic Aspects

Because not everyone exposed to HSV develops clinical infection, it appears that host defense mechanisms are paramount in protecting against infection. Chronic, persistent labial and genital infections are seen in immunosuppressed individuals. The cell-mediated immune system is undoubtedly the major factor in determining the outcome of herpes exposure; that is, whether it leads to resistance, latent infection, or clinical disease.

DIAGNOSIS

Isolation of HSV from tissue scrapings is the gold standard for diagnosis. Cytopathic effects are typically seen within 2 to 7 days. A more rapid diagnostic test for mucocutaneous lesions is direct staining of skin scrapings. Type-specific serologic tests are now widely used to diagnose unrecognized HSV-1 and HSV-2 infections or to confirm suspected cases.

THERAPEUTIC CONSIDERATIONS

Prevention of recurrent herpes is recommended to decrease the number and severity of outbreaks, reduce asymptomatic viral shedding, and prevent transmission to partner and/or fetus. Three or more people may benefit when one person takes preventive measures. Education regarding transmission and asymptomatic viral shedding is imperative.

Enhancement of the host's immunologic status is a key goal in the control of herpes infection. In addition to general immune support (for a complete discussion, see Chapter 56) one of the key natural measures to strengthen cell-mediated immunity is the use of polypeptide-rich bovine thymus extracts. These have been shown to be effective in preventing both the number and severity of recurrent infections in immune-suppressed individuals.[4] Thymus extract appears to increase the lymphoproliferative response to HSV, natural killer cell activity, and interferon production, thus preventing viral activation by potentiating these cell-mediated immune responses.

Nutritional Supplements

Zinc

Oral supplementation with zinc (50 mg/day) has been shown to be effective in clinical studies.[5] Although zinc is an effective inhibitor of HSV replication in vitro, its effect in vivo is probably related to its role in enhancing cell-mediated immunity. The topical application of 0.01% to 0.025% zinc sulfate solutions has also been shown to be effective in both ameliorating symptoms and inhibiting recurrences of HSV infection.[6]

Vitamin C

Both the oral consumption and topical application of vitamin C increase the rate of healing of herpetic ulcers. In a randomized double-blind study, an ascorbic acid–containing pharmaceutical formulation (Ascoxal) applied with a soaked cotton wool pad three times daily for 2 minutes resulted in patients reporting fewer days with scabs and fewer cases of worsening of symptoms. Cultures yielded herpes complex viruses significantly less frequently in the treatment group.[7] In another study, 20 patients with herpes labialis were treated with a complex of 600 mg water-soluble bioflavonoids and 600 mg vitamin C given orally in equal increments three times daily. Twenty episodes of herpes labialis were treated with a complex of 1000 mg water-soluble bioflavonoids and 1000 mg of vitamin C in equal increments five times daily. Ten episodes were treated with a lactose preparation. This approach was maintained for 3 days after the recognition of symptoms. The water-soluble bioflavonoid–vitamin C complex was shown to reduce vesiculation and to prevent disruption of the vesicular membrane. The therapy was most beneficial when it was initiated at the beginning of the disease. Those treated with the 1000-mg regimen saw their blisters heal in 4.4 days, compared with 10 days for the placebo group. Optimal remission of symptoms was observed in 4.2 +/- 1.7 days with the 600-mg dosage of the water-soluble bioflavonoid/ascorbic acid complex.[8] Vitamin C has also been employed intravenously with benefit in the treatment of patients with HSV infection, including AIDS patients.[9]

Lysine and Arginine

A lysine-rich/arginine-poor diet has become a popular treatment for HSV infections. This approach came from research showing that lysine has antiviral activity in vitro owing to its antagonism of arginine metabolism.[10] HSV replication requires the synthesis of arginine-rich proteins, and arginine itself is suggested to be an operon coordinate inducer.[11] A preponderance of lysine over arginine is believed to act as either an allosteric enzyme inhibitor or an operon coordinate repressor.

Double-blind studies on the effectiveness of lysine supplementation with uncontrolled avoidance of arginine-rich foods have shown inconsistent results.[11-14] These outcomes may be due to the relatively low levels of lysine used (1200 mg/day) and the severity of the cases in some of the studies (placebo and treated groups had lesions for 40% of the time in one negative study).[11,12] In one study, lysine was given at a larger dosage (1 g three times daily) along with the dietary restriction of nuts, chocolate, and gelatin.[13] At 6 months, lysine was rated as effective or very effective by 74% of those receiving lysine compared with only 28% of those receiving the placebo. The mean number of outbreaks was 3.1 in the lysine group compared with 4.2 in the placebo group.

Theoretically, this approach should be effective, because in vitro studies have shown that HSV replication depends on adequate levels of arginine and low levels of lysine.[14] As dibasic amino acids, they compete with each other for intestinal transport, and rats fed a lysine-rich diet displayed a 60% decrease in brain arginine levels, although there was no change in serum levels.[9] Because HSV is believed to reside in the ganglia during latency, lysine supplementation and arginine avoidance seem appropriate. However, this approach is not curative—it only inhibits recurrences. In some patients, withdrawal from lysine is followed by relapse within 1 to 4 weeks.[14]

Topical Preparations

Melissa officinalis

One of the most widely used topical preparations in the treatment and prevention of herpes outbreaks is a concentrated extract (70:1) of *Melissa officinalis* (lemon balm). Rather than a single antiviral chemical, *Melissa* contains several components that work together to prevent the virus from infecting human cells. When *Melissa* cream was used in patients with an initial herpes infection, results from comprehensive trials in three German hospitals and a dermatology clinic demonstrated that there was not a single recurrence.[16] In other words, by using the cream, not a single patient with a first herpes outbreak developed another cold sore.

Furthermore, it was noted in these studies that the *Melissa* cream produced an interruption of the infection and promoted healing of the herpes blisters much faster than normal. The control group receiving other topical creams had a healing period of 10 days, while the group receiving the *Melissa* cream healed completely within 5 days. The *Melissa* cream was also studied in patients suffering from recurrent cold sores. Researchers found that if subjects used this cream regularly, they would either stop having recurrences or experience a tremendous reduction in the frequency of recurrences (an average cold sore–free period of >3.5 months).[17]

The *Melissa* cream should be applied to the lips two to four times daily during an active recurrence. It can be applied fairly thickly (1 to 2 mm). Detailed toxicology studies have demonstrated that it is extremely safe and suitable for long-term use. Extracts of other species of the Lamiaceae family have also shown in vitro efficacy against the adsorption, but not replication of HSV-1 and HSV-2, including *Mentha piperita, Prunella vulgaris, Rosmarinus officialis, Salvia officinalis,* and *Thymus vulgaris*.[18]

Glycyrrhiza glabra

Another popular ingredient for the topical treatment and prevention of herpes outbreaks is glycyrrhetinic acid. This triterpenoid component of *Glycyrrhiza glabra* (licorice root) inhibits both the growth and cytopathic effects of herpes simplex as well as vaccinia, Newcastle disease, and vesicular stomatitis viruses.[19] Topical glycyrrhetinic acid has been shown in clinical studies to be helpful in reducing the healing time and pain associated with cold sores and genital herpes.[20-22]

Resveratrol

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a natural component of certain foods such as grapes; it has been shown to have anti-HSV activity in vitro. Intriguing research in mice has shown that the topical application of a cream rich in resveratrol (12.5% to 25%) effectively blocked replication of the HSV virus and stopped lesion eruption if applied early and frequently.[23,24] No human studies have been reported; however, subsequent in vitro studies have yielded data indicating that resveratrol suppresses HSV-induced activation of NF-kappaB within the nucleus and impairs the expression of essential immediate-early, early, and late HSV genes and the synthesis of viral DNA.[25]

Vitamin E

In two uncontrolled trials, topical vitamin E decreased pain and healing time in oral herpes. Lesions responded best when the content of a vitamin E capsule was applied every 4 hours.[26]

THERAPEUTIC APPROACH

The therapeutic aim is to shorten the current attack and prevent recurrences. Support of the immune system is of primary importance, necessitating control of food allergens and optimizing nutrients necessary for cell-mediated immunity. Inhibition of HSV replication through manipulation of the lysine/arginine ratio in the diet has been found useful. Strengthening the immune system can be effective at reducing the frequency, duration, and severity of recurrences.

Diet

A diet that avoids major food allergens and limits arginine-rich foods while promoting lysine-rich foods is recommended (see Table 172-1). The foods with the worst arginine-to-lysine ratio are chocolate, peanuts, and almonds.

TABLE 172-1 **Arginine and Lysine Content of Selected Foods**

FOOD	SERVING	ARGININE	LYSINE
Almonds	70 nuts	2730	580
Bacon	12 slices	2100	2000
Beans, green	3/4 cup	80	80
Beans, lima	3.5 oz	1170	1470
Beans, mung	3.5 oz	1320	1930
Beans, red	1/3 cup	340	420
Beef, chuck	3.5 oz	1600	2200
Brazil nut	3.5 oz	2250	470
Bread, whole wheat	4 slices	510	290
Buckwheat	3.5 oz	1200	460
Carob	3.5 oz	710	340
Cashews	40 nuts	1990	740
Cheese, cheddar	3.5 oz	850	1700
Chicken	3.5 oz	1930	2700
Chocolate	3.5 oz	4500	2000
Clams	1/2 cup	830	840
Coconut	3.5 oz	470	148
Crustaceans	3.5 oz	1330	1260
Eggs	2 large	840	820
Fish sticks, breaded	4–5 sticks	940	1400
Flax seeds	3.5 oz	2030	810
Garbanzo beans	3.5 oz	1900	1380
Halibut	3.5 oz	140	2220
Hazelnuts	3.5 oz	3510	690
Lentils	3.5 oz	2100	1740
Liver, beef	3.5 oz	1590	1950
Milk, whole	3.5 oz	130	280
Millet	3.5 oz	410	260
Oatmeal, cooked	1/3 cup	130	70
Oysters	5–8 medium	310	280
Peanuts, without skins	3.5 oz	3240	1090
Peas, green	5/8 cup	420	220
Pecans	3.5 oz	2030	810
Pork, lean	3.5 oz	1510	1850
Rice, brown	2/3 cup	120	100
Salmon	3.5 oz	1530	2350
Sardines	7 medium	190	1850
Sesame seeds	3.5 oz	2590	580
Shrimp	3.5 oz	1360	2130
Soybeans, boiled	2/3 cup	620	620
Sunflower seeds	3.5 oz	1190	540
Tuna	5/8 can	1530	2530
Turkey	3.5 oz	1700	2450
Walnuts, English	27 whole	2250	490
Yeast	3.5 oz	1940	3510

Supplements

- Vitamin C: 2000 mg/day
- Bioflavonoids: 1000 mg/day
- Zinc: 25 mg/day
- Lysine: 1000 mg three times daily
- Thymus extract: the equivalent to 120 mg pure polypeptides with molecular weights less than 10,000 daltons

Topical Treatments

- Sunscreen
- Ice: 10 minutes on, 5 minutes off during prodrome
- Zinc sulfate solution: apply 0.025% solution three times a day
- Melissa cream: apply twice a day
- Glycyrrhetinic acid: apply twice a day
- Vitamin E: apply every 4 hours

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CHAPTER 173

HIV/AIDS: Naturopathic Medical Principles and Practice

Kevin L. Conroy, ND, and Steven C. Milkis, ND

DIAGNOSTIC SUMMARY

- A diagnosis of human immunodeficiency virus–positive (HIV+) infection is most commonly made after a positive test for HIV antibodies by enzyme-linked immunosorbent assay (ELISA); it is confirmed via Western blot analysis.
- An acute onset (acute antiretroviral syndrome) resembles common influenza. Most persons experience this syndrome 2 to 6 weeks after initial infection; it often goes undiagnosed as HIV owing to its similarity to the flu. Signs and symptoms can include fever, lymphadenopathy, skin rash, pharyngitis, myalgia, arthralgia, headache, diarrhea, and oral ulcerations. Laboratory findings might include leukopenia, thrombocytopenia, and elevated transaminases.
- An insidious onset may manifest as an acquired immunodeficiency syndrome (AIDS)–associated opportunistic infection (OI) or as unexplained progressive fatigue, weight loss, fever, diarrhea, or generalized lymphadenopathy.
- AIDS is diagnosed after positive serology and either a CD4+ T-cell count at or below 200/mm^3 or the presence of a designated AIDS-indicator condition (from the Centers for Disease Control and Prevention [CDC] guidelines of 2008). Primary infection is also characterized by a high level of virus production, high concentrations of viral particles and RNA in plasma, and a rapid and steep decline in CD4+ T-helper cells. Peak viral titers can reach 10^7 virons per milliliter during this phase. Viral production can range up to 10 billion copies per day. After the initial viremia, high levels of viral p24 antigen appear.
- The lower the CD4+ count and the higher the viral load, the higher the risk of contracting OIs, neoplasms, or neurologic abnormalities and the higher the mortality rate.
- Groups at high risk for contracting HIV include injection drug users, homosexual and bisexual men, hemophiliacs and others receiving transfused blood or other blood products (highest risk to recipients before May 1985, when regular screening of the blood supply began), regular sex partners of people in the aforementioned groups, heterosexual people with greater than one sex partner in the past 12 months, and those who have had unprotected sex during the previous 6 months.

INTRODUCTION

HIV has been described as a retrovirus containing two single strands of RNA. It enters the body via the transfer of body fluids and subsequently binds to and infects CD4-expressing cells of the human immune system (T-helper lymphocytes, blood monocytes, tissue macrophages, Langerhans cells in the skin, and microglial and multinucleated cells in the central nervous system). AIDS is a secondary syndrome resulting from long-term HIV infection. AIDS is defined by one or more of the following: levels of CD4+ cells, the presence of certain specific indicator conditions, or secondary malignancies known to be associated with HIV. Many theories exist as to what causes AIDS, ranging from HIV to multifactorial (environmental and infectious) assaults on the immune system. In this science's infancy, there is no definitive answer, but current medical thinking is that AIDS is caused by HIV.

Focus and Goals of Chapter

This chapter is written for the naturopathic physician, although conventionally trained physicians and other holistic practitioners may find the perspective, treatment

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principles, and some of the treatment suggestions helpful. The field of HIV/AIDS medicine is rapidly changing. HIV/AIDS was first reported to the CDC only in 1981, and it has since exploded into an international pandemic. Highly active antiretroviral drug therapy (HAART), introduced in 1996, is the use of multiple drugs in combination with the goal of decreasing viral load and increasing CD4+ T-cell counts. Although this innovation resulted in a dramatic slowing in the death rate from AIDS, with it came complicated drug side effects, drug interactions, and unique symptoms that require frequent follow-up between the patient and physician and affect the quality of life of individuals on those regimens.

Studies indicate that more than 70% of HIV+ persons are using some form of complementary/alternative medicine (CAM) in their treatment, resulting in improvements in their quality of life and better outcomes.[1] The goal of this chapter is to help the physician better understand the condition and to appropriately guide this affected population with unique and complicated health issues.

BIOLOGY OF HIV

Two types of HIV have been identified. HIV-1 is found throughout the world. The majority of infections in the United States are caused by HIV-1. HIV-2 was first identified in West Africa in 1986 and has been found to have a genetic sequence approximately 50% similar to HIV-1. HIV-2 is considered less virulent than HIV-1 and shows lower rates of sexual and perinatal transmission and a lower viral load with a slower rate of CD4 cell decline. This results in a slower rate of disease progression in infected people.[2] Research shows that the virus is mutating, and multiple subtypes or clades are spreading throughout the world.[1] The existence of multiple clades raises the theoretical possibility that a single individual could become infected with multiple subtypes of the virus. Research has not conclusively demonstrated the existence of a "superinfection," but the possibility of this phenomenon would significantly enhance virulence as well as increase resistance to present treatments.

Existing research has failed to isolate an intact HIV entity; although fragments believed to belong to the HIV virus have been isolated and identified. Despite this shortcoming, the virus is believed to consist of a bilayer lipid envelope covered with envelope glycoproteins (gp120 receptor and gp41 transmembrane), a viral core containing two single strands of RNA and the reverse transcriptase enzyme, and structural core proteins (p24 capsid protein and p18 matrix protein). It is believed that HIV binds to CD4-expressing cells of the immune system and, through a series of steps, replicates itself and incorporates its genome into the host cell's genome.

The various classes of antiretroviral medications have been developed to interrupt viral replication during various steps in this process. The key to understanding the mechanisms of action of the various medications is to understand those steps. *Fusion* is the process by which the HIV particle contacts and binds to the target cell. This occurs through the interaction of the viral gp120 and gp41 transmembrane proteins with CD4 and chemokine receptors on the cell's membrane. Fusion inhibitors are designed to inhibit this process by altering the cellular receptor sites. *Transcription* occurs when the viral reverse transcriptase enzyme translates the viral RNA into a double strand of DNA. Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) are designed to disrupt this process.

Integration occurs when the double strand of proviral DNA migrates to the cell's nucleus and is inserted into the host's chromosome via the integrase enzyme. The provirus is then permanently integrated into the host DNA. It can remain essentially dormant (equilibrium of viral production and destruction) or become activated and initiate the production of large chains of new viral RNA subunits independent of the host cell's replication process. Integrase inhibitors prevent the integrase enzyme from inserting the viral DNA into the host DNA. After a period of normal cell function, the infected cell becomes activated, initiating *transcription* of the proviral DNA into mRNA, which is then *translated* in the cytoplasm to produce long chains of viral polypeptides. *Cleavage* occurs when the protease enzyme cuts up these viral polypeptides. The pieces are then joined together to form new retroviruses. Protease inhibitors block the action of the protease enzyme and thereby prevent the reassembly of new viral polypeptides. *Packaging* is a poorly understood step in this process, where the new RNA viruses are wound up tightly and encapsulated into new viral particles. *Budding* occurs when the HIV nucleocapsid containing the new viral RNA moves to the host cell's membrane and binds to the inside of the membrane. It is then enveloped by the membrane as it leaves the cell.

TRANSMISSION

HIV has been found in body fluids and tissues that contain lymphocytes. This includes blood and blood products, semen, vaginal fluids, breast milk, cerebrospinal fluid, synovial fluid, pleural fluid, amniotic fluid, and infected tissues. It has also been found in small amounts in saliva, tears, feces, and urine. According to the CDC, the only documented cases of transmission are via blood, semen, vaginal secretions, breast milk, and transplanted organs from an infected person. Variables affecting transmission rates include the infectivity of the source partner (higher viral load), the presence of sexually transmitted diseases (STDs) (especially with ulcerations), and the type of contact (increased risk with anal intercourse and vaginal intercourse during menses because blood is present).

The most significant routes of transmission are via sexual contact (vaginal, anal, and less frequently oral intercourse); intravenous drug use (sharing contaminated needles and syringes); transfusion of blood or blood products (highest risk prior to May 1985 when screening of the blood supply in the United States for HIV began); and from an HIV-infected mother to her baby (before or during birth or through breastfeeding). Transmission can also potentially occur via percutaneous needlestick, mucous membrane exposure, or exposure of infected fluid into an open wound. Studies show the risk of seroconversion following a needlestick from an HIV+ source to be 0.25% per exposure. They also show that there have been no known seroconverters following splash exposure. The CDC has identified one documented case of transmission from acupuncture.

There is no evidence that HIV can be transmitted via air, water, insects, or dried body fluids. Universal infection control precautions as developed by the CDC should always be employed by health care workers to minimize the risk of HIV transmission in the health care setting. Always assume that all blood and body fluids are potentially hazardous and that all patients are potentially infected.[3]

THE IMMUNE SYSTEM'S RESPONSE

Both the humoral and cellular immune systems have a role in the body's response to HIV infection. The humoral response involves the initial production of transient IgM antibodies to viral core and envelope proteins. Permanent IgG antibodies are subsequently

BOX 173-1 Centers for Disease Control and Prevention (CDC) 2008 Surveillance Case Definition for HIV Infection among Adults and Adolescents above 13 Years of Age*

Stage 1: CD4+ T-lymphocyte count of >500/microliter (μl) or >29%; no clinical evidence required and no AIDS-defining condition present
Stage 2: CD4+ T-lymphocyte count of 200 to 299/μL or 14% to 28%; no clinical evidence required and no AIDS-defining condition present
Stage 3 (AIDS): CD4+ T-lymphocyte count <200 /μL or <14% or documentation of an AIDS-defining condition
Stage unknown: no information of CD4+ T-lymphocyte count or percentage; no information on presence of AIDS-defining conditions

The specific AIDS indicator conditions include the following:
Candidiasis of esophagus, bronchi, trachea, or lungs
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month's duration)
Cytomegalovirus disease (other than liver, spleen, or lymph nodes), onset at age >1 month
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV-related
Herpes simplex with chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month's duration)
Kaposi sarcoma
Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex
Lymphoma—Burkitt's, immunoblastic, primary (brain/central nervous system)
Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis of any site, pulmonary, disseminated, or extrapulmonary
Pneumocystis jirovecii pneumonia
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age >1 month
Wasting syndrome due to HIV—involuntary weight loss >10% of baseline plus chronic diarrhea (>2 loose stools/day for >30 days) or chronic weakness and documented enigmatic fever >30 days

From Schneider E, Whitmore S, Glynn KM, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years United States, 2008. *Morbidity Mortality Weekly Report,* 2008, Dec 5; 57(RR10);1-8.
*In all stages laboratory confirmation is required.

established (this may take several weeks) to core p24 and envelope gp160, gp120, and gp41, corresponding to the resolution of clinical symptoms. The development of these IgG antibodies results in a rapid decrease in circulating virons and p24 antigen titers. *Seroconversion* occurs when the body starts making antibodies to HIV antigens and those antibodies become detectable by conventionally used laboratory tests (enzyme-linked immunoassays and Western blot analysis).

There is a window of time between initial infection (when patients remain antibody-negative or seronegative as measured by ELISA tests) and when seroconversion (antibody-positive or seropositive by ELISA) occurs. The length of this window varies depending on the individual and can range from 10 to 14 days to 6 months. The cellular immune response is characterized by the elevation of various cytokines (including interferons and tumor necrosis factor), CD4+ lymphopenia, and CD8+ lymphocytosis. Cytotoxic T cells reduce the plasma viremia, whereas natural killer (NK) cells may be involved with killing infected T cells.

CLINICAL PROGRESSION TO AIDS

Assuming no antiretroviral treatment, a typical scenario of HIV infection might unfold as follows: Within 2 to 3 weeks of initial infection with the virus, an acute retroviral syndrome occurs. Recovery and seroconversion usually follow in 2 to 3 weeks. After recovery from the initial acute syndrome, HIV plasma concentrations decline to a viral "set point" and equilibrium is established between the production and destruction of CD4+ cells. The level of viral replication after acute infection and seroconversion coupled with the CD4+ count is predictive of long-term prognosis. A lower level of replication with a higher CD4+ count indicates a longer asymptomatic course. Conversely, a higher level of replication with lower CD4+ counts generally indicates a shorter asymptomatic course. Over time, a gradual decline in T-cell numbers begins with a concurrent gradual increase in the amount of virus in the body. This period can last 5 to 15 years. Eventually there are not enough T cells for the body's immune system to function properly. This is when the risk of OIs increases, with the ultimate result being death.[4]

Box 173-1 lists the CDC's 2008 revised surveillance case definition of AIDS for adults and adolescents (13 years of age or older). It creates stages of HIV infection based on CD4+ cell counts/percentages and/or clinical symptoms. The primary criterion used is positive serology (i.e., positive for antibodies to HIV via ELISA and Western blot testing and/or positive HIV antigen detection via polymerase chain reaction [PCR] or other specific HIV antigen test). Given a positive serology, a diagnosis of stage 3 HIV or AIDS is given when CD4+ counts fall below 200/mm^3 (<14%), any of the noted AIDS-defining conditions occurs, or both.[5]

Clinically, patients tend to be susceptible to certain complications (both infectious and noninfectious) on the basis of their CD4+ cell counts.[6] Although there is always individual variation, these data are helpful in predicting probable clinical presentations. Generally a higher viral load represents a greater risk for complications and should always be factored into any such consideration.

- When the CD4+ cell count is greater than 500/mm^3, a patient could manifest acute retroviral syndrome, candidal vaginitis, persistent generalized lymphadenopathy (PGL), Guillain-Barré syndrome, myopathy, or aseptic meningitis.
- When the CD4+ count is between 200 and 500/mm^3, possible complications include pneumococcal or other bacterial pneumonia, pulmonary tuberculosis, herpes zoster, oropharyngeal candidiasis/thrush, cryptosporidiosis (self-limited), Kaposi sarcoma, oral hairy leukoplakia, cervical and anal dysplasia/cancer, B-cell lymphoma, anemia, mononeuritis multiplex, idiopathic thrombocytopenic purpura, Hodgkin's lymphoma, or lymphocytic interstitial pneumonitis.

BOX 173-2 Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health Care Settings as of 2006

Screening for HIV Infection

- Routine testing for all patients 13 to 64 years old
- Pregnant women
- All patients initiating treatment for tuberculosis
- All patients seeking treatment or evaluation at clinics treating sexually transmitted diseases
- All persons with signs or symptoms consistent with HIV or with an opportunistic infection consistent with HIV/AIDS

Repeat Screening

- Annual screening (minimally) for persons in high-risk groups (includes injection-drug users and their sex partners, persons who exchange sex for money or drugs, sex partners of HIV-infected persons, and men who have sex with men or heterosexual persons who themselves or whose sex partners have had more than one sex partner since their most recent HIV test)
- Patients and their prospective partners before initiating a new sexual relationship
- Any person whose blood or body fluid is the source of an occupational exposure to a health care provider should be informed of the incident and tested at the time of the exposure

Data from Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *Morbidity Mortality Weekly Report*, 2006, Sept 22;55(RR14):1-17.

- When the CD4+ count is below 200/mm^3, complications might include *Pneumocystis jirovecii* pneumonia, disseminated histoplasmosis and coccidioidomycosis, miliary/extrapulmonary tuberculosis, progressive multifocal leukoencephalopathy (PML), wasting, peripheral neuropathy, HIV-associated dementia, cardiomyopathy, vacuolar myelopathy, progressive polyradiculopathy, or non-Hodgkin's lymphoma.
- When the CD4+ count is below 100/mm^3, complications might include disseminated herpes simplex, toxoplasmosis, cryptococcosis, chronic cryptosporidiosis, microsporidiosis, or candidal esophagitis.
- When the CD4+ count is below 50/mm^3, complications might include disseminated cytomegalovirus (CMV), disseminated *Mycobacterium avium* complex (MAC), or central nervous system lymphoma.

DIAGNOSIS AND WORK UP

Diagnostic Testing

Box 173-2 lists the most recent CDC guidelines for HIV testing.[7] Standard serologic testing for the presence of HIV begins with an ELISA test using recombinant antigens to measure antibodies to HIV in the blood.[8] If this test is positive, it is repeated on the same blood sample. If it is positive a second time, a Western blot test (using electrophoresis to detect antibodies to specific HIV proteins) is used for confirmation.[9] Together, these tests have a sensitivity and specificity approaching 100%.

A number of rapid HIV tests have been developed and are currently approved for use by the U.S. Food and Drug Administration (FDA). They all use similar technology to detect antibodies and vary in category assigned by the Clinical Laboratory Improvement Amendments (CLIA) from "waived" to "moderately complex." Options include OraQuick Advance, Uni-Gold Recombigen, Reveal G-3, MultiSpot Rapid Test, Clearview Stat-Pak, Clearview Complete, and Vitros. Additionally, Home Access Health Corp. (www.HomeAccess.com) produces a kit where the specimen is self-obtained at home and mailed in for analysis. Results are available in 1 or 5 days depending on the price paid. These tests use either whole blood, serum, plasma, or oral fluids and have sensitivity and specificity rates of 99% to 100%.[10,11] If an ELISA test is negative and risk factors suggest likely infection, the test should be repeated at 6-week, 3-month, and 6-month intervals. There is no reason to repeat if one of those tests comes back positive.

Although routine testing is now recommended, HIV testing remains voluntary. Testing recommendations should be discussed with each individual patient and informed consent (either written or verbal) obtained prior to testing. Patients have the right to opt out should they wish to do so. Risk screening should be incorportated into routine primary care and risk reduction counseling offered as applicable. All states require that newly diagnosed cases of HIV/AIDS be reported to local health departments and that providers have case reporting forms available.

Medical History

Initiation of care of an HIV+ patient should begin with a standard medical history including a detailed diet history, exercise patterns, and a complete review of systems. A number of additional historical details should be obtained as well (Box 173-3).

Laboratory Assessment and Monitoring

Basic initial screening tests for all HIV+ patients should include a complete blood count (CBC) and a fasting serum chemistry panel (to monitor liver, kidney, and pancreatic function; electrolytes; blood proteins; glucose; and lipids). The baseline serum albumin level can serve as an independent predictor of prognosis in HIV+ women.[12] Additional testing should include a urinalysis, screening for STDs (syphilis, *Chlamydia*, gonorrhea, herpes simplex), hepatitis (A, B, and C), toxoplasmosis, tuberculosis, and varicella (if unknown history of chickenpox or shingles). An optional test is glucose-6-phosphate dehydrogenase (based on risk factors).[11] Female patients should have regular Pap smears with initial testing for human papillomavirus (HPV), because there is a significant increase in cervical cancer rates in HIV+ women.[13] A recent development is the use of the anal Pap smear in male patients engaging in anal sex. Anal squamous cell cancer is similar to cervical cancer in that it is caused by HPV infection and rates are increased in HIV+ men as compared with the general population. Currently, there is some controversy about the use of this test, with no clear consensus on whether to make it part of routine screening. Studies are ongoing.[11]

HIV-specific testing includes measurement of viral load and T-cell counts as part of the initial evaluation and then at 3- to 6-month intervals. The viral load test detects the presence of viral RNA in the plasma or DNA in white blood cells (WBCs) and uses PCR branched-chain DNA (bDNA) or nucleic acid sequence–based amplification technology. A number of viral load tests exist with varying levels of sensitivity. The most sensitive test currently available detects virus to 20 copies per cubic millimeter of plasma.[14] Below any specific test's threshold, the viral load is deemed "undetectable." This means that the virus may exist in concentrations in the blood below the ability of the given test to

BOX 173-3 **Historical Data Recommended for HIV-Positive Patients**

- Dates of infection and subsequent diagnosis, as well as probable source of infection (IV drug use, sexual contact, transfusion). If date of infection is unknown, the naturopathic physician should determine if there was any history of acute retroviral syndrome. Additionally, past and current risk factors for HIV exposure should be determined. This information helps to estimate overall health and vital force and long-term prognosis.
- Vaccination history and adverse reactions to past vaccines.
- History of other sexually transmitted diseases. This information should include date and duration of infection as well as therapies (efficacy, adverse reactions, and duration of treatment). Particular infections to screen for include syphilis, gonorrhea, *Chlamydia*, herpes simplex (all types), hepatitis (A, B, and C or E), and HPV (skin, genital, or anal).
- Chronologic history of HIV-related problems including history of OIs or cofactor viruses/infections (mononucleosis, EBV, molluscum contagiosum, CMV, or yeast infections—vaginal, gastrointestinal, skin), skin rashes or other lesions, oral lesions or tongue coating, lymphadenopathy, fevers, night sweats, weight loss, diarrhea, anorexia, fatigue, malaise, shortness of breath, or cough.
- Specific for females, history of abnormal Pap smears and frequency of gynecologic examinations.
- HIV viral load and trend of CD4 count; good indicators of the patient's susceptibility to OIs, indication for and effectiveness of HAART, as well as long-term prognosis.
- History of all past and present HAART as well as all other prophylactic antibiotic prescription medication with duration of treatment, response and side effects, intolerance, and allergies.
- Family history of chronic disease, with particular emphasis on cardiovascular disease (including lipid problems), diabetes, and cancer.
- History of psychoemotional trauma and issues (abuse history, anxiety, depression).
- Patients' spiritual lives and support systems, life goals, and meaning of HIV in their lives.
- Clear identification of complete medical care team as well as reasons for seeking naturopathic medical care.
- The initial physical examination must be both comprehensive and appropriately focused as directed by the history. In addition, all patients should have particularly thorough examinations of the mouth and throat, skin, and genitalia. If a full pelvic examination and Pap smear cannot be done on a new female patient at the initial evaluation, these should be scheduled for shortly thereafter.

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAART, highly active antiretroviral drug therapy; HIV, human immunodeficiency virus; HPV, human papillomavirus; IV, intravenous; OI, opportunistic infection.

detect. Additionally, note that these assays are not reflective of viral presence or concentration in body compartments beyond the blood (e.g., tissues, cerebrospinal fluid, breast milk). This is an important point for patients to understand, as they can still infect others even if the virus is "undetectable" according to the test they were given.

Other key tests involve T-cell counts. CD4+ helper cells and CD8+ suppressor cells are quantified (absolute numbers and relative percentages), along with the CD4:CD8 ratio. This information is used to stage HIV, predict susceptibility to various OIs, and monitor response to antiretroviral therapy. Many factors can influence CD4+ cell counts, including total WBCs, acute infection, certain medications (e.g., corticosteroids, interferon), as well as other medical conditions. There are also seasonal and diurnal variations in these counts.

Resistance to antiretroviral medications is a growing problem in treatment-naive patients and remains a problem in patients currently undergoing this therapy. Therefore, resistance testing is now recommended at the time of diagnosis as part of baseline screening as well as before changing therapy owing to failure of a current regimen. Two types of tests are available: genotypic and phenotypic. There are advantages and disadvantages to each, but in general this testing can help to identify antiviral medications that the patient might be either resistant or susceptible to and thereby allow the physician to formulate the most effective medication regimen.[11]

THERAPEUTIC CONSIDERATIONS

Medical Management of HIV and AIDS

The medical understanding and treatment of HIV/AIDS continue to evolve. AIDS is a complex, multifactorial disease that has both immunodeficiency and autoimmune inflammatory aspects involving virtually every system of the body. HIV enters the body and infects CD4+-expressing cells of the immune system. It inserts itself into cellular DNA and can lie dormant indefinitely. Those cells can be activated for the reproduction and multiplication of HIV virions by antigens, oxidative stress, proinflammatory cytokines, and overstressed liver detoxification and immune systems.

Conventional medical management of HIV/AIDS revolves around the following treatment principles:

- Frequent monitoring, including laboratory and physical examination
- Vaccinations administered as appropriate (may include hepatitis A, hepatitis B, influenza, mumps-measles-rubella [MMR], pneumonia tetanus-diptheria, varicella, HPV, and travel-related vaccines)[11]
- Highly active antiretroviral therapy (HAART) for inactivation or slowing HIV replication and increasing CD4+ cell counts
- Antibiotic prophylaxis for patients with abnormally low CD4 lymphocyte counts
- Antimicrobial treatment of OIs
- Symptomatic care of HIV- or HAART-induced adverse drug reactions
- Radiation, chemotherapy, or both for HIV-related neoplasms
- Psychosocial support via counseling, clinical social work, and medication

Up-to-date resources should always be consulted prior to making any management decisions. The AIDS information website, administered by the U.S. Department of Health and Human Services (www.aidsinfo.nih.gov/) provides an excellent resource for determining the most up-to-date conventional treatment guidelines as well as information on prevention, FDA-approved and investigational drugs, clinical trials, and vaccinations. Another fine resource is the Johns Hopkins AIDS website (www.hopkinsguides.com). Their HIV guide provides detailed information on the diagnosis and management of HIV and its associated OIs, medications, and resistance. Johns Hopkins University School of Medicine/Knowledge Source Solutions LLC also publishes a helpful text called the Medical Management of HIV Infection, 2009-10, 15th ed, by JG Bartlett, JE Gallant, and PA Pham. It can be ordered on the website. The best resource for

patient education is www.thebody.com/index.shtml. This site contains valuable information on signs, symptoms, treatments, and future possibilities, all from a patient-centered perspective.

Naturopathic Management of HIV and AIDS

The naturopathic medical management of HIV and AIDS revolves around a number of treatment principles that should guide the physician in helping patients to optimize their health, slow disease progression, improve their quality of life, and improve immune function.

Specific goals include the following:

- Enhance overall integration with primary care physicians and build a caregiving team
- Complement and enhance the positive effects of conventional medical treatment and minimize the negative effects
- Establish a foundation of health and wellness on the basis of naturopathic principles
- Establish a core nutrient protocol:
 - Replace nutrient deficiencies known to exist with HIV.
 - Provide other nutrients to support optimal immune function.
- Provide therapies to address constitutional symptoms, medication side effects, and symptoms of immunosuppression
- Provide specific antiviral therapy and immunomodulation using other nondrug treatments
- Educate and guide patients seeking alternatives to conventional treatment

A resource specifically geared toward complementary practitioners is *AIDS and Complementary and Alternative Medicine, Current Science and Practice* by Standish, Calabrese, and Galantino, published by Churchill Livingstone in 2002.

Enhance Overall Integration with Primary Care Physicians and Build a Caregiving Team

In the area of HIV, naturopathic physicians should lead the effort to optimize integrated care. A holistic provider who identifies advantages of all available treatments and encourages positive relationships with all available providers creates a unique and trusting relationship with patients who have often experienced lifetimes of fear, discrimination, victimization, and abuse. Naturopathic medicine offers an important opportunity to empower HIV+ patients.

One of the first priorities is to ensure that each HIV+ patient has a complete care-providing team beginning with a conventional Western medicine HIV specialist. HIV specialists ensure the accessibility of HAART when appropriate and have the greatest familiarity with the multitude of signs, symptoms, adverse reactions, and other issues unique to the HIV+ population. A growing body of literature reports that HIV+ patients have better objective indices of health (low viral load and high CD4 counts), better compliance with medications, and better long-term survival when they work with HIV specialists.[15,16]

The specialist's obligations constitute a full-time job, precluding many other aspects of care that have demonstrated efficacy for the overall health of HIV+ patients. Additional providers can support HIV+ patients with general health and lifestyle promotion, specific nutrient and other nondrug recommendations, social services, psychoneuroimmunologic support, counseling, personal empowerment, and end-of-life care. In fact, although naturopathic physicians might be legally able to prescribe prophylactic antimicrobial therapy and HAART in a growing number of states, the greater need is to provide nondrug holistic care in the areas just mentioned.

Complement and Enhance the Positive Effects of Conventional Medical Treatment and Minimize the Negative Effects

One of the paradigms of natural/preventative/holistic medicine is to minimize the need for higher-force (drug, surgery, radiation) interventions. This goal remains valid in the care of patients with HIV, but there are no therapies known to be as effective as HAART in suppressing viral load or increasing CD4 T-lymphocyte cell numbers. CAM providers may be the best practitioners to teach HIV+ patients that there are no realistic "alternatives" to HAART. Risks of OIs and other serious complications increase exponentially when CD4 cell counts drop below 200/μL. The current standard of care is to initiate HAART when the CD4 count drops below 350/μL in asymptomatic patients, those with an AIDS-defining illness (regardless of CD4 count), pregnant women, patients with HIV-associated nephropathy, or hepatitis B coinfection (when treatment of the hepatitis is indicated). HAART initiation may be considered when CD4 cell counts are greater than 350/μL in discordant relationships (one partner is HIV+ and the other HIV–), rapid CD4 decline, advanced age, or high viral load (more than 100,000 copies per milliliter).[17] The choice of specific antiretrovirals for either initial regimens or the modification of existing therapy is complex, and there are many factors to consider. Additionally, the guidelines change frequently. The best resource for the most current recommendations is the "Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents," available on the AIDS information website (www.aidsinfo.hih.gov/ContentFiles/AdultandAdolescentGL.pdf). The most recent guidelines were compiled on December 1, 2009.

Some HIV+ patients may never need HAART and others may be resistant to HAART, but the option of HAART should always be considered and should not be discouraged. With or without HAART, there is significant evidence that HIV+ patients receive many benefits from nondrug therapies.[18] Naturopathic physicians must actively understand, integrate, and use the entire therapeutic order (most subtle, lower force through most high force, often invasive therapies) to ensure that each patient has the best options to maximize his or her quality of life as well as length of life. Finally, physicians working with HIV must stay current with the global effort to find solutions for this pandemic in order to provide the best possible treatment options to match patients' short-term needs while also including strategic health goals and future possibilities.

Factors to be considered in the holistic care of HIV+ patients include complications (from immune suppression) of health challenges that existed prior to HIV infection. In addition, the social, psychological, and spiritual challenges that exist with the diagnosis of HIV create a need for health care that extends far beyond the best drug or nutrient necessary for optimal heath. Holistic physicians have a vital role in the care of each patient with HIV.

The majority of HIV+ patients in North America are using HAART. Many of those same patients are also using CAM therapies. Therefore, one of the first priorities of the naturopathic provider should be to ensure that the patient is safe from adverse drug-nutrient interactions. In order to ensure safety, it is necessary to understand the mechanisms of HAART as well as those of common nutrients being used by HIV+ patients.

Five main classes of HAART are currently being used in the care of HIV+ patients in various combinations designed to disrupt the virus' life cycle at multiple junctures.[17] These include:

- Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs, or "nukes")
- Nonnucleoside reverse transcriptase inhibitors (NNRTIs, or "nonnukes")

- Protease inhibitors (PIs)
- Entry inhibitors (including fusion inhibitors and CCR5 inhibitors)
- Integrase inhibitors

Additionally, a number of fixed-dose formulations exist that combine multiple drugs and classes. This has helped to simplify dosing and decrease pill burden for patients using HAART.

As a result of the rapidly evolving resistance of HIV to specific drugs, there has been great pressure to quickly develop and approve new medications. As a result, most HAART medications have been generally fast-tracked through the FDA approval process. Therefore, new drugs are typically prescribed as soon as they are approved and usually before the full extent of their adverse reactions are known. As the adverse drug reactions and interactions with HAART are myriad and potentially quite harmful, the clinician is advised to consult up-to-date resources to determine specific issues with each individual medication.

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors. NRTIs were the first class of antiretroviral drugs approved for use in the United States by the FDA. These drugs work during the transcription phase of the HIV life cycle by competitive inhibition of HIV reverse transcriptase (RT), leading to DNA chain termination. Nucleoside (or nucleotide) analogues act as substrates and bind to the active site of the RT enzyme. Then they are added to the new chain of DNA. Once they have been inserted, the normal links between pieces of the chain will not form and the viral chain will be terminated without being inserted into the cell's DNA.

The following is a list of NRTIs. All are nucleoside analogues except tenofovir, which is the only nucleotide analogue that is FDA-approved:

- 3TC: lamivudine (Epivir)
- ABC: abacavir (Ziagen)
- AZT: azidothymidine, zidovudine (Retrovir; the first FDA-approved HIV medication in 1986)
- DDC: zalcitabine (Hivid; no longer manufactured)
- DDI: didanosine (Videx, Videx EC)
- D4T: stavudine (Zerit)
- FTC: emtricitabine (Emtriva)
- TDF: tenofovir, disoproxil (Viread, a nucleo*tide*)

The NRTIs are fairly well tolerated after introduction (initial mild to severe nausea usually resolves), with minimal long-term adverse effects. Exceptions include AZT and the remaining "D" drugs (DDI and D4T). A common side effect of AZT is bone marrow suppression, leading to macrocytic anemia.[19] The D drugs are less commonly used today except in the case of multidrug resistance. They have been associated with mild to severe peripheral neuropathy and, of greater concern, pancreatitis.[20] These side effects manifest secondary to neural inhibition of mitochondrial DNA polymerase and reduced mitochondrial DNA content.[21] Therefore, patients on D drug therapy should be provided with ample mitochondrial support. Acetyl-L-carnitine, coenzyme Q_{10} (CoQ_{10}), essential fatty acids (EFAs), α-lipoic acid, and B vitamins have been shown to decrease signs or progression of these side effects when taken in large doses.[22-26] Additionally, the thymidine analogues (d4T, ddI, AZT) have been associated with lipoatrophy, also as a result of mitochondrial toxicity. Because the NRTIs have been on the market longer than the other drugs, it is no surprise that they are backed with the greatest amount of research regarding nutrient interactions. Although there are no studies indicating that vitamins or other nutrients deplete AZT, there is evidence that AZT may deplete cellular levels of carnitine, copper, zinc, and vitamin B_{12}.[27,28] With the exception of carnitine, these nutrients can be found in a good hypoallergenic multivitamin/multimineral supplement. In addition to deficiency caused by NRTI drugs, carnitine deficiency has been found in HIV+ patients not on HAART. Further, there are many other indications for carnitine in patients with HIV, making this nutrient a high priority for supplementation.

Some nutrients have been found to enhance the efficacy of NRTIs when taken in combination with these drugs, including vitamin E, zinc, and folate.[29-31] These nutrients are easily supplemented through a nutritious diet full of whole grains, colorful vegetables and fruits, and a good multivitamin/multimineral supplement.

Overall, NRTIs are fairly well tolerated and some have the additional benefit of being active against hepatitis B virus (3TC, FTC, TDF).[32-34]

Nonnucleoside Reverse Transcriptase Inhibitors. The second class of HAART comprises the NNRTIs. NNRTIs also affect the transcription process and work by allosterically binding to HIV-1 reverse transcriptase and inhibiting both RNA- and DNA-directed DNA polymerase functions of the RT enzyme.

The following is a list of the NNRTIs:

- EFV: efavirenz (Sustiva)
- ETV or TCM-125: etravirine (Intelence)
- DLV: delavirine (Rescriptor; rarely used)
- NVP: nevirapine (Viramune)
- RPV, TMC278: rilpivirine (Edurant)

NNRTI drugs are also fairly well tolerated after introduction, with low long-term toxicity. Other than an initial transient mild to severe skin rash, typical side effects (depending on the specific drug) include insomnia, abnormal dreams, elevated liver enzymes, and gynecomastia (all manageable with naturopathic support).[35-37] Resistance to this class of HAART can occur easily if the viral load is unsuppressed, so this type of medication may not be an optimal choice for someone who is inconsistent with taking medications. No nutrients are known to be depleted by NNRTIs or to enhance their efficacy.

Large randomized, double-blind placebo-controlled studies have shown that when used in combination with NRTIs, NNRTIs produce sustained reductions in plasma viral loads and improvements in immunologic responses.[38-41] The advantage of this type of protocol is the fewest number of side effects, excellent long-term viral suppression, and ease of dosing (fewer pills).

Protease Inhibitors. The third class of HAART is the PIs. PIs intervene during the cleavage part of the viral life cycle by binding competitively to the substrate site of the viral protease (the enzyme responsible for the posttranslational processing), resulting in inhibition of the enzyme and the production of immature virus particles.

The following is a list of the PIs:

- ATV: atazanavir (Reyataz)
- DRV: darunavir (Prezista)
- FPV: fosamprenavir (Lexiva); amprenavir (Agenerase, formulation discontinued)
- IDV: indinavir (Crixivan)
- LPV-r: lopinavir+ritonavir (Kaletra; fixed-dose combination)
- NFV: nelfinavir (Viracept)
- SQV: saquinavir (Invirase; Fortovase formulation discontinued)
- TPV: tipranavir (Aptivus)
- RTV: ritonovir (Norvir; always used in combination with another PI to increase effectiveness)

Although PIs are effective at viral suppression, they are associated with the greatest number and most significant adverse drug reactions. These include chronic and persistent gastrointestinal

(GI) abnormalities; lipodystrophy and lipoatrophy; elevations of cholesterol and triglycerides; insulin resistance leading to diabetes; and liver, kidney, and musculoskeletal complaints.

It is essential to realize that NNRTIs and PIs also work by inhibiting cytochrome P450 3A4 enzyme metabolism. Inhibition of this enzyme slows down the metabolic breakdown of the drug and effectively prolongs higher blood levels, which results in better viral suppression. Many foods, nutrients, and botanicals have been known to upregulate this enzyme function, and two have gained noteworthy attention. Some small studies (of fewer than 25 subjects) in healthy HIV-negative (HIV–) individuals as well as in vitro studies have demonstrated that garlic and St. John's wort decrease NNRTI and PI drug levels. In the human trials, subjects initiated NNRTI or PI therapy to establish the drug levels necessary to suppress viral load. Garlic or St. John's wort was then introduced at levels typically used for therapeutic effect. Blood levels were then measured and found to be lower than the levels believed to be necessary to maintain optimal viral suppression. Garlic or St. John's wort was then discontinued and NNRTI or PI blood levels subsequently measured and found to be back in the therapeutic range.[42-45] Although these studies certainly do not conclusively demonstrate that garlic and St. John's wort interfere with HAART viral suppression (small number of participants, single antiretroviral vs. typical multidrug HAART protocol, HIV– vs. HIV+, drug-naive vs. long-term HAART), these therapies should be avoided in patients with HIV on HAART. The lesson learned from these studies is to be intimately aware of the mechanisms of action when adding new nondrug therapies intended for patients on multidrug treatments. The potential for drug-nutrient interactions also should encourage and reinforce the use of the multitude of low-force interventions (e.g., diet, lifestyle, homeopathy, physical medicine, counseling) for conditions commonly treated by garlic or St. John's wort in order to avoid potentially decreasing NNRTI or PI blood levels and risking increases in drug resistance.

Milk thistle may be considered for the treatment of significant GI and liver complications with PIs. To date, there have been limited studies investigating the drug interactions of this herb. In one with 10 HIV–, drug-naive patients taking milk thistle at 175 mg three times daily, investigators concluded that milk thistle did not significantly alter blood levels of indinavir despite a decrease of as much as 25% in trough levels.[46] Another study showed no effect on indinavir levels in healthy subjects.[47] Yet another tested cellular uptake of ritonavir in the presence of various herbal substances including milk thistle (silybinin) and found no change in the efflux of ritonavir or any effect on CYP 3A4.[48] An in vivo study with coadministration of nifedipine and silymarin in 16 healthy male volunteers concluded that silymarin is not a potent CYP 3A4 inhibitor in vivo.[49] Currently there is no evidence suggesting that milk thistle should be avoided by HIV+ patients on HAART, but more studies are necessary. No nutrients are known to be depleted by PIs or to enhance their efficacy. However, if gastrointestinal side effects are present it could lead to micro- and macronutrient deficiencies.

Entry Inhibitors. There are currently two classes of entry inhibitors, fusion inhibitors and CCR5 inhibitors. Both are designed to prevent the HIV virion from initially entering the CD4+ cell through its membrane.

ENF, T-21, or enfuvirtide (Fuzeon), is a fusion inhibitor that was approved by the FDA in 2003. It blocks the fusion of the virus with the target-cell membrane by binding with cell receptor gp41 proteins and thereby preventing the virus from entering the cell. This drug is unique because it is the only HAART medication administered via injection (two subcutaneous injections per day into the upper arm, thigh, or abdomen). Because of its cost and difficulty of use, Fuzeon has served as "last resort" or salvage therapy in heavily treatment-experienced individuals and in the presence of extensive viral resistance and is not designed to be used alone. With the approval of numerous new medications recently, Fuzeon is now rarely used. It is fairly well tolerated with the exception of injection-site irritation, allergic reactions, and an increased risk of bacterial pneumonia. There are no known drug-nutrient interactions of any clinical significance.

MVC, or maraviroc (Selzentry), is a CCR5 inhibitor approved by the FDA in 2007. After HIV binds to CD4 receptors on the T-cell membrane, it then binds to one of two coreceptors, CCR5 or CXCR4. MVC is an antagonist that specifically blocks CCR5 coreceptors and prevents HIV from binding to them so that it cannnot enter the cell. The limitation with this drug is that different viruses may express various coreceptors: CCR5, CXCR4, or both. A relatively expensive test called a tropism assay must be run in any individual in whom the use of MVC is being considered. This test determines whether the specific virus present binds to CCR5, CXCR4, or both types of receptors. MVC will be effective only on a patient with a CCR5-tropic virus. Significant possible side effects include an allergic reaction (rash) and liver toxicity. Other side effects can include cough, fever, cold, muscle/joint pain, stomach pain, and dizziness. If MVC is used, doses of other medications may have to be adjusted (including but not limited to NNRTIs, PIs, oral contraceptives, certain other antimicrobials). Another potential issue is that other cells of the immune system exhibit CCR5 receptors, and MVC may affect them and potentially increase the risk of other infections and cancers. As of the date of writing, this has not been seen in clinical trials.

Integrase Inhibitors. RAL, or raltegravir (Isentress), was approved by the FDA in 2007 and belongs to this newest class of antiretroviral drugs. Currently several more integrase inhibitors are in development. These drugs disrupt the integrase enzyme, which facilitates the incorporation of HIV DNA into human DNA and thereby prevents viral replication in the T cell. RAL is relatively well tolerated, easy to take, and has demonstrated a remarkable ability to increase CD4 counts and drop viral load to undetectable levels in highly treatment-experienced patients with significant resistance issues. The most common side effects include diarrhea, nausea, headache, and fever. Some other possible issues may include hypersensitivity reaction, anemia, and liver toxicity. No significant nutrient interactions have been identified.

Combinations and Dual-Class Drugs. The creation and approval of these fixed-dose combination formulations have allowed the simplification of dosing and significantly decreased the pill burden for patients taking them. Issues, side effects, and interactions for the individual components are applicable to these combinations.

Single-class combinations (all NRTIs):

- 3TC and AZT (Combivir)
- 3TC, AZT, and ABC (Trizivir)
- FTC and TDF (Truvada)

Dual-class combinations (NRTI + NNRTI):

- FTC, TDF, EFV (Atripla)
- FTC, TDF, RPV, (Complera)

Of these combinations, FTC/TDF and FTC/TDF/EVF are being used quite extensively in the current standard of care. FTC/TDF/RPV was approved by the FDA in August 2011 and has the advantage of replacing EFV with RPV, thereby eliminating the EFV side effects.

Establish a Foundation of Health and Wellness on the Basis of Naturopathic Principles

The naturopathic standard of incorporating healthy diet and lifestyle practices cannot be overemphasized for HIV+ individuals. These patients are likely to be taking a large number of medications, nutritional supplements, or both, resulting in additional biochemical stress on the body. Therefore, each patient should be clearly encouraged and continually reminded to maintain dietary habits designed to ensure optimal GI health and nutritional intake.

The most important recommendation is to encourage a high intake of filtered or safe water so as to decrease oxidative stress and reduce the toxic load of the HIV and medications.[50] These patients should also be encouraged to maintain an optimal intake of protein.[51,52] Protein requirements can be as high as 100 to 150 g per day, particularly when patients are experiencing malabsorption and/or diarrhea; it may be necessary to provide supplemental protein to prevent weight loss. Studies using large doses of whey protein and amino acids (L-glutamine, L-arginine) have proved effective in reversing or preventing HIV-induced wasting.[53-55] Essential fatty acids have also been found to be deficient in HIV+ patients. Studies have demonstrated that HIV+ patients consuming generous amounts of EFAs have an increased body cell mass and a decreased risk of progression to AIDS.[56-58] HIV+ patients and healthy subjects ingesting fruit juices or a fruit-vegetable concentrate on a long-term basis were found to have higher micronutrient and antioxidant levels.[59,60] From this it can be concluded that HIV+ patients should be continually encouraged to include colorful vegetables and fruits in their diets to help maintain levels of essential micronutrients and fiber.[61,62]

HIV+ patients commonly require appetite stimulation, digestive enzyme support, or both to combat the adverse effects of HIV, HAART, and prophylactic antibiotics on the GI system.[63,64] Further, with high oxidation already present in the digestive system, all patients should be strongly encouraged to avoid additional GI stressors such as high-sodium, high-fructose corn syrup in processed foods, alcohol, caffeine, fried foods, and cigarette smoke. Raw eggs, unpasteurized milk, undercooked meat or fish, and potentially contaminated foods must also be avoided to decrease the risk of gastrointestinal OIs and parasites.

Naturopathic physicians should exercise extreme caution in considering allergy elimination diets in HIV+ patients owing to the likelihood of nutrient deficiencies, maldigestion, and malabsorption caused by HIV itself and HAART medications. A safer alternative is to recommend replacement of common food allergens one food at a time in order to make sure that patients can maintain replacement diets without decreasing caloric and nutrient intake over time. Removing food vices and irritating foods may be one of the most challenging aspects of moving HIV+ patients toward optimal wellness, because there are so many other higher-priority challenges and a vital need to maintain body mass.

Lifestyle factors should be part of the naturopathic foundation with each HIV+ patient. Aerobic exercise has been demonstrated to provide benefit to individuals with immunodeficiency diseases, particularly through stress alleviation and mood enhancement. HIV+ individuals had increases in CD4, CD8, and NK cells immediately following aerobic exercise, and long-term exercise has demonstrated increases in immune parameters.[65,66] HIV+ individuals practicing Tai Qi demonstrated a greater overall perception of health and significant improvements in several measures of physical function as compared with controls.[67] Other patients practicing yoga reported increased self-confidence and a quicker return to athletic activities after medical interventions.[68]

All patients should be encouraged to create an optimal sleeping environment and to sleep 8 to 10 hours each night. Sleep is essential for the repair and rebuilding of tissues and has been demonstrated to increase circulating NK cells and lymphocytes.[69,70]

HIV+ patients involved with group activities have better prognoses as well as decreased stress and anxiety. Anecdotal evidence links long-term AIDS survival with one or more of the following: having a positive attitude toward the illness, participating in health-promoting behaviors, engaging in spiritual activities, and taking part in activities that support the HIV+ community. Structured, brief group intervention for bereavement due to the loss of loved ones has been shown to decrease plasma cortisol and improve several immune markers in patients with HIV.[71,72] Other forms of stress relief and management have proved effective for HIV+ patient health care. Cognitive behavioral stress management is a guided form of relaxation training. It has been shown to improve the quality of life in HIV+ women, decrease herpes simplex 2 antibody titers in HIV+ men, improve HIV laboratory values, and have lasting effects on quality of life and psychological well-being of patients.[73-78]

Engaging in prayer, including distance healing, has demonstrated fewer new AIDS-defining illnesses, decreased illness severity, significantly fewer doctor visits, fewer hospitalizations, and significant improvements in mood.[79] For individuals not on HAART, participation in spiritual activities (prayer, meditation, affirmations, psychic healing, visualizations) resulted in a reduced risk of death over a one-year period.[80] Finally, laughter has been associated with improvement in WBC values and decreased stress.[81]

Establish a Core Nutrient Protocol

Replace Known Nutrient Deficiencies Caused by HIV. Vitamin and mineral replenishment has been demonstrated to be efficacious in HIV+ patients.[82-84] A double-blind placebo-controlled study involving 1078 pregnant Tanzanian women infected by HIV reported that taking vitamin A (preformed vitamin A and beta-carotene) and a low-cost multivitamin (vitamins B, C, and E) resulted in delayed progression to AIDS as well as a delay in the requirement to initiate antiretroviral therapy. Adding the low-cost multivitamins was statistically significant versus placebo or vitamin A alone.[85] Numerous vitamin and mineral deficiencies have been identified with HIV disease progression.[86] These deficiencies are likely due to loss, poor absorption, or rapid use and consumption.

Box 173-4 summarizes the nutrients that have been found to be deficient in patients with HIV. Typical daily doses required to replete deficiencies taken in divided doses throughout the day are noted in parentheses followed by the rationale or benefits.

Nutrient deficiencies (high doses of beta-carotene, vitamin D, acetyl-L-carnitine, dehydroepiandrosterone [DHEA], testosterone, reduced glutathione, and catalase) not commonly included in a multivitamin/multimineral supplement must be replaced through specific dietary regimens or through additional supplementation. Natural forms of beta-carotene should be used, as evidence suggests that synthetic forms can increase the risk of lung cancer in individuals who smoke.[87] Consider acetyl-L-carnitine as a high-priority nutrient, despite its high cost, on the basis of the number of benefits.

Provide Other Nutrients to Support Optimal Immune Function. Box 173-5 summarizes nutrients that have been found to

BOX 173-4 **Nutrient Deficiencies in HIV Patients**

- Vitamin A (15,000-30,000 IU taken with food) slows progression to AIDS and decreases mortality, improves growth in infants, decreases stunting associated with chronic diarrhea, and prevents GI deterioration in mothers and infants.[214-217] May increase the risk of HIV transmission by breastfeeding but has no effect on mortality by 24 months.[218] Deficiencies can be due to decreased dietary intake, poor GI absorption, high urinary loss, impaired hepatic protein synthesis, and increased needs due to chronic infection.
- Beta-carotene (60-120 mg/150,000 IU taken with food) replenishment increased CD4+ count, CD4/CD8 ratios, total lymphocyte count, and decreased mortality.[219-221] Deficiency found in all HIV+ patients is likely due to poor digestion, decreased free radical elimination, and high lipid peroxidation.[222]
- Folate (400 mcg) normalized cell differentiation. Deficiency is most likely due to malabsorption; AZT-induced deficiency may increase risk of bone marrow toxicity.[223,224]
- Vitamin B_1 (50 mg) replenishment is associated with increased survival in HIV+ patients and decreased progression to AIDS.[225-227]
- Vitamin B_6 (50 mg) is essential in nucleic acid and protein metabolism and cellular and humoral immune responses.[228,229] Vitamin B_6 repletion both alone and in conjunction with CoQ_{10} increased circulating IgG, CD4+ cells, and CD4/CD8 ratios.[230]
- Vitamin B_{12} (1000 mcg hydroxy-, methyl- or cyanocobalamin best taken via intramuscular injections 3 times a week—alternate form is daily 1000 mcg sublingual) is important in several parameters of immune function, proper cell differentiation and nerve function, and in decreasing homocysteine levels. Vitamin B_{12} repletion can improve lymphocyte counts, CD4/CD8 ratios, and NK cell activity.[231] Supplementation has also been found to reverse AIDS dementia complex when associated with low levels.[232] Deficiency has been associated with increased risk of progression to AIDS and with HIV disease in general.[233-235]
- Vitamin D (5000 IU) deficiency commonly found in urban HIV-infected men with suppressed viral load and CD4 > 200; tobacco use was correlated with severe deficiency.[236] Undetectable levels of vitamin D in HIV+ patients correlated with more advanced HIV infection, lower CD4 count, higher levels of TNF-alpha.[237] Lower bone-mineral density was found HIV patients using tenofovir/emtriciabine combination.[238]
- Vitamin E (800 IU daily—mixed tocopherols taken with food) is indicated to decrease lipid peroxidation, protect against AZT-induced oxidative damage to cardiac mitochondria, normalize immune function, and slow progression to AIDS.[239-244] Deficiency is found in most HIV+ patients, with wasting, and in progression to AIDS.[245]
- Copper (2 mg) can inhibit HIV protease and viral replication.[246] Deficiencies of copper are associated with AZT therapy and AIDS.[247,248]
- Magnesium (300 mg) deficiency is found in AIDS patients.[249,250]
- Selenium (400 mcg) to suppress the progression of HIV-1, viral burden, and provide indirect improvement of CD4 count.[251] Decreases HIV-associated mortality, decreases anxiety in HIV+ recreational drug users, and decreases hospitalizations and costs of caring for HIV+ patients.[252-255] Severity of deficiency in patients progressing to AIDS may be due to decreased calorie and protein intake, malabsorption, and various infections.[256]
- Zinc (15 mg—optimal intake levels have not been determined) has been found to decrease frequency of OIs.[257,258] Deficiency is noted in all HIV+ patients progressing to AIDS.[259]
- Acetyl-L-carnitine (2-6 g best taken away from other proteins to optimize absorption) is essential for proper energy supply as well as critical metabolic functions. Deficiency is common in HIV+ patients and increases the risk for alterations in fatty-acid oxidation.[260-262] Repletion has also been linked with a reduction in serum triglycerides, decreased risk of wasting, increase in CD4 cells and reduced apoptosis, increased levels of serum insulin-like growth factor, reduction in mitochondrial neurotoxicity, and treatment of peripheral neuropathy.[263-268] It has also been demonstrated as an effective treatment for NRTI-induced lactic acidosis.[269]
- DHEA (15-50 mg taken with food) repletion helps to increase CD4 count, stimulate immune function, and improve quality of life.[270,271]
- Testosterone (intramuscular injection weekly) is indicated if serum levels are low in order to decrease loss of lean body and muscle mass.[272]
- Glutathione/GSH (increased through selenium and N-acetyl-cysteine or whey protein powder) has been found to decrease disease progression and mortality.[273-276] Deficiencies are found in both symptom-free HIV+ and AIDS patients.[277,278]

Many of these nutrients can be replenished through the use of a highly nutritious diet and a good multivitamin. A few multivitamins have been specifically developed to replace the deficiencies of HIV+ patients and include high doses of carotenoids, B vitamins, antioxidants, and sometimes digestive enzymes. Taking one multivitamin designed specifically for HIV reduces pill burden and enhances compliance. Conversely, it is generally more cost effective to use a basic multivitamin and supplement individually with additional nutrients.

AIDS, acquired immunodeficiency syndrome; DHEA, dehydroepiandrosterone; GI, gastrointestinal; GSH, growth-stimulating hormone; HIV, human immunodeficiency virus; NK, natural killer; NRTI, nucleoside/tide reverse transcriptase inhibitors; OI, opportunistic infection.

replace or reduce other nutrient deficiencies or have beneficial action in patients with HIV, their daily doses divided throughout the day, and effects of supplementation.

All these nutrients have benefits, but they significantly increase overall cost and pill burden. Therefore priority should be given to the most essential (EFAs and DHEA) and lower-cost (vitamin C) nutrients or to address specific symptoms as described in the next section.

Provide Therapies to Address Constitutional Symptoms, Medication Side Effects, and Symptoms of Immunosuppression

The following are some approaches for specific health conditions and OIs. The naturopathic physician should endeavor to identify and remove the cause, tonify systems, and, treat each patient individually.

Candida albicans/Oral Thrush. Overgrowth of this fungal organism may occur as a result of HIV itself (a low CD4+ count, reducing the body's immune capacity) or secondary to prophylactic antibiotic treatment. Orally, it can cause pain and make eating difficult, which can lead to reduced caloric intake and subsequent problems. In the intestines, it can cause inflammation and compromise nutrient absorption. In the esophagus, it can cause pain and should be dealt with swiftly via antifungal pharmaceuticals.

For treatment, patients should avoid foods that promote yeast growth, such as simple carbohydrates, sugar, baked goods, and starchy vegetables. These options should be considered:

- Probiotics: Provide and support healthy flora via the consumption of fermented foods as well as using supplements with at least 8 billion colony-forming units (CFUs), best taken with

BOX 173-5 Nutrients That Have Been Found to Replace or Reduce Other Nutrient Deficiencies or Have Beneficial Actions in HIV Patients

- *Silybum marianum*/milk thistle (300 mg standardized extract away from HAART) is indicated for all patients on HAART to improve liver function, decrease liver damage, and increase the antioxidant activity of blood cells.[279]
- NAC (2-8 g best taken away from other nutrients but may need to be taken with food to decrease GI distress) is indicated to prevent loss of sulfur containing amino acids, increase GSH, decrease TNF-α activity, and increase CD4 cell count.[280-282]
- CoQ_{10} (100-300 mg) optimized mitochondrial function and replaced deficiency.[283,284] Repletion with CoQ_{10} increased circulating IgG, CD4+ cells, and CD4/CD8 ratios.[285,286]
- Vitamin C (2-6 g) when combined with vitamin E significantly lowered oxidative stress and has demonstrated a trend toward lowered viral load.[287]
- Alpha-lipoic acid (600 mg) protected the liver, inhibited viral replication, increased intracellular GSH, increased CD4/CD8 ratios, and potentially decreases peripheral neuropathic pain by its antioxidant effect on nervous tissue.[288-293]
- L-arginine (7.4 g taken away from food) improved lean body mass and increased NK cell activity. Must be used with caution because large amounts of arginine can aggravate herpesvirus outbreaks. Prophylactic L-lysine may prevent or reduce this effect.
- EFAs (5 g taken with food; best from fish oil) improved lean body mass, increased NK cell activity, and was beneficial as adjuvant therapy in patients with tuberculosis.
- L-Methionine (1000 mg taken away from other proteins) slowed decline of CD4 cells.[294]

CoQ_{10}, Coenzyme Q_{10}; EFAs, essential fatty acids; GSH, growth stimulating hormone; HAART, highly active antiviral therapy; NAC, N-acetylcysteine; NK, natural killer; TNF-α, tumor necrosis factor alpha; EFAs, essential fatty acids.

food. Beneficial species include *Lactobacillus acidophilus/bifidus; Lactobacillus GG*, a well-researched strain from Germany; or *Saccharomyces boulardii*, which is best for antibiotic-induced colitis and can help displace pathogenic flora.[88-92]

- Garlic (1 to 2 g best taken before meals): Garlic is a potent antifungal found to spare nonpathogenic flora; note that patients on HAART should not take supplemental garlic.[93]
- Oregano oil (300 mg best taken away from food): This is also a potent antifungal.[94]
- Nystatin and fluconazole: Both are pharmaceutic antifungals.

Cardiovascular Disease. This issue is becoming increasingly problematic and prevalent in the HIV+ population. The adverse effects on serum lipids and glucose that accompany the use of HAART medications (specifically PIs and D-type NRTIs) significantly promote cardiovascular disease, particularly in patients already at high risk (where there are predisposing factors such as a positive family history).

All patients on HAART should be encouraged to institute a preventive diet, adopt a healthy lifestyle, and implement exercise recommendations to promote cardiovascular health. Exercise in particular has been demonstrated to increase functional aerobic capacity, eliminate functional aerobic impairment, and improve measures of exercise performance (improved peak oxygen consumption, oxygen pulse, tidal volume, ventilation, and leg power).[95,96] Garlic should be avoided owing to its adverse interaction with HAART medications. The following specific nutrients should be considered:

- Acetyl-L-carnitine (2-6 g best taken away from other proteins to optimize absorption) repletion has also been linked with a reduction in serum triglycerides.
- CoQ_{10} (100-300 mg) may enhance cardiovascular function.[97]
- Arginine (7.4 g taken away from food) decreases atherosclerosis.[98]
- EFAs (5 g taken with food) may lower lipids.[99]

Diarrhea. This is a common complaint and an issue that can greatly affect quality of life. An HIV+ person might develop diarrhea for numerous reasons; the specific etiology guides the choice of treatment. Causes might include HIV-associated enteropathy, HAART side effects (see specific medications—this is particularly an issue with PIs), antibiotic side effects, gastrointestinal infections, and food allergies or intolerances. An osmotic-type diarrhea can also result from the consumption of too many indigestible gelcaps (from medications and supplements) building up in the intestinal lumen.

The first treatment priority is to remove the cause if at all possible. There is an increased incidence of gluten intolerance in HIV+ individuals.[100] Lactose intolerance and irritable bowel syndrome are also possibilities. Food allergies/sensitivities should be cautiously ruled out. Stool cultures and testing for ova and parasites should be considered to screen for suspected infectious causes, and patients should be treated as indicated for each microbial etiology. All nutrient supplementation may be stopped on a temporary basis to screen for an osmotic cause and then reintroduced one at a time to determine potential causes.

Steps for prevention include avoiding unfiltered tap water, unpasteurized milk or dairy products, ice made from unfiltered tap water, raw fruits and vegetables unless they can be peeled personally or washed with appropriate antimicrobial agents, raw or rare meat and fish, meat or shellfish that is not hot when served, and food from street vendors. Dehydration can be prevented by replacing electrolytes; broths, soups, fruit and vegetable juices, or high-nutrient drinks should be included.

Prevent malnutrition; if diarrhea is present, malabsorption of nutrients is a likely consequence. Ensure adequate micro- and macronutrient intake with a multivitamin/multimineral supplement and maintain adequate protein intake (requirements may increase to 100 to 150 g/day). Initial dietary intervention may include simplifying the diet (BRAT diet: *b*ananas, *r*ice, *a*pplesauce, *t*oast) or using 1 tbsp tomato juice combined with 1 tbsp sauerkraut juice (a protocol taught by Dr. John Bastyr to two generations of naturopathic students and used with considerable clinical success by the senior editor to facilitate electrolyte replacement and promote enterocyte healing). Carob powder is an astringent that can help symptomatically. Begin with 1 tsp in applesauce and increase up to 6 tsp/day as needed.

Consider these additional supplements:

- Provide and support healthy flora as described earlier in the care of candidal infection.[88-92]
- L-glutamine (9 to 40 g best taken away from other proteins) is an amino acid that provides fuel for small intestinal enterocytes. Using a powder is most efficient and cost-effective. Start with 3 g three times daily. This can be increased up to 40 g daily if necessary. This high dose can lead to psychoses, so the patient should be monitored closely.[101]
- Diphenoxylate and atropine (Lomotil), loperamide (Imodium), and psyllium husk (Metamucil) are common pharmaceutical interventions.

Herpes Simplex Virus/Herpes Zoster/Shingles. All conditions with a herpes-type virus etiology are considered together, as the treatment approach is similar for each. The sequelae of herpesviruses tend to manifest on the skin in a dermatomal pattern of distribution. These symptoms can occur secondary to various types of stress, hormonal fluctuations, or a poor immune system response. First and foremost, try to identify and remove causes of stress (including dietary, emotional, and sunlight exposure) and support immune function. Secondarily, address the symptoms (most often pain is at the forefront).

Naturopathic physicians should consider the following:

- Dietary suggestions include eliminating foods high in L-arginine (promotes herpes replication), such as chocolate, nuts, and peanuts, and increasing foods high in L-lysine (antagonizes L-arginine), such as whole grains, dairy, fish, lima beans, and soy.
- L-lysine: 1000 mg three times daily away from food during an outbreak; 500 mg three times daily away from food prophylactically.[102]
- Olive leaf extract: 2000 mg is an effective antiviral.[103]
- Monolaurin: this antiviral, taken at 300 to 600 mg three times daily, is effective against encapsulated DNA viruses.[104]
- *Melissa officinalis:* an antiviral botanical used topically.[105]
- *Glycyrrhiza glabra:* an antiviral oral and topical botanical.[106]
- Herbal tincture (as parts): *Hydrastis* (1), *Taraxacum officinale* (the root) (2), *Lomatium* (2), *Passiflora* (1), *Astragalus* (1), *Gelsemium* (15 drops/oz); 60 drops every 2 hours during prodrome, four times daily during an outbreak, twice daily for prevention.
- Acyclovir/valacyclovir: pharmaceutical antiviral therapy.

Kaposi Sarcoma. Kaposi sarcoma (KS) is an HIV-associated neoplasm of vascular origin that tends to occur when CD4+ counts fall below 500/mm^3. KS is rarely found outside of the HIV+ population. The etiology of AIDS-associated KS is poorly understood, but several factors are thought to contribute, including the presence of human herpesvirus (HHV) type 8, a compromised immune response, and hormones (it occurs rarely in women, and androgen therapy causes increased proliferation of the tumors). It is most commonly found in iron-rich geographic areas. Interestingly, 90% of AIDS-related cases in the United States occur in homosexual men, making it rare in heterosexual men, women, and IV drug users.

KS begins as macules or elevated papules and can progress to large plaques or nodules. The color ranges from pink to purple or brownish-black. The lesions may be round or oval and do not blanch when pressure is applied to them. The lesions often appear first on the skin of the upper body or mucosal surfaces. In their aggressive form they can become widely disseminated and can manifest anywhere on the skin, mucous membranes, lymph nodes, or viscera (including the GI tract from the mouth to anus, lungs, liver, spleen, or pancreas).

KS tumors secrete increased amounts of angiogenic growth factors, tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, basic fibroblast growth factor, platelet-derived growth factor, and oncostatin-M.[107-112]

The level of immunosuppression of an affected person determines the clinical course of KS in AIDS. Currently there are no known cures; the various local and systemic approaches are aimed at palliation.

Treatment may involve the use of chemotherapeutic agents such as doxorubicin as well as standard HAART. Surgical excision can successfully remove a lesion, but there is a high rate of recurrence at the affected site. Other researched options that have produced varying results include radiation therapy, cryotherapy with liquid nitrogen, and electrical stimulation with direct current.

The following treatments should also be considered:

- Topical and systemic retinoids.[113]
- Topical vitamin D (1, 25-dihydroxyvitamin D3).[114]
- Iron has been shown to stimulate the growth of KS cells in vitro, whereas iron chelators reduced their growth.[115,116] Given this information, it may be sensible to limit iron intake and ensure that serum iron and ferritin levels are at the low end of normal.
- The use of various cytokine inhibitors and antiangiogenesis compounds might have a benefit for reducing the proliferation of these vascular tumors.
- Because there are no known curative therapies and the palliative treatment of KS is difficult at best, naturopathic physicians have an opportunity to be creative and make a contribution in this area. Given the association between KS and HHV type 8, it may be beneficial to use antiherpetic therapies if a patient is known to be herpes simplex virus–positive.[117] Topical application of a medicinal peat preparation has resulted in remission of topical KS lesions in several patients. Glutathione (NAC as a precursor) could be helpful in the treatment of KS lesions as well.[118-120]

Lipodystrophy. Lipodystrophy is a redistribution of adipose tissue from the extremities to the trunk. It often manifests with a Cushingoid "buffalo hump" over the upper thoracic region of the back or with truncal obesity. Self-image issues are often most significant for patients experiencing this condition. Lipodystrophy can occur as a result of alterations in lipid metabolism secondary to HAART or simply chronic HIV infection (greater than 15 years).[121] Given the appearance of the buffalo hump, it is possible that adrenal abnormalities contribute to the problem. Increases in serum cortisol lead to increases in insulin release from the pancreas, which drives blood glucose into storage in adipose cells. This leads to increased truncal obesity,[122-125] a physiologic mechanism that bears consideration in the therapeutic approach as well as in future research. Lipodystrophy has also been found to increase with lack of exercise.[126] In addition to correcting dietary nutrient insufficiencies, supplementing nutrients as per the general protocol, increasing exercise, and ensuring that blood glucose is appropriately regulated, use of the following can be considered:

- L-glutamine (10 g in divided doses away from food).[127,128]
- Acetyl-L-carnitine (2-6 g away from food) to optimize mitochondrial function.[129-131]
- Uridine (36 g three times daily for 10 consecutive days per month) to normalize subcutaneous fat.[132]
- Testosterone (10 g of testosterone gel daily) in HIV+ men with abdominal obesity and low testosterone; decreased whole-body, total, and abdominal fat mass; and increased lean body mass.[133]
- Nandrolone decanoate (150 mg IM every 2 weeks) may increase lean body mass more effectively than testosterone.[134]
- Tesamorelin, a growth hormone–releasing factor analogue (2 mg per subcutaneous injection), decreases visceral adipose tissue and triglycerides without aggravating glucose.[135]
- Dimethyl sulfoxide (DMSO)/bromelain (5% bromelain compounded in DMSO gel applied two to three times daily). Topical applications have resulted in the reduction of Cushingoid adipose deposits.
- Conventional treatment may include surgical removal of the truncal adipose deposits. Although this may not be the most desirable approach owing to its invasiveness, patients who undergo this procedure tend to be happy afterward because of their more positive self-image.

- Buccal injections of polylactic acid (PLA/Nufill) have been found to be safe and can reduce the cosmetic signs and depressive symptoms of lipodystrophy and wasting.[136]

Macrocytic Anemia. Macrocytic anemia can be a secondary effect from the malabsorption of nutrients or a side effect of HAART (AZT causes bone marrow toxicity; PIs may cause malabsorption).[137,138] The following treatments can be considered:

- Vitamin B_{12} (hydroxycobalamin/methylcobalamin/cyanocobalamin 1000 mcg/mL given IM three times a week) is an important nutrient for proper cell division and differentiation.[139] If an IM injection is unavailable, sublingual tablets at 1000 mcg/day can be used to bypass intestinal absorption issues.
- Folic acid (400 mcg/day, found in most good multivitamin/multimineral supplements) and vitamin B complex (3 mL IM each week) are also indicated for proper cell division and differentiation.[140,141]

Neuropathy. This is usually manifested in the periphery, particularly in the feet. It can work its way proximally as it increases in severity. It is most often seen either as a result of long-term HIV infection or as a side effect of the D-type NRTIs and their toxic effect on the mitochondria in neurons.[142,143] Diabetes mellitus type 2 can also be a factor, as can overdoses of vitamin B_6 (greater than 200 mg/day).[144]

The following treatments can also be considered:

- Acetyl-L-carnitine (2 to 6 g best taken away from other proteins to optimize absorption) decreases the risk for alterations in fatty-acid oxidation and energy supply, improves critical metabolic functions, and decreases pain.[145]
- EFAs (5 g/day with food) are antiinflammatory agents and components of healthy cell membranes.[146]
- Vitamin B_{12} (1000 mcg/mL IM three times weekly) is an important nutrient for proper cell division and differentiation.
- Vitamin B complex (1 mL IM three times weekly) is indicated for proper cell division and differentiation.[147,148]
- CoQ_{10} (100-300 mg) is indicated to optimize mitochondrial function.[149,150]
- Alpha-lipoic acid (600 mg/day) may decrease pain.[151]

Psychological Conditions. Issues such as depression, anxiety, post-traumatic stress disorder, sexual dysfunction, and substance abuse are extremely common in the HIV+ population. These problems potentially have physiologic as well as psychological components but may not be adequately addressed by other providers.

Suicidal ideations and suicide attempts can also be an issue for this population. As quality of life deteriorates, the burden of ongoing medical treatment increases, and close friends die, the desire to live can wane. It is critical that practitioners always be vigilant for signs of suicidal thinking or loss of hope in patients. These signs should be taken seriously, and there should be no hesitation in bringing in experienced professional help to assist these patients.

In contemplating the treatment of any psychological issue in this patient population, extreme caution must be exercised owing to issues of polypharmacy and drug-nutrient interactions. Many of these patients are taking a substantial number of pharmaceutical medications. Interactions among many nutrients and these medications and even among the medications themselves are likely. Before instituting any treatment, all potential interactions must be researched, identified, and considered.

An example of this problem is the potential use of St. John's wort, a commonly used herbal antidepressant. As previously discussed, St. John's wort is an inducer of the cytochrome P-450 detoxification enzyme 3A4 in the liver and has been found to reduce serum levels of various HAART medications. Therefore, it can theoretically reduce the effectiveness of those medications and potentially lead to increased issues with resistance. The use of St. John's wort should be avoided in any patient who is undergoing HAART.

Modalities such as counseling, lifestyle modification, and homeopathy can be quite useful in treating these psychological conditions. Meditation and mindfulness have been found to be effective for psychological health. For example, a mindfulness-based stress reduction meditation program showed stabilization of CD4+ T-lymphocyte counts independent of antiretroviral medication use.[152] In another study, mantram repetition—a word or phrase with spiritual associations repeated silently throughout the day—was found to reduce anger as well as to increase spiritual faith and spiritual connectedness; it was inversely associated with non-HIV-related intrusive thoughts and positively associated with quality of life, total existential spiritual well-being, and meaning/peace.[153] Additional therapies to consider follow:

- Multivitamin supplementation (B complex, C, and E) resulted in a reduction in risk of elevated depressive symptoms and improvement in quality of life.[154]
- Androgens (DHEA 50 mg or testerosterone 300 mg IM weekly) can improve mood, quality of life, and overall survivability and also decrease fatigue.[155,156]
- Amino acids (if levels are found to be low by specialty laboratory analysis) should be prescribed in combinations tailored to replenish deficiencies.[157,158]
- Zinc (25 mg/day) can serve to normalize levels and improve the efficacy of antidepressants.[159]
- EFAs (5 g/day with food) have been found to be useful as adjunctive treatment in depressive disorders.[160,161]
- SAMe (1600 mg/day) has been shown to be as effective as imipramine (150 mg) in treating major depression and is better tolerated.[162]

Wasting. In 1987, the CDC defined HIV-associated wasting syndrome as an involuntary weight loss of greater than 10% of baseline body weight accompanied by chronic fever, weakness, or diarrhea. A more complete definition is available in *The AIDS Reader*[163] (Box 173-6).

Body cell mass (BCM) can be measured via bioimpedance assay. Research shows that BCM is a better predictor of survival than CD4 counts. Key issues to be addressed with patients include perceived weight loss, changes in appetite, diarrhea, energy level, and difficulties in performing activities of daily living.

The etiology of wasting is most likely multifactorial in nature; some possible etiologies include the following[164]:

- Decreased food intake—anorexia (decreased desire to eat or loss of appetite with corresponding decrease in food intake) or nausea secondary to medications, systemic illness, or GI pathology; finances; dependence on others; poor food choices.

BOX 173-6 AIDS Wasting Syndrome Criteria

AIDS wasting syndrome must meet one of the following criteria:
- Unintentional weight loss of >10% over 12 months
- Unintentional weight loss of >7.5% over 6 months
- BCM loss of <5% over 6 months
- Men: BCM <35% of TBW and BMI <27 kg/m^2
- Women: BCM <23% of TBW and BMI <27 kg/m^2
- BMI <20 kg/m^2

BCM, body cell mass; BMI, body mass index; TBW, total body weight

- Malabsorption/chronic diarrhea—results in decreased nutrient intake; influenced by many pathologies and dysfunctions (affecting any part of the GI tract: oral, esophageal, stomach, pancreatic, biliary, hepatic, and small and large intestine); problems might include infections, medication side effects, enzyme deficiencies, and malignancies; all might result in the inability to absorb macro- and micronutrients.
- Alterations of metabolism—studies show that resting energy expenditure (REE) is higher in HIV/AIDS patients than in HIV–controls; studies also show the REE does not downregulate if anorexia or malabsorption is present (therefore, the combination of decreased caloric intake with a metabolic rate that does not adjust to that state would result in a negative energy balance and weight loss).
- Cytokine abnormalities—not well understood; TNF, IL-1 may induce anorexia and affect lipid, protein, and carbohydrate utilization; an example is cachexia in cancer.
- Endocrine abnormalities—thyroid abnormalities, adrenal insufficiency (cortisol, DHEA), hypogonadism (testosterone), growth hormone deficiency.
- Alcohol abuse—studies show that progression to AIDS is much quicker in HIV+ patients who consume large amounts of ethyl alcohol (ETOH) versus normal expectations; ETOH can stimulate HIV production, suppress immune defenses (lower CD4 cell counts), and deplete tissue micronutrients (specifically, antioxidants).

As per general recommendations, the naturopathic physician should endeavor to remove the cause if it is identifiable and removal is feasible. Then he or she should identify and remove possible food allergies/intolerances (gluten and dairy in particular) and ensure adequate and appropriate nutritional intake via dietary counseling; patients should also be helped to access social service assistance if necessary. Patients are likely to need superdoses of nutrients. Protein intake should be increased to 100 to 150 g/day. Patients should be active and engage in daily exercise.

The following therapies can be considered:

- EFAs (5 g/day with food), which are essential in a healthy diet[165]
- Acetyl-L-carnitine (2 to 6 g/day) to optimize fatty acidic metabolism[166]
- L-Glutamine (10 to 40 g), an essential amino acid for enterocytes[167,168]
- DHEA (50 mg) to promote lean body mass[169]
- Melatonin (20 mg at bedtime) to decrease cachexia and TNF[170]
- Marijuana (smoked, four times daily) or oral dronabinol (5-10 mg four times daily) to increase daily caloric intake and body weight[171]
- Progesterone (800 mg) to decrease cachexia[172]
- Testosterone in hypogonadal men to increase lean body mass and muscle strength[173]
- Anabolic steroids (nandrolone decanoate, oxandrolone, oxymetholone) to increase lean body mass[174,175]
- Thalidomide, a cytokine modulator, to increase BCM and extracellular fluid[176]

Provide Specific Antiviral Therapy and Immunomodulation Using Other Nondrug Treatments

This section summarizes the botanical, homeopathic, and physical medicine studies that have been found to have potential for patients with HIV. They are not substitutes for HAART. This list is intended to assist health providers to find additional nondrug solutions that resonate with the unique needs of individual HIV+ patients. Further, the majority of the following studies are based on initial or empirical findings encouraging additional areas for research and exploration.

Botanical Medicines

Box 173-7 includes botanicals that have demonstrated efficacy in treating HIV.

Homeopathy

Homeopathy may offer a most interesting possibility in the care of HIV+ patients. The *British Journal of Homeopathy* published a report on the use of constitutional homeopathic remedies (30C-1M doses) given to 129 asymptomatic HIV+ patients in India. As a result, 12 patients became ELISA negative after 3 to 16 months.[177] In another study, 100 HIV+ patients between 17 and 50 years of age (71% men) were randomized to receive either a single homeopathic remedy or a placebo. The experimental group receiving remedies showed statistically significant increases in CD4+ T cells after 6 months.[178]

Other studies in homeopathy have demonstrated success with symptom care in HIV.[179] For example, Bissuel and colleagues[180] reported the use of homeopathic sulfamethoxazole and trimethoprim (Bactrim), preventing the hypersensitivity reaction commonly associated with this drug. In a randomized, double-blind, placebo-controlled trial of 24 HIV+ adults with baseline CD4+ counts between 125 and 500/mL, as reported by Brewitt and colleagues,[181] oral doses of homeopathic growth hormone resulted in statistically significant improvements in CD4 cells, CD8 cells, ESR, weight gain, and viral load; reduced occurrences of OI; and increased platelet counts.

The use of constitutional homeopathy should be considered an essential aspect of the care of all HIV+ patients considering the amazing potential, minimal side effects, and overall affordability.

Physical Medicine and Acupuncture. Physical medicine is another low-cost therapy that HIV+ patients can seek through a naturopathic provider. A growing body of evidence suggests that these therapies also play a pivotal role in the care of HIV+ patients:

- Whole-body hyperthermia (twice weekly at 108°F for 20 minutes) may elevate CD4 count, but extreme caution must be used in heat-intolerant individuals.[182]
- Ozone (rectal and aural insufflation) may inactivate HIV-1.[183-185]
- Acupuncture and moxibustion (three treatments weekly) has been demonstrated to decrease diarrhea as well as illicit drug (cocaine and heroin) cravings.[186-188]
- Electroacupuncture (by continually stimulating acupuncture/conductance skin points associated with nervous and immune systems), has been demonstrated to ameliorate the complications of HIV-related peripheral neuropathy, raise CD4+ counts, and raise other lymphocyte counts.[189,190]
- Massage therapy has been demonstrated to increase NK cells, CD3 and CD4 cell counts, and CD4:CD8 ratios, improve quality of life, and decrease health care costs.[191,192]

Other studies have demonstrated increased growth and development and overall behavior in HIV-exposed newborns as well as improved immune preservation in HIV+ children in the absence of antiretroviral therapy.[193,194]

- Therapeutic touch, reducing anxiety in children.[195]
- Cranioelectrical stimulation (microcurrent 0.1 mA at 100 Hz to alligator clips attached to the earlobes 20 minutes twice daily), can decrease anxiety, insomnia, and depression.[196]

BOX 173-7 **Botanicals That Have Demonstrated Efficacy in Treating HIV**

- *Glycyrrhiza glabra*/licorice (1500 mg) inhibited HIV fusion and viral transcription.[295-297] It should not be used in patients with a history of hypertension or with renal or cardiac problems.
- *Curcuma longa*/tumeric (1200 mg) inhibited HIV integrase and proteases and viral transcription and decreased nuclear factor kappa β.[298-300]
- *Olea* sp./olive leaf extract (2-6 g) increased NK-cell function and was effective against HIV and herpesviruses.[301,302]
- *Phyllanthus amarus* (1200 mg) demonstrated in vitro and ex vivo HIV-1 inhibition of reverse transcriptase, receptors, and proteases and is also effective against HBV.[303]
- *Lentinus edodes*/shitake mushrooms (1-5 mg IV twice weekly) inhibited reverse transcriptase, increased CD4 couts, and decreased p24 (surface marker).[304,305]
- *Andrographis paniculata* (1500 mg) inhibited fusion, viral replication, and HIV-1 cell-to-cell transmission. It also stimulated objective measures of immune function, increased the effectiveness of AZT, protected against liver damage, and decreased diarrhea.[306] Toxicity questions remain; further study is necessary.
- *Silybum marianum*/milk thistle (300 mg extract) improved liver function and antioxidant activity of blood cells.
- *Hyssopus officinalis*/hyssop (1-4 ml tincture) exhibited anti-HIV activity and inhibited integration of proviral genome into host genome.[307,308]
- *Prunella vulgaris*/self-heal (10 mg/mL IV) inhibited HIV replication and binding and prevented cell-to-cell infection.[309,310]
- *Rosmarinus officinalis*/rosemary (use liberally in food) decreased HIV replication and protease activity.[311]
- *Momordica charantia*/bitter melon (6 oz fresh juice) normalized CD4+/CD8+ ratios and inactivated viral DNA.[312]
- *Spirulina platensis*/blue-green algae (use liberally in food) reduced fusion and viral production.[313]
- *Scutellaria baicalensis*/skullcap (6-15 g whole root) inhibited HIV-1 reverse transcriptase.[314]
- *Podophyllum* resin (25% solution as a single topical application) resulted in resolution of hairy leukoplakia.[315]
- *Melaleuca leucadendron*/tea tree oral solution was effective for fluconazole-refractory oropharyngeal candidiasis in patients with AIDS.[316]
- *Hypericum perforatum*/St. John's wort (900 mg) inhibited protein kinase C and viral uncoating, fusion, and assembly.[317] Do not use in patients on NNRTI or PI.
- *Allium sativa*/garlic (4 g fresh garlic) selectively killed HIV-1 infected cells in vitro.[318] It should not be used in patients on NNRTI or PI.

AIDS, acquired immunodeficiency syndrome; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IV, intravenous; NK, natural killer; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Movement therapies may also be useful:

- Aerobic exercise has been demonstrated to provide benefit to individuals with immunodeficiency diseases, particularly through stress alleviation and mood enhancement. One exercise study demonstrated that HIV+ individuals had significant improvements in both CD8 and NK cells.[197-200]
- Tai Chi has demonstrated a greater overall perception of health and significant improvements in all functional measures in 13 HIV+ individuals when compared with controls.[201]
- Yoga has shown improvements in self-confidence and a return to athletic activities after the intervention.[202,203]

Provide Education and Guidance to Patients Seeking Alternatives to Conventional Treatment

As mentioned earlier, there are currently no known therapies as effective as HAART in suppressing viral load or increasing CD4 lymphocyte cells. CAM providers must avoid the temptation to allow their patients to believe otherwise.

If a patient is aware of the risk of a high HIV viral load, low CD4 count, or both yet still does not desire to initiate HAART or antibiotic prophylaxis, ensure that this patient has access to a conventional Western HIV specialist. This specialist can provide clear education on conventional Western medical approaches to HIV and help diagnose and treat OIs should they arise. Concurrently, initiate a foundation of care including healthy diet and lifestyle, nutritional support, and additional therapies as described earlier. Furthermore, ensure that the patient is scheduled for frequent follow-ups with health care providers to regularly screen for and monitor potential or existing opportunistic infections.

If a sole practitioner is treating a patient who refuses to undergo conventional Western medical and pharmaceutical intervention, specific use of the following therapies should be considered to decrease viral load and increase CD4 cell count:

- *Curcuma longa*/tumeric (1200 mg) to inhibit HIV integrase, proteases, and viral transcription.
- *Olea* sp./olive leaf extract (2 to 6 g) to increase NK-cell function and oppose HIV and herpesviruses.
- *Phyllanthus amarus* (1200 mg), which has been shown to inhibit HIV-1, reverse transcriptase, receptors, and proteases in vitro and ex vivo.
- *Lentinus edodes*/shitake mushrooms (1 to 5 mg IV twice a week), which can increase CD4 and decrease p24 (a surface marker).
- Ozone (rectal and aural insufflations), which may inactivate HIV-1.

For patients seeking advice on the discontinuation or interruption of HAART (a structured treatment interruption/STI or "drug holiday"), naturopathic physicians should ensure that patients clearly communicate this desire to their primary care physicians and HIV specialists. Treatment interruptions may be indicated in the following situations[17]:

- Severe or life-threatening toxicity, unexpected inability to take oral medications, or antiretroviral medication nonavailability (a short-term interruption).
- Where the patient has to be relieved of the inconvenience, toxicity, and cost of antiretroviral therapy.
- Where the response to salvage therapy (treatment regimens used in patients who have failed other HAART regimens) can be improved by allowing the re-emergence of wild-type virus (the predominant virus type in a given individual as unaffected by HAART therapy).

Potential problems with treatment interruptions include viral rebound, immune decompensation, and clinical progression of HIV. Multiple studies have been done over time to examine strategies for discontinuing and reintroducing HAART as well as to evaluate the safety of such discontinuations; however, there has been no clear resulting consensus.[204-210] The most recent studies include the SMART, TRIVACAN, and DART trials, which have not had positive outcomes.[211-213] The SMART study was the largest, with over 5000 subjects, and interrupted HAART when the CD4 cell count was greater than 350/mm^3 and reinitiated treatment when it fell below 250/mm^3. This trial was

discontinued when there was a clearly increased risk of disease progression and death compared with the arm on continuous HAART. The current recommendation of the Department of Health and Human Services is that HAART interruptions should not be recommended except in the case of clinical trials or an acute problem.[11]

THERAPEUTIC SUMMARY

HIV is a chronic disease with no known cure; naturopathic physicians are encouraged to apply the principles of naturopathic medicine in the search for treatments and refinements of care. In addition, naturopathic physicians must be familiar with all aspects of this disease, because HIV+ patients are actively seeking treatment options unique to naturopathic medical training. Naturopathic medicine already offers important possibilities in the care of HIV, and all fields in health care must collaborate to find solutions for this worldwide health problem. Each patient should have a complete and appropriate caregiving team, including an infectious disease expert, primary care physician, and specialist providing psychosocial support.

Diet

A natural, whole-foods diet and a high caloric intake are recommended. This diet should be low in simple carbohydrates (e.g., sugar, white flour, fruit juice, honey, processed foods), low in natural and synthetically saturated fats, and low in oxidized or trans fatty acids. It should also be high in protein, fiber, and filtered water. Patients should abstain from alcohol, nicotine, and caffeine. Digestive stimulation is recommended if appropriate. Broad-spectrum allergy-elimination diets should be avoided.

Lifestyle

Aerobic or mind-body exercise (e.g., Tai Qui, yoga) and 8 to 10 hours of sleep each night are optimal. Prayer, spiritual activities, and activities that support the HIV+ community, guided forms of stress relief, and relaxation training are beneficial.

Nutritional Supplements

Potential interactions with HAART must always be investigated in considering the use of any nutritional or botanical supplement.

- A high-potency hypoallergenic multivitamin/multimineral supplement, preferably designed specifically to replace known nutrient deficiencies of HIV
- Beta-carotene (150,000 IU/day best taken as food)
- Vitamin D (5000 IU/day best taken with food)
- DHEA (15-50 mg/day best taken with food)
- Acetyl-L-carnitine (2 to 6 g/day in divided doses best taken away from other proteins)
- EFAs (5 g/day taken with food)
- Probiotics (8-12 billion CFU a day taken with meals)
- Botanical medicines:
 Silybum marianum/milk thistle extract (300 mg/day) for all patients on HAART
- Homeopathic medicines:
 Constitutional intake and remedy provided for each patient
 Acute remedies as indicated
- Physical medicine and acupuncture:
 Whole-body hyperthermia—use extreme caution in patients with heat intolerance or peripheral neuropathies
 Movement therapies—as indicated
 Acupuncture and electroacupuncture—as indicated

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CHAPTER 174

Hypertension

Michael T. Murray, ND

DIAGNOSTIC SUMMARY

- Prehypertension: 120 to 139/80 to 89 mm Hg
- Stage 1 hypertension: 140 to 159/90 to 99 mm Hg
- Stage 2 hypertension: 160 and higher/100 and higher mm Hg

GENERAL CONSIDERATIONS

Elevated blood pressure (BP) is a major risk factor for a heart attack or stroke. In fact, it is generally regarded as the most significant risk factor for stroke. More than 70 million Americans have high BP, including more than half (54.3%) of all Americans 65 to 74 years of age and almost three quarters (71.8%) of all American blacks in the same age group (Box 174-1). Additionally, 37% of U.S. adults have a blood pressure of 120 to 139/80 to 89 mm Hg, classified as prehypertension, which is associated not only with a greater likelihood of developing hypertension and cardiovascular disease, but also diabetes and cognitive impairment.[1]

Individuals with a normal diastolic pressure (<80 mm Hg) but elevated systolic pressure (>140 mm Hg), meaning an increased pulse pressure (>60 mm Hg), usually suffer from decreased compliance of the aorta (arteriosclerosis) and have a twofold increased risk of cardiovascular death as compared with those whose systolic pressure is normal (<120 mm Hg).[1a] Increased stroke volume due to aortic regurgitation, thyrotoxicosis, fever, and so on can also be a cause of increased pulse pressure.

Hypertension is also classified as to the cause. However, more than 90% of patients with hypertension are classified as suffering from essential hypertension, in which no discernible cause is given. Patients with essential hypertension are further divided into groups on the basis of the level of renin, an enzyme secreted by the juxtaglomerular cells of the kidneys and linked with aldosterone in a negative feedback loop. Renin plays a central role in vascular reactivity through its effects in generating the vasoconstricting peptide angiotensin II. Renin secretion is influenced primarily by the individual's fluid volume status and salt intake.

Patients with low renin essential hypertension have low renin activity. In these patients, aldosterone production is not being suppressed, leading to a mild degree of hyperaldosteronism, with its resulting increased sodium retention, fluid volume, and BP. The same phenomenon occurs in patients with normal renin hypertension, indicating that such patients may be at the end of a continuum of those with essential hypertension. Patients with low renin levels can also display an increased sensitivity to angiotensin II.

Normal renin essential hypertensives typically are insulin resistant and display abdominal obesity. However, several studies have found that hyperinsulinemia and insulin resistance are present even in lean hypertensive patients without non–insulin-dependent diabetes mellitus, suggesting that there is a strong relationship between insulin sensitivity and BP. Several theories have been suggested to explain this connection, with the most plausible being that, because insulin modifies ion transport across the cell membrane, insulin insensitivity can lead to decreased cytosolic magnesium levels and increased cytosolic calcium levels within the vascular smooth muscle, resulting in increased vascular reactivity. Normal renin essential hypertensives typically do not respond to sodium restriction.

High renin essential hypertensives make up approximately 15% of patients with essential hypertension. The elevation in renin (and associated high BP) is

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thought to be secondary to an increase in sympathetic nervous system activation.

Categorizing BP by renin level does not remain constant in a given patient. For example, a patient might be labeled as having low renin essential hypertension due to insulin resistance secondary to obesity. If the patient lost weight, regained insulin sensitivity, and yet the BP did not normalize, he or she would then be categorized as having normal or high renin essential hypertension. The categories based on renin level are primarily useful in identifying possible therapeutic interventions, as shown in Box 174-2.

"White-Coat Hypertension"

White-coat hypertension has been defined as the persistent elevation of BP at the clinic or office only. Its prevalence may be as high as 20% to 45% of people diagnosed as hypertensive.[1] It appears to be more frequent in women, older patients, and persons with Stage 1 hypertension. White-coat hypertension should not be confused with the *white-coat effect,* which signifies the difference in BP between the office and daytime ambulatory BP and occurs in patients with white-coat hypertension as well as in those with other causes of hypertension. The current conventional wisdom among naturopathic physicians is to treat white-coat hypertension as if it were essential hypertension. The reason for this stance is that current data suggest that the pressor response elicited mirrors real-life reactions to stress; that is, studies have suggested that white-coat hypertension is not an innocent phenomenon.[2,3] In regard to the latter, a 21-year study comprising 536 men, those with a white-coat effect had a significantly higher rate of mortality than normotensive men and were nearly twice as likely to develop sustained hypertension.[3]

Ambulatory BP monitoring is a clinically useful tool for assessing suspected white-coat hypertension and cardiovascular risk.[4] In patients with confirmed white-coat hypertension, drug treatment is usually not indicated; instead, treatment should consist of lifestyle and dietary modifications, weight reduction, regular exercise, smoking cessation, and correction of glucose and lipid abnormalities.[1] In addition, semiannual or annual follow-up with ambulatory BP monitoring is advised.

BOX 174-1 Classification of Blood Pressure

Optimal
- Systolic <120 mm Hg
- Diastolic <80 mm Hg

Prehypertension
- Systolic 120-139 mm Hg
- Diastolic 80-89 mm Hg

Stage 1 Hypertension:
- Systolic 140-159 mm Hg
- Diastolic 90-99 mm Hg

Stage 2 Hypertension:
- Systolic 160 and higher mm Hg
- Diastolic 100 and higher mm Hg

Etiology

Essential hypertension is most likely the result of any number of factors that disrupt the regulation of arterial pressure and fluid volume. Vascular, hormonal, renal, and neurologic factors function in a complex interrelationship to maintain normal BP; disruption of any single facet disrupts the entire system and creates a cascading effect on regulatory mechanisms. Although genetic factors play a role, dietary, lifestyle, psychological, and environmental factors are the underlying causes in most cases of essential hypertension. Dietary factors include obesity; high sodium-to-potassium ratio; a low-fiber, high-sugar diet; high saturated fat and low omega-3 fatty acid intake; and a diet low in calcium, magnesium, and vitamin C. Important lifestyle factors that may cause high BP include stress, lack of exercise, and smoking. The dietary factor that has received the greatest attention is salt intake. Between 40% and 60% of hypertensive patients are salt sensitive. This factor is discussed below under "Therapeutic Considerations."

BOX 174-2 Classifications of Hypertension

I. Essential hypertension (>90% of all cases of hypertension)
 - A. Low renin
 - B. Normal renin
 - C. High renin

II. Renal etiology
 - A. Chronic pyelonephritis
 - B. Acute and chronic glomerulonephritis
 - C. Polycystic renal disease
 - D. Renovascular stenosis or renal infarction
 - E. Most other severe renal diseases (e.g., arteriolar nephrosclerosis, diabetic nephropathy)
 - F. Renin-producing tumors

III. Endocrine etiology
 - A. Adrenocortical hyperfunction
 - B. Cushing's disease and syndrome
 - C. Primary hyperaldosteronism
 - D. Congenital or hereditary adrenogenital syndromes (17-hydroxylase and 11-hydroxylase defects)
 - E. Pheochromocytoma
 - F. Myxedema
 - G. Acromegaly

IV. Neurogenic etiology
 - A. Psychogenic
 - B. Diencephalic syndrome
 - C. Familial dysautonomia (Riley-Day)
 - D. Polyneuritis (acute porphyria, lead poisoning)
 - E. Increased intracranial pressure (acute)
 - F. Spinal cord section (acute)

V. Miscellaneous
 - A. Toxemia of pregnancy
 - B. Acute intermittent porphyria
 - C. Coarctation of aorta
 - D. Increased intravascular volume (excessive transfusion, polycythemia vera)
 - E. Polyarteritis nodosa
 - F. Hypercalcemia
 - G. Medications (e.g., glucocorticoids, cyclosporine, oral contraceptives)

Exposure to heavy metals like lead, mercury, cadmium, and arsenic may also be a significant factor in some patients. The kidneys are end-organ targets of heavy metals. Although studies of blood lead levels have not consistently shown an association, it is important to point out that blood lead levels reflect primarily acute exposure.[5-7] Studies looking at bone lead, for example, have upheld that exposure to heavy metals is associated with an increased risk of hypertension.[8] Specifically, the data suggest that lead has an acute effect on BP via either a recent exposure or cumulative dose. These associations were demonstrated in a cross-sectional analysis of 2001 to 2002 data from a community-based cohort in Baltimore, Maryland, of 964 men and women aged 50 to 70 years (40% African American, 55% white, 5% other race/ethnicity). Both blood lead and tibial lead were determined, along with systolic and diastolic BP. Blood lead was a strong and consistent predictor of both systolic and diastolic BP in models adjusted and not adjusted for race/ethnicity and socioeconomic status. Tibial lead was also associated with hypertension status before and after adjustment for race/ethnicity and socioeconomic status.[8a]

THERAPEUTIC CONSIDERATIONS

Because more than 90% of patients with higher than optimal blood pressure have either prehypertension or Stage 1 hypertension, most can be brought under control through changes in diet and lifestyle.[8b] In fact, in head-to-head comparisons, many non-drug therapies such as diet, exercise, and relaxation therapies have proved superior to drugs in cases of prehypertension and Stage 1 hypertension. For Stage 2 hypertension, pharmacologic therapy may be necessary. Ideally, drug treatment should be used only until the dietary, lifestyle, and supplement strategies take hold. However, sometimes long-term drug therapy is required.

Current Pharmacotherapy of Hypertension

For many years the drug of first choice for high BP was a thiazide diuretic alone or in combination with a beta blocker. Because of the questionable effectiveness of this combination in reducing the cardiovascular death rate and the side effects noted in numerous studies, this approach has somewhat fallen out of favor but is still quite popular. Currently, the most common treatment is a diuretic used alone or in combination with newer medications designed to relax the arteries, such as angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and calcium channel blockers.

The use of a diuretic or any of the above-mentioned other drugs alone is referred to as a "step 1" therapy. Thiazide diuretics are still the most popular step 1 drugs but may soon be displaced by calcium channel blockers or ACE inhibitors. Beta blockers are not suitable step 1 drugs owing to their known side effects.[9] Step 2 therapy comprises two medications, step 3 uses three, and step 4 approach involves four. Physicians are instructed to use single therapies before going on to the combinations, unless compelling indications are present, such as diabetes or heart failure.[10]

Other types of BP–lowering medications that can be used in step 3 or 4 approaches include those that act on the central nervous system, such as clonidine, methyldopa, and reserpine as well as some that are potent dilators of the blood vessels, like nitroprusside sodium, hydralazine, prazosin, minoxidil, and hydralazine. But these drugs have fallen out of favor with the development of the newer calcium channel blockers and ACE inhibitors. Nonetheless, they may be appropriate in certain situations.

Overview of Dietary and Lifestyle Factors

Hypertension is closely related to lifestyle and dietary factors. Some of the important lifestyle factors linked to hypertension include smoking, stress, and lack of exercise. The most important dietary factors include obesity; high sodium-to-potassium ratio; low-fiber, high-sugar diet; high saturated fat and low essential fatty acids (EFAs) intake; a diet low in calcium, magnesium, or vitamin C; and excessive alcohol or caffeine intake.

In addition to the following discussion, several of these dietary and lifestyle factors are also discussed in Chapter 148, because the health of the artery is critical to maintaining normal BP.

Stress

Stress can be the causative factor of hypertension in many instances, although, as in other health conditions, it has more to do with the response to and processing of stress than with stress itself. Relaxation techniques such as deep breathing exercises, biofeedback, autogenics, transcendental meditation, yoga, progressive muscle relaxation, and hypnosis have all been shown to have some value in lowering BP.[11] Although the effect is only modest, a stress reduction technique is a necessary component of a natural BP-lowering program.

One of the most powerful methods of producing less stress and more energy in the body is diaphragmatic breathing. Regular short exercise sessions of slow, regular diaphragmatic breathing have also been shown to lower BP in hypertensive individuals in several studies.[12–14] One study in particular has shed light on the effect of breathing in hypertension.[15] Volunteers with normal BP were taught shallow breathing. Measurement of the amount of sodium and potassium then excreted in their urine indicated that shallow breathing led to the retention of sodium in the body. It was suggested that this breathing pattern may play a causative role in some cases of hypertension owing to the retention of sodium. However, slow breathing (6 breaths per minute) has also been shown to improve oxygen saturation, exercise tolerance, and baroreflex sensitivity.[16]

RESPeRATE is a medical device that interactively guides the user toward slow, regular breathing by synchronizing voluntary respiration to musical tones. When used for 15 minutes daily, this device can lead to a significant reduction in BP. In one 8-week study, systolic BP was reduced 10.0 mm Hg and diastolic BP by 3.6 mm Hg, but not in the controls, and greater BP reduction was observed in those who demonstrated increased compliance with the device.[17]

Exercise

Epidemiologic studies have consistently demonstrated an inverse association between physical activity (or fitness) and hypertension. In addition to this evidence, clinical trials in hypertensive patients have clearly established that regular exercise is an effective treatment for high BP.[18–22] Although it is generally thought that the greater the intensity of aerobic exercise, the greater the hypotensive effect, it has recently been shown that even mild to moderate aerobic exercise in as few as three exercise sessions per week with durations as short as 20 minutes produces a hypotensive effect.[22] The degree of BP reduction from a regular exercise program is typically in the range of 5 to 10 mm Hg for both the systolic and diastolic readings. Patients with prehypertension and Stage 1 hypertension can typically bring their BP readings into the normal range with regular exercise.

Dietary Recommendations

The most important dietary goal for most patients with hypertension is achieving normal body weight. Obesity is the major dietary

cause of hypertension, and achieving their ideal body weight is the most important therapeutic goal for most patients with any form of hypertension. From prehypertension all the way to chronic renal failure, weight loss can lead to complete elimination of the health issue, significant improvement, or at least a reduction in the number of prescriptions to be taken.[23,24]

Next to attaining ideal body weight, perhaps the most important dietary recommendation is to increase the proportion of plant foods in the diet. Vegetarians generally have lower BP levels and a lower incidence of hypertension and other cardiovascular diseases than nonvegetarians.[25]Although dietary levels of sodium do not differ significantly between these two groups, a vegetarian's diet typically contains more potassium, complex carbohydrates, EFAs, fiber, calcium, magnesium, and vitamin C and less saturated fat and refined carbohydrates, all of which have a favorable influence on BP.

An increased intake of fruits and vegetables has been shown to lower BP.[26] This effect may be due to increased antioxidant concentrations. Hypertensive patients have been shown to have increased oxidative stress, and antioxidants have been shown to block angiotensin II–induced increases in BP as well as to promote proper nitric oxide synthesis.[27,28]

The most useful foods for people with hypertension include the following:

- Celery
- Garlic and onions
- Nuts and seeds or their oils for their EFA content
- Cold-water fish (e.g., salmon, mackerel)
- Green leafy vegetables for their calcium and magnesium
- Whole grains and legumes for their fiber
- Foods rich in vitamin C, like broccoli and citrus fruits
- Foods rich in active flavonoids, including berries, cherries, grapes, and small red kidney beans

Celery is a particularly interesting recommendation for hypertension. It contains 3-n-butyl phthalide, a compound that has been found to lower BP. In animals, a small amount of this compound lowered BP by 12% to 14% and cholesterol by about 7%.[29] The equivalent dose in humans can be supplied in about four to six ribs of celery. The research was prompted by the father of one of the researchers, who, after eating a quarter pound of celery daily for 1 week, observed that his BP had dropped from 158/96 to 118/82.

Garlic and onions are also important foods for lowering BP. Although most recent research has focused on the cholesterol-lowering properties of these vegetables, both have also been shown to lower BP in hypertension.[30] In addition, commercial garlic supplements may be of benefit. The usual response to the use of garlic is fairly modest, roughly 8 to 11 mm Hg for the systolic and 5 to 8 mm Hg for the diastolic BP (see Chapters 62 and 63 for a full discussion and dosages).

"Dietary Approaches to Stop Hypertension"

Clinical studies of the "Dietary Approaches to Stop Hypertension" (DASH) were funded by the National Heart, Lung, and Blood Institute (NHLBI) to evaluate the efficacy of a system of dietary recommendations in the treatment of hypertension. The DASH diet is rich in fruits, vegetables, and low-fat dairy foods and low in saturated and total fat. It is also low in cholesterol; high in dietary fiber, potassium, calcium, and magnesium; and moderately high in protein.

The first study showed that a diet rich in fruits, vegetables, and low-fat dairy products can reduce BP in the general population and people with hypertension.[31] The original DASH diet did not require either sodium restriction or weight loss—the two traditional dietary tools to control BP—to be effective.[32] The second study from the DASH research group found that coupling the original DASH diet with sodium restriction is more effective than either dietary manipulation alone.[33] In the first trial, the DASH diet produced a net BP reduction of 11.4 and 5.5 mm Hg systolic and diastolic, respectively, in patients with hypertension. In the second trial, sodium intake was also quantified at a "higher" intake of 3300 mg/day; an "intermediate" intake of 2400 mg/day; and a "lower" intake of 1500 mg/day. Compared with the control diet, the DASH diet was associated with a significantly lower systolic BP at each sodium level. The DASH diet with the lower sodium level led to a mean systolic BP that was 7.1 mm Hg lower in participants without hypertension and 11.5 mm Hg lower in participants with hypertension. These results are clinically significant and indicate that a sodium intake below the recommended level of 2400 mg daily can significantly and quickly lower BP.

Table 174-1 lists a brief description of the components of the DASH eating plan on the basis of a 2000-calorie daily diet.

Potassium and Sodium

Considerable evidence indicates that a diet low in potassium and high in sodium is associated with hypertension and plays a major role in the development of cancer and cardiovascular disease (e.g., heart disease, hypertension, stroke).[34–36] In regard to hypertension, there is overwhelming evidence that dietary sodium chloride (salt) is a major cause of raised BP and that a modest reduction in salt intake can lower BP, which is predicted to reduce cardiovascular disease, because there is a direct relation between salt intake and cardiovascular risk.[37] In advising a patient to decrease salt consumption, one must ensure that he or she is getting enough iodine from alternative sources. Conversely, a diet high in potassium and low in sodium is protective against cardiocascular diseases. In the case of hypertension, as evident from the second DASH study and others, this type of diet can be therapeutic.

It is a well-established fact that excessive consumption of dietary sodium chloride coupled with diminished dietary potassium is a common cause of high BP, especially in "salt-sensitive" individuals. However, numerous studies have shown that in many cases, sodium restriction alone does not significantly improve BP control—it must be accompanied by a high potassium intake. In a typical Western diet, only 5% of sodium intake comes from the natural constituents in food. Prepared foods contribute 45% of the sodium intake, 45% is added during cooking, and another 5% is added as a condiment.

Most Americans have a potassium-to-sodium (K:Na) ratio of less than 1:2. Epidemiologic and experimental research suggests a dietary K:Na ratio of greater than 5:1 is necessary to maintain health. However, even this level may not be optimal. A natural diet rich in fruits and vegetables can produce a K:Na ratio greater than 100:1, because most fruits and vegetables have a K:Na ratio of at least 50:1.

Many studies have now shown that an increased dietary potassium intake can lower BP.[38] In addition, several studies have shown that potassium supplementation alone can produce significant reductions in BP in hypertensive subjects. Results from 33 randomized controlled trials (2609 participants) in which potassium supplementation was the only difference between the intervention and control conditions were used in one meta-analysis. Using a random-effects model, potassium supplementation was associated with a significant reduction in mean systolic and diastolic BP of 4.44 and 2.45 mm Hg, respectively. The effects of

TABLE 174-1 **Basic Components of the DASH Diet (2000 Calories a Day)**

FOOD GROUP	DAILY SERVINGS	SERVING SIZES	EXAMPLES	SIGNIFICANCE OF EACH FOOD GROUP TO THE DASH DIET PATTERN
Grains and grain products	7-8	1 slice bread ½ cup dry cereal ½ cup cooked rice, pasta, or cereal	Whole wheat bread, English muffin, pita bread, bagels, cereals, grits, oatmeal	Major sources of energy and fiber
Vegetables	4-5	1 cup raw leafy vegetables ½ cup cooked vegetables 6 oz vegetable juice	Tomatoes, potatoes, squash, broccoli, turnips, greens, collards, kale, spinach, artichokes, sweet potatoes, beans	Rich sources of potassium, magnesium, and fiber
Fruits	4-5	6 oz fruit juice 1 medium fruit ¼ cup dried fruit ½ cup fresh, frozen, or canned fruit	Apricots, bananas, dates, oranges, orange juice, mangoes, melons, peaches, pineapples, prunes, raisins, strawberries, tangerines	Important sources of potassium, magnesium, and fiber
Low-fat or nonfat dairy foods	2-3	8 oz milk 1 cup yogurt 5 oz cheese	Skim or 1% milk, skim or low-fat yogurt, part-skim mozzarella cheese, nonfat cheese	Major sources of calcium and protein
Meats, including poultry and fish	≤2	3 oz cooked meats, poultry, or fish	Select only lean; trim away visible fats; broil, roast, or boil instead of frying; remove skin from poultry	Rich sources of protein and magnesium
Nuts, seeds, and legumes	4-5 weekly	5 oz or ⅓ cup nuts ½ oz or 2 tbsp seeds ½ cup cooked legumes	Almonds, filberts, mixed nuts, peanuts, walnuts, sunflower seeds, kidney beans, lentils	Rich sources of energy, magnesium, potassium, protein, and fiber

DASH, Dietary Approaches to Stop Hypertension.

potassium supplementation appeared to be enhanced in subjects who had a high intake of sodium, indicating that this is an important recommendation for the prevention and treatment of hypertension in those who are unable to reduce their intake of sodium. The dosage of potassium typically used in the studies ranged from 2.5 to 5 g/day.

In one study 37 adults with hypertension received either 2.5 g/day of potassium, 2.5 g/day of potassium plus 480 mg/day of magnesium, or a placebo for 8 weeks; then they were crossed over to receive one of the other treatments for another 8 weeks; and then they were crossed over again in another 8 weeks.[39] The potassium supplementation lowered systolic BP an average of 12 mm Hg and diastolic BP an average of 16 mm Hg. Interestingly, the additional magnesium offered no further reduction in BP; nonetheless magnesium supplementation has been shown to be helpful in other studies (discussed later).

Potassium supplementation may be especially useful in the treatment of hypertension in persons above age 65 who often do not fully respond to antihypertensive drugs. In one double-blind study, 18 untreated elderly patients (average age 75 years) with a systolic BP of greater than 160 mm Hg, a diastolic BP of greater than 95 mm Hg, or both were given either potassium chloride (2.5 g of potassium) or a placebo each day for 4 weeks.[40] After this relatively short treatment period, the group receiving the potassium experienced a drop of 12 mm Hg in their systolic BP and 7 mm Hg in their diastolic BP. These results compare quite favorably with the reduction of BP produced by drug therapy, but without the negative effects and side effects.[41]

Potassium supplements are available by prescription, as well as over the counter (OTC). However, the FDA restricts the amount of potassium available in OTC potassium supplements to a mere 99 mg per dose because of problems associated with high-dosage prescription potassium salts, yet so-called salt substitutes such as the popular brands NoSalt and Nu-Salt are, in fact, potassium chloride and provide 530 mg of potassium per ⅛ tsp. The prescription and OTC supplements are either potassium salts (chloride and bicarbonate), potassium bound to various mineral chelates (e.g., aspartate, citrate), or food-based potassium sources. Potassium chloride preparations are the most popular by prescription and are available in a vast array of formulations (timed-release tablets, liquids, powders, and effervescent tablets) and flavors. Potassium salts are commonly prescribed in the dosage range of 1.5 to 3 g/day. However, potassium salts can cause nausea, vomiting, diarrhea, and ulcers when given in pill form at high dosages. These effects are not seen when potassium levels are increased through the diet only. This difference highlights the advantages of using foods or food-based potassium supplements rather than pills to meet the human body's high potassium requirements.

Potassium supplementation is relatively safe except for patients with kidney disease. Their inability to maintain appropriate potassium homeostasis may result in heart arrhythmias and other consequences of potassium toxicity. Potassium supplementation is also contraindicated in using a number of prescription medications including digitalis, potassium-sparing diuretics, and the ACE inhibitor class of antihypertensive drugs.

Magnesium

Potassium interacts in many body systems with magnesium, and low intracellular potassium levels may be the result of a low magnesium intake. It is therefore appropriate to supplement magnesium (400 to 1200 mg/day in divided doses) along with potassium. This may also lower BP.

A meta-analysis of 14 clinical trials that tested the effects of magnesium supplementation on hypertension demonstrated clear dose-dependent BP reductions—a drop of 4.3 mm Hg systolic and 2.3 mm Hg diastolic for each 10 mmol/day increase in magnesium dose.[42]

In one double-blind clinical study, 21 male patients with hypertension were given 600 mg/day of magnesium (as magnesium oxide) or placebo.[43] Mean BP (the average between the systolic and diastolic) decreased from 111 to 102 mm Hg. The patients who responded best were those with reduced red blood cell potassium. After therapy with magnesium, the levels of intracellular sodium, potassium, and magnesium normalized, suggesting that one of the ways in which magnesium lowers BP is through activation of the cellular membrane pump that pumps sodium out of the cell and potassium into it.

Considerable evidence indicates that a high intake of magnesium is associated with lower BP in population studies. The principal source of magnesium in early studies was water. Water that is high in minerals like magnesium is often referred to as "hard water." Numerous studies have demonstrated an inverse correlation between water hardness and high BP.[44]

These early studies gave way to more extensive dietary studies looking at the association of magnesium with hypertension. These later studies found the same results as the hard water studies. In one of the most extensive studies—the Honolulu Heart Study—systolic BP was 6.4 mm Hg lower and diastolic BP 3.1 mm Hg lower in the group with the highest magnesium intake compared with that having the lowest magnesium intake.[45]

Studies of magnesium supplementation in the treatment of hypertension have yielded mixed results. Although the overall results in a meta-analysis of the data are quite favorable, it appears that the hypertensive patients who respond are those taking a diuretic who have a high level of renin, with low RBC magnesium, or with elevated intracellular sodium or a decreased intracellular potassium.

The recommended daily intake for magnesium in hypertensive patients appears to be approximately 6 to 10 mg/kg body weight.

Magnesium is available in several forms. Although most are equally well absorbed, magnesium bound to aspartate or the Krebs cycle intermediates (malate, succinate, fumarate, and citrate) is usually preferable to magnesium oxide, gluconate, sulfate, or chloride. Absorption studies indicate that magnesium is easily absorbed orally, especially when it is bound to citrate (and presumably aspartate and other members of the Krebs cycle).[46,47] In addition, magnesium bound to aspartate or Krebs cycle intermediates may also help with fatigue. Aspartate feeds into the Krebs cycle, the final common pathway for the conversion of glucose, fatty acids, and amino acids to chemical energy (adenosine triphosphate, or ATP), while citrate, fumarate, malate, and succinate are actual components of the Krebs cycle. Minerals chelated to the Krebs cycle intermediates are better absorbed, used, and tolerated compared with inorganic or relatively insoluble mineral salts including magnesium chloride, oxide, or carbonate. In addition, although inorganic magnesium salts often cause diarrhea at higher dosages, organic forms of magnesium generally do not.

In general, magnesium is well tolerated. Magnesium supplementation can sometimes cause a looser stool, particularly magnesium sulfate (Epsom salts), hydroxide, or chloride. Magnesium supplementation must be used with great care in patients with kidney disease or severe heart disease (such as high-grade atrioventricular block).

Calcium

Population-based studies have suggested a link between hypertension and a low intake of calcium.[39] However, the association is not as strong as the one for magnesium and potassium. In addition to the epidemiologic data, several clinical studies have demonstrated that calcium supplementation can lower BP in hypertension, but the results have been inconsistent.[48]

To clarify the effectiveness of calcium supplementation in patients with hypertension, a double-blind placebo-controlled crossover study was performed on 46 patients with either salt-sensitive or salt-resistant hypertension.[49] During the calcium supplementation phase, patients received 1.5 g/day of calcium (as calcium carbonate) for 8 weeks. The calcium supplementation was found to effectively reduce BP in blacks and in patients who are salt sensitive but not in those having salt-resistant hypertension. Better results have been found for calcium citrate versus calcium carbonate.[50]

Another group that appears to respond to calcium supplementation is elderly hypertensive patients. One study used 24-hour monitoring of BP to evaluate the effect of calcium supplementation on essential hypertension in elderly hospitalized patients. The mean systolic and diastolic BPs over a 24-hour period declined by 13.6 mm Hg and 5 mm Hg, respectively, in patients whose diets were supplemented with 1 g of elemental calcium.[51]

Vitamin C

Population-based and clinical studies have shown that the higher the intake of vitamin C, the lower the BP. The results from several preliminary studies showing a modest BP-lowering effect with vitamin C supplementation in people with mild elevations of BP has been confirmed in two double-blind trials.[52,53] One of the key findings of these studies was that a daily dose of 500 mg produced the same benefit as higher doses (i.e., 1000 and 2000 mg daily). Vitamin C supplementation can produce decreases of up to 4.5 mm Hg in the systolic and 2.5 mm Hg in the diastolic BP.

One of the mechanisms by which vitamin C exerts this antihypertensive effect is by promoting the excretion of lead. Chronic exposure to lead from environmental sources, including drinking water, is associated with hypertension and increased cardiovascular mortality. Areas with a soft water supply have an increased lead concentration in drinking water due to the increased acidity of the water, and people living in these areas may be predisposed to hypertension. It should be noted that soft water is, of course, low in calcium and magnesium as well, two minerals that have also been shown to protect against hypertension.

Vitamin C is likely to be more effective when it is used with other antioxidant nutrients. The combination of 500 mg of vitamin C, 600 mg of α-tocopherol, 200 mg of zinc sulfate, and 30 mg of beta-carotene daily produced mild reductions in the systolic BP compared with the placebo phase both in subjects receiving antihypertensive therapy and those who were normotensive.[54]

Folic Acid and Vitamin B_6

Folic acid and vitamin B_6 reduce plasma homocysteine levels—a known contributor to atherosclerosis. A 2-year trial of folic acid and vitamin B_6 therapy to lower homocysteine was associated with a 3.7-mm Hg lower systolic and a 1.9-mm Hg lower diastolic BP.[55] Vitamin B_6 supplementation alone has also been shown to lower BP. In one study, vitamin B_6 supplementation at a single daily oral dose of 5 mg/kg for 4 weeks in 20 people with hypertension demonstrated significant reductions in systolic and diastolic BPs as well

as serum norepinephrine levels.[56] The effects on BP were significant: systolic pressure dropped from 167 to 153 mm Hg and the diastolic pressure dropped from 108 to 98 mm Hg.

Omega-3 Oils

An increased intake of omega-3 fatty acids can lower BP. More than 60 double-blind studies have demonstrated that fish oil supplements are effective in lowering BP.[57,58] Typically, fish oils produced a reduction of 2.1 mm Hg in the systolic and 1.6 mm Hg in the diastolic BP at a typical dose of 3000 mg of omega-3 (EPA/DHA) daily. Flaxseed oil may also lower BP. The key to getting results with flaxseed oil may lie in reducing the intake of saturated fat and omega-6 fatty acids. In one study, along with reducing the intake of saturated fat, 1 tbsp/day of flaxseed oil reduced both the systolic and diastolic readings by up to 9 mm Hg.[59] Another study found that for every absolute 1% increase in body alpha-linolenic acid content, there was a decrease of 5 mm Hg in the systolic, diastolic, and mean BPs.[60]

Arginine

Arginine, an amino acid, is important in the formation of nitric oxide. This compound plays a central role in determining the tone of blood vessels and renal function. Specifically, it exerts a relaxing effect on blood vessels, thereby improving blood flow as well as renal plasma flow and glomerular filtration rate. Normally the body makes enough arginine even when the diet is lacking. However, in some instances the body may not be able to keep up with increased requirements, in which case supplementation may prove useful. In high BP, even in mild cases, there appears to be a derangement of endothelial nitric oxide production, especially in the kidneys.

Arginine supplementation has been shown to be beneficial in a number of cardiovascular diseases including hypertension. By increasing nitric oxide levels, arginine supplementation improves blood flow, reduces the formation of blood clots, and improves blood fluidity. In hypertension, the degree of improvement offered by arginine supplementation can be quite significant in some cases[61,62]; in general, however, a dosage of 4 g three times daily will produce only modest decreases (e.g., 5 mm Hg) in systolic BP with little meaningful change in diastolic BP.[63] Arginine supplementation may prove to be most beneficial in younger subjects with essential hypertension, because aging hypertensive patients appear to have a derangement in nitric oxide–dependent renal mechanisms. In a study comparing the renal response with an intravenous infusion of arginine in young and aged patients with essential hypertension, arginine induced a significant increase in renal plasma flow, arginine glomerular filtration rate, and natriuresis and kaliuresis in the younger subjects without changes in filtration fraction.[64] These effects were not observed in older subjects.

Anti-ACE Peptides

Various naturally occurring peptides have been shown to inhibit ACEs, including peptides from milk, chicken, and fish. The best-studied of these peptides is composed of a purified mixture of nine small peptides (proteins) derived from muscle of the fish bonito (a member of the tuna family).[65-68] Anti-ACE bonito peptides do not appear to produce the side effects typical of ACE inhibitors (according to human safety studies) and do not lower BP in people with normal BP, even when administered at levels 20 times greater than the dose level that lowers BP in people with high BP. A possible reason is that its mechanism of action in inhibiting ACEs is different from that of the drugs. Research bears out this theory. The drugs basically indiscriminately block ACEs by interfering with their action, whereas the bonito anti-ACE peptides interact much differently. ACEs convert angiotensin I to angiotensin II by cleaving off a small peptide. Drugs work by directly blocking this action. Naturally occurring anti-ACE peptides work differently, as ACEs actually react with the peptides instead of angiotensin. In addition to competing with angiotensin via this effect, anti-ACE peptides are transformed into even more potent inhibitors of ACEs. Technically speaking, the bonito anti-ACE peptides are considered a "prodrug," since the transformed peptides exert an 800% greater activity.

Four clinical studies have shown that fish-derived anti-ACE peptides (three with the bonito peptides and one with a dipeptide from sardine) exert significant BP-lowering effects in people with high BP.[66–69] The degree of BP reduction in these studies was quite significant, typically reducing the systolic BP by at least 10 mm Hg and the diastolic BP by 7 mm Hg in people with hypertension. Greater reductions are seen in people with higher initial BP readings.

Coenzyme Q_{10}

Coenzyme Q_{10} (CoQ_{10}), also known as ubiquinone, is an essential component of the mitochondria. Although CoQ_{10} can be synthesized within the body, deficiency states have been reported. In hypertension, CoQ_{10} deficiency has been shown to be present in 39% of patients. This finding alone suggests a need for CoQ_{10} supplementation. However, CoQ_{10} appears to provide benefits beyond correction of a deficiency.

The majority of studies exploring CoQ10 in the treatment of high BP have been uncontrolled or have used CoQ10 in combination with conventional antihypertensive medical treatments, making these studies difficult to interpret. A Cochrane review on CoQ10 in the treatment of hypertension (12 clinical trials, 362 patients) concluded that in hypertensive patients, CoQ10 has the potential to lower systolic and diastolic BP without significant side effects.[70] Among all included studies, decreases in systolic BP ranged from 11 to 17 mm Hg and in diastolic BP from 8 to 10 mm Hg. In 3 of the 12 studies, CoQ10 was given in addition to existing antihypertensive medication, and in one of these more than 50% of the patients were able to cease taking at least one antihypertensive medication during the trial. These results are consistent with some of the uncontrolled studies. For example, in one uncontrolled study, the dose of CoQ_{10} was adjusted in 109 patients with essential hypertension according to clinical response and blood CoQ_{10} levels (the aim was to attain blood levels >2 mg/mL). The average CoQ_{10} dose was 225 mg/day in addition to these patients' usual antihypertensive regimen. The need for antihypertensive medication declined gradually; after a mean treatment period of 4.4 months, about half of the patients were able to discontinue between one and three of their drugs.[71]

It is important to keep in mind that the antihypertensive effect of CoQ_{10} is usually not seen until after 4 to 12 weeks of therapy. Thus, CoQ_{10} is not a typical BP-lowering drug; rather, it seems to correct some metabolic abnormality, which in turn has a favorable influence on BP. For more information, see Chapter 79.

Caffeine

Caffeine consumption from coffee or tea can produce an immediate short-lived increase in BP, and regular coffee drinking has been associated with slight increases in BP. However, it is generally thought that a tolerance to the hypertensive effects of caffeine develops in habitual coffee or tea drinkers.[72–74] Yet some studies have shown that with repeated administration of caffeine, a persistent pressor effect is produced. For example, in 11 short-term trials

looking at the pressor effect of caffeine consumption (ranging from 14 to 79 days), the average dose of 5 cups of coffee per day was associated with an increase in systolic BP by 2.4 mm Hg and diastolic BP by 1.2 mm Hg.[75] Although the overall benefit of long-term avoidance of caffeine (from coffee, tea, chocolate, cola drinks, and some medications) on BP is unclear, it appears that some patients appear to respond quite favorably to caffeine avoidance. It should therefore at least be attempted in patients with hypertension.

Botanical Medicines

Crataegus Species

Extracts of hawthorn berries as well as of the flowering tops are widely used by physicians in Europe because of their cardiovascular effects. Several studies including double-blind trials have demonstrated that hawthorn extracts are effective in lowering BP and improving heart function.[76,77] However, the BP-lowering effect of hawthorn is mild. It usually takes at least 2 to 4 weeks before this agent begins to exert any effect. For more information, see Chapter 82.

Olive (Olea europaea)

The leaves of the olive tree (*Olea europaea* L.) have been used since ancient times to combat high BP, and this agent has significant support in recent animal and human studies both as an antihypertensive as well as for lowering cholesterol. The active substances are oleuropein (a polyphenolic iridoid glycoside)[78] as well as oleacein and oleanolic acid, which act as natural calcium channel blockers. Hydroxytyrusol is a metabolite of oleuropein that exerts antioxidant effects. Often olive extracts are standardized for hydroxytyrusol, but this compound is devoid of any significant antihypertensive effect. Oleuropein is also found in the olive's fruit and oil, but in significantly smaller quantities than the leaf.

In an initial small double-blind study of patients with essential hypertension, 12 consulting for the first time and 18 currently on antihypertensive drugs, olive leaf extract at a dose of 400 mg four times daily for 3 months produced a modest yet statistically significant decrease of BP with no side effects.[79]

More recent studies have used Benolea (EFLA943), standardized to oleuropein (16%-24%) and polyphenols. In a preliminary clinical study, 20 monozygotic adult twin pairs with mild hypertension received either a dose of 500 or 1000 mg daily for 8 weeks or a placebo.

After 8 weeks, BP remained unchanged from baseline in the placebo group and the 500-mg/day group but was significantly decreased for the group receiving 1000 mg/day (137 vs. 126).[78]

In another study with Benolea, 232 patients with hypertension were given either the olive leaf extract (500 mg twice a day) or captopril (12.5 mg twice daily). Mean BP at baseline was 149.3/93.9 mm Hg in the group receiving olive leaf extract and 148.4/93.8 mm Hg in group on captopril. Mean reductions in systolic BP from baseline to the end of the study were 11.5 and 13.7 mm Hg in olive leaf extract and captopril groups, respectively. of the parallel reductions in diastolic BP were 4.8 and 6.4 mm Hg, respectively.[80]

Allium sativum and Allium cepa

As discussed earlier, garlic and onion are useful antihypertensive additions to the diet, as are various garlic extracts. A meta-analysis of published and unpublished randomized controlled trials of garlic preparations was conducted to determine the effect of garlic on BP relative to placebo.[30] Eight trials (seven double blind, one single blind) were identified as meeting analytic criteria. A total of 415 subjects were included in the analysis. All trials used a dried garlic powder standardized to contain 1.3% allicin at a dose of 600 to 900 mg daily (corresponding to 7.8 and 11.7 mg of allicin or the equivalent of approximately 1.8 to 2.7 g of fresh garlic daily). The meta-analysis concluded that garlic preparations designed to yield allicin can lower systolic and diastolic BPs over a 1- to 3-month period. The typical drop from pooled data was 11 mm Hg in the systolic BP and 5 mm Hg in the diastolic BP.

Hibiscus sabdariffa

Hibiscus tea and extracts prepared from the dried flowers (calyces) of *H. sabdariffa* have demonstrated antihypertensive properties in clinical trials. The active components are anthocyanidin glycosides. One double-blind placebo-controlled clinical trial was conducted in 65 prehypertensive and mildly hypertensive adults 30 to 70 years of age who were not taking antihypertensive medications. They were given either three 240-mL servings per day of brewed hibiscus tea or a placebo beverage for 6 weeks. At 6 weeks, hibiscus tea was found to have lowered systolic BP compared with placebo (by 7.2 vs. 1.3 mm Hg). Diastolic BP was also lower, although this change did not differ from placebo. Participants with higher systolic BP at baseline showed a greater response to the hibiscus treatment.[81]

In another double-blind study, the effect of hibiscus tea was compared with that of black tea in 60 diabetic patients with hypertension who were not taking antihypertensive or lipid-lowering drugs. The mean of systolic BP in the hibiscus group decreased from 134.4 mm Hg at the beginning of the study to 112.7 mm Hg after 1 month, whereas it increased from 118.6 to 127.3 mm Hg in the group drinking black tea. The intervention had no statistically significant effect on the mean of diastolic BP in either group.[82]

Another study with hibiscus tea did show an effect on diastolic BP (reducing it by 10.7%) as well as systolic BP (reducing it by 11.2%) after 12 days of treatment.[83]

Two clinical studies featured a standardized extract of hibiscus in patients with high BP. In one double-blind study, 193 patients with hypertension were given either hibiscus extract (250 mg of total anthocyanins daily) or 10 mg of lisinopril (control group). Results showed that the hibiscus extract decreased BP from 146.48/97.77 to 129.89/85.96 mm Hg, reaching an absolute reduction of 17.14/11.97 mm Hg. The hibiscus treatment showed therapeutic effectiveness of 65.12% as well as tolerability and safety of 100%. BP reductions and therapeutic effectiveness were lower than those obtained with lisinopril. Hibiscus treatment lowered plasma ACE activity from 44 to 30 U/L.[84]

Similar effects on BP were shown in another double-blind study with a standardized hibiscus extract (a daily dose of 9.6 mg of total anthocyanins) compared with captopril (50 mg/day). Results showed no significant differences in lowering BP between the two treatments. Hibiscus extract decreased the systolic BP from 139.05 to 123.73 mm Hg and the diastolic BP from 90.81 to 79.5 mm Hg.[85]

Viscum album

V. album, or mistletoe, exhibits hypotensive action in animal studies. The mechanism of action for its hypotensive effect is not fully understood, however, and no recent investigations have been published. *V. album* has been shown to inhibit the excitability of the vasomotor center in the medulla oblongata and to possess cholinomimetic activity.[81]

Its hypotensive activity may depend on the form in which the mistletoe is administered and the host tree from which it was collected. Studies indicate that aqueous extracts are more effective; the highest hypotensive activity was demonstrated by a macerate of leaves of mistletoe parasitizing on willow and gathered in January (see Chapter 134 for further discussion).

THERAPEUTIC APPROACH

Prehypertension (120-139/80-89 mm Hg), or White-Coat Hypertension

- Reduce excessive weight (see Chapter 192 for more information).
- Substantially reduce or eliminate salt (sodium chloride) intake.
- Follow a healthy lifestyle. Avoid alcohol, caffeine, and smoking. Exercise and use stress-reduction techniques.
- Follow a potassium-rich diet that is high in fiber and consistent with either the Mediterranean or DASH diet.
- Increase dietary consumption of celery, garlic, and onions.
- Reduce or eliminate the intake of animal fats while increasing the intake of monounsaturated vegetable oils.
- Supplement the diet with the following:
 - A high-potency multivitamin and mineral formula
 - Vitamin C: 500 to 1000 mg three times a day
 - Magnesium: 600 to 1200 mg/day
 - Fresh garlic: the equivalent of 4000 mg/day
 - Omega-3 fatty acids such as flaxseed oil, 1 tbsp/day, or fish oils, 3 g total EPA/DHA content per day

If, after following these recommendations for a period of 3 months, BP has not returned to normal, the recommendations for Stage 1 hypertension given below may be followed.

Stage 1 Hypertension (140-159/90-99 mm Hg)

- Employ all the measures mentioned earlier plus the following:
- CoQ_{10}: 100 mg two to three times a day
- Anti-ACE peptides from bonito: 1500 mg/day
- Take one of the following:
 - Hawthorn extract (10% procyanidins or 1.8% vitexin-4%-rhamnoside): 100 to 250 mg three times a day
 - Olive leaf extract (17% to 23% oleuropein content): 500 mg twice a day
 - Hibiscus: three 240-mL servings a day or an extract providing 10 to 20 mg anthocyanidins a day

These guidelines should be followed for 1 to 3 months. If the BP has not dropped below 135/85, the patient may have to be placed on antihypertensive medications.

Stage 2 hypertension (160+/100+ mm Hg)

Drug intervention is required. All the measures mentioned previously should be employed. When satisfactory control over the high BP has been achieved, the patient can taper off the medication gradually.

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CHAPTER 175

Hyperthyroidism

Alan Christianson, ND, and Michael T. Murray, ND

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DIAGNOSTIC SUMMARY

- Weakness, sweating, weight loss, nervousness, loose stools, heat intolerance, irritability, fatigue
- Tachycardia; warm, thin, moist skin; stare; tremor
- Diffuse nonpainful goiter
- Increased T_4, free T_4, and free T_4 index
- Failure of thyroid suppression with T_3 administration
- In Graves' disease: goiter (often with bruit), ophthalmopathy

GENERAL CONSIDERATIONS

Hyperthyroidism, also known as thyrotoxicosis, denotes a group of clinical disorders characterized by increased levels of free thyroxine, also known as tetraiodothyronine (T_4) and triiodothyronine (T_3). The autoimmune disorder Graves' disease accounts for up to 85% of all cases of hyperthyroidism. It is much more common in women than men (ratio 8:1) and typically begins between the ages of 20 and 40. Diffuse, nonpainful goiter with hyperthyroidism is the most common presentation of Graves' disease. Other less common signs and symptoms include exophthalmos, pretibial myxedema and other skin changes, nail changes (acropachy), and even paralysis in some groups.[1]

Although no single immunologic abnormality explains all of the clinical features of the disease, the common denominator is the presence of antibodies against thyroid-stimulating hormone (TSH) receptors. The exophthalmos and skin changes can progress independently from thyroid dysfunction (euthyroid Graves' disease), making it difficult to predict the course of the disease in a given individual.

There are definite patterns of susceptibility in autoimmune disease in general and in Graves' disease in particular. Many of these patterns have been recognized by common observation, while others have come to light only with careful study.

Disease Risk

Gender

The most obvious pattern is that of gender. Practically all the original cases described by Parry, von Basedow, and Graves were women. The female:male ratio in published series is 7:1 to 10:1, but the ratio in those with ophthalmic complications is about 1:1.[2]

Stress

Recent stress has been recognized as a precipitating factor since Graves' disease was first recognized. In fact, the most common precipitating event is an "actual or threatened separation from an individual upon whom the patient is emotionally dependent."[3] Studies now support the long-held observation that the onset of Graves' disease often follows some kind of emotional shock, in particular some sort of loss, such as divorce, death, or difficult separation.[4]

Genetics

Genetic susceptibility to Graves' disease is apparently significant in some people. Graves' disease is statistically more prevalent in some human leukocyte antigen (HLA) haplotypes, such as HLA-B8 and HLA-DR3 in Caucasians, HLA-Bw35 in

the Japanese, and HLA-Bw46 in the Chinese.[3] HLA identical twins have a 50% chance of presenting with Graves' disease if one twin is affected and a 9% chance for fraternal twins.[5] Some haplotypes appear to offer protection from manifesting Graves' disease.[6] Genetic haplotype does not seem to affect the clinical course of Graves' disease or the response to treatment.

Additional evidence but not proof for a genetic etiology comes from an interesting case of bone marrow transplantation between siblings—a sister donated her bone marrow to her brother 8 years before her diagnosis with Graves' disease. His bone marrow genotype was 98% 46, XX 8 years after the transplant. He contracted Graves' disease 2 months after his sister's subtotal thyroidectomy.[7] The authors, while admitting that the manifestation of Graves' disease in both siblings could be due to chance, proposed that the brother passively acquired a clone of programmed or activated lymphocytes from his sister and that his hyperthyroidism was not primarily dependent on any exposure to a specific thyroid-derived antigen.[7]

Left-Handedness

One study showed a statistically significant trend for left-handed people to present with Graves' disease and other autoimmune diseases. Wood and Cooper,[8] using only male subjects, found that 70% of the Graves' patients had some degree of left-handedness as compared with only 24% of controls. They also found some evidence for a higher rate of dyslexia in Graves' patients.[8]

Smoking

Smoking is known to raise the risk and severity of ophthalmopathy among patients with Graves' disease.[9-11]

Along with known patterns of susceptibility, certain factors are known to cause Graves' disease to manifest.

Iodine Supplementation

An interesting study evaluated the effects of mandatory consumption of iodized salt in a whole population of 267,330 inhabitants of Galicia. The incidence of thyrotoxicosis, diagnosed as elevated T_4 and suppressed TSH levels, increased throughout the whole study period, with 4.89 new cases per 100,000 population. The rate of increase among females (8.03) was much greater than that among males (1.34). The increased incidence of thyrotoxicosis comprised both nodular and diffuse goiters. The authors concluded that dietary iodine supplementation in iodine-sufficient areas can increase the incidence of thyrotoxicosis in susceptible individuals.[12]

Globally, many other similar scenarios have occurred. When a population's intake of iodine suddenly increases, even to appropriate levels, many individuals lapse into hyperthyroid states. This is more common among the elderly, those with positive thyroid antibodies, and those with marginal selenium status. Iodine from other sources in doses above 600 mcg can trigger Graves' disease and toxic multinodular goiter. Common sources include potassium iodide, an iodine/potassium iodide (Iodoral) supplement, medications such as amiodarone, and imaging contrast agents.[12]

Infection

The TSH receptor antibodies in Graves' disease share a similar structure with antibodies against several known pathogens. It has been shown that cases of Graves' have started during or shortly after acute infection with *Yersinia enterocolitica* and *Borrelia burgdorferi*.[13]

Other factors that may initiate Graves' disease include corticosteroid use and local trauma to the thyroid.

Drugs

In older patients with hyperthyroidism, a toxic reaction to prescription drugs must be considered. Exposure to iodine-containing contrast agents during medical procedures is a common scenario. Some sources recommend TSH screening prior to administration of iodine-containing contrast agent.[14] The most common cause of hyperthyroidism in the elderly is a low intake of iodine and higher use of amiodarone, an antiarrhythmic drug.[15] In addition, symptoms of hyperthyroidism vary somewhat in older adults, with apathy, tachycardia, and weight loss being more common. This response is more probable in those with subclinical hyperthyroidism (lack of symptoms, normal T_4, but low TSH).

DIAGNOSIS

Clinical Presentation

The typical clinical presentation of Graves' disease is a young adult female complaining of the following:

- Nervousness
- Irritability
- Sweating
- Palpitations
- Insomnia
- Tremor
- Frequent stools
- Unexplained weight loss

Physical examination often reveals a smooth, diffuse, nontender goiter; tachycardia, especially after exercise; loud heart sounds (often a systolic murmur); and mild proptosis, lid retraction, lid lag, and tremor.

Other signs and symptoms include muscle weakness and fatigue, anxiety, heat intolerance, and pretibial myxedema. However, in atypical cases, especially in elderly patients, any or all of the previously mentioned symptoms may be absent. This presentation is known as apathetic thyrotoxicosis and has been known to present in the elderly with the only symptom being depression. Special care must be taken to avoid missing the diagnosis with this presentation. A screening laboratory test for suppressed TSH is helpful in these patients. Also, it is useful to keep in mind that an increase in thyroid hormone can present as a worsening of already present cardiac symptoms such as angina pectoris, congestive heart failure, and atrial fibrillation.

The skin can show characteristic changes, becoming moist, warm, and finely textured. Perspiration increases as a response to the increased body temperature. Pigment changes such as vitiligo can be associated with Graves' disease, as well as increased pigmentation of areas such as skin creases and the knuckles. Hair may thin or fall out in patches or altogether (alopecia). Nails may separate prematurely from the nail bed (onycholysis). Localized, nonpitting edema typically occurs along the shins (myxedema) but may occur elsewhere, generally on the extensor surfaces, and is often pruritic and red.

Other symptoms can be associated with Graves' disease, including glucose intolerance, dyspnea, polyuria and polydipsia, myopathy, paralysis, parkinsonian or choreoathetoid affect, and others.[16,17]

Although in severely hyperthyroid states symptoms are predictable, some symptoms can be paroxysmal, manifesting in both mild hyper- and hypothyroid states. These include anxiety, palpitations, weight gain, fatigue, and insomnia. The relevance is that in managing patients for either hypo- or hyperthyroidism, it is not safe to assume that they have too much or too little thyroid hormone based solely on symptoms.

TABLE 175-1 **Relative Frequency of Primary Causes of Hyperthyroidism**

ETIOLOGY	RELATIVE FREQUENCY*
Graves' disease	70%-85%
Toxic multinodular goiter	5%-15%
Toxic uninodular goiter	3%-30%
Thyroiditis (including so-called hashitoxicosis)	4%-23%
Drug-induced	Commonly in the elderly; rare in the young except in cases where iodine is administered to a population
Postradiation	

*Overall frequency; relative frequency may be altered in certain populations (e.g., the elderly, individuals living in regions of endemic goiter).

Differential Diagnosis

Graves' disease is the most common diagnosis of hyperthyroidism, but several other conditions present with a similar symptom picture. The next most common cause is toxic nodular goiter. These ailments include toxic adenoma and multinodular goiter. Other causes of hyperthyroidism include early Hashimoto's thyroiditis (also known as hashitoxicosis), painless thyroiditis, and radiation thyroiditis. Hyperthyroidism can also result from exogenous causes including iatrogenic hyperthyroidism, factitious hyperthyroidism (often seen in dieters who are taking thyroxine for weight loss), and iodine-induced hyperthyroidism (Jod-Basdow disease).

Rarer causes of hyperthyroidism include thyroid carcinoma, ectopic hyperthyroidism, trophoblastic tumors (i.e., hydatidiform mole, choriocarcinoma, embryonic carcinoma of the testis), excessive thyroid-stimulating hormone (i.e., pituitary adenoma, nonneoplastic pituitary secretion of TSH), and struma ovarii.

Table 175-1 indicates the relative frequency of the various causes of hyperthyroidism.

Laboratory Diagnosis

The laboratory is where the definitive diagnosis is made, and quite a number of tests are available to the physician to assess thyroid function and functional anatomy.

Although many tests are available, for the vast majority of cases a few simple tests will confirm the diagnosis. Serum freeT_3 and freeT_4 are usually elevated while TSH will be suppressed below 0.2. TSH receptor antibodies (TSH-R Ab) or thyroid stimulating immunoglobulins (TSI) are present in 80% of cases of Graves' disease.

During the initial workup of a hyperthyroid patient, if a nodule or diffuse swelling is present on palpation or ultrasound, a thyroid uptake scan should be performed to help rule out cancer and guide treatment. The determination of serum antibodies can also be useful in ruling out cancer in patients with firm lobular goiters. High antibody levels suggest chronic thyroiditis in these cases. The presence of a nodule in the absence of abnormal thyroid function tests always warrants ultrasound and possible biopsy. Iodine scans show diffuse heightened iodine uptake in Graves' disease and localized heightened iodine uptake, also known as "hot" nodules, in toxic nodular goiter. "Cold" nodules on scans are regions of poor iodine uptake and are assumed to be cancerous until proved otherwise.

THERAPEUTIC CONSIDERATIONS

The chief objective of the natural treatment of Graves' disease and hyperthyroidism is to reduce symptoms while trying to reestablish normal thyroid status. Few treatments short of antithyroid drugs (ATD), radiation, or surgery will have a significant impact on the immediate severity of hyperthyroid symptoms. Nonetheless, adjunctive treatments and sound naturopathic lifestyle recommendations can lower the dose or duration of ATDs or raise the likelihood of disease remission with conventional treatment.

Practical steps include reduction of risk factors (i.e., stress, smoking, excess iodine intake) and increased rest. Stress control is the single most important action the patient can take to assist normalization of the thyroid. The patient should avoid anything that will excite him or her and increase agitation. Counseling can and should be used to prevent a return to stress-generating life strategies. Rest should be increased, including a daily nap after lunch and a full night's sleep.[18]

Comorbidities

Patients with autoimmune thyroid disease are more likely than the general population to suffer from the following[19]:

- Celiac disease
- Osteoporosis
- Mitral valve prolapse
- Type 1 diabetes

TREATMENT OF HYPERTHYROIDISM

Conventional treatment of hyperthyroidism in the United States focuses on radioactive iodine ablation as the first-line treatment. Advantages include a high rate of response and lack of the need for ongoing suppression. Disadvantages include progression to hypothyroidism and an elevated risk of nonlocalized cancers and parathyroid disease.

Overall surgery to remove all or part of the gland is less commonly used for hyperthyroidism. It is a consideration when the patient is very young or pregnant and iodine or ATDs are less preferred. It can also be a consideration when the gland is enlarged enough to create anatomic impingement on adjacent structures or cosmetic concerns. Disadvantages include laryngeal nerve damage, parathyroid abnormalities through localized trauma or inadvertent removal, and general surgical complications.

Globally, ATDs are more commonly relied on as mainstays of treatment for hyperthyroidism. The majority of cases can be given a trial of an ATD for 18 to 24 months; these individuals may not need ongoing treatment afterward. The disadvantage is that they can have hepatic and hematologic toxicities, so that monitoring is required.[20]

ATDs work by entering the thyroid via active transport mechanisms, accumulating inside the thyroid and inhibiting binding of iodine to tyrosine therefore disrupting hormone synthesis. In Europe and Japan, ATD treatment is considered a first-line approach for Graves' and Plummer's diseases. Most cases are known to resolve within 18 months and most remain euthyroid or hypothyroid for life. In the United States, radioactive iodine (RAI) is considered first-line therapy, with ATDs only being used for initial management.[21]

Fluoride in the form of sodium fluoride is a natural compound with antithyroid properties significant enough to allow for its use instead of conventional ATD or in conjunction with ATDs allowing for lower doses of medications. Historically, sodium fluoride or fluorotyrosine were used as oral antithyroid agents prior to

propylthiouracil (PTU) and methimazole. Common doses used to manage adult hyperthyroidism range from 200 to 450 mg/day in divided doses for PTU and 5 to 20 mg/d in divided doses for methimazole. Fluoride is pregnancy category C and is known to cause gastrointestinal side effects at doses starting at 3 mg/kg and toxicity at doses starting at 5 mg/kg.[22]

In the early management of hyperthyroidism, 4 to 6 weeks of ATD are needed to see clinical benefit owing to the high amount of protein bound iodine already stored within the thyroid gland. Excess levels of both T_4 and T_3 are known to be reabsorbed through enterohepatic recirculation. It has been shown that cholestyramine can speed the elimination of thyroid hormone via blocking enterohepatic recirculation.[23]

It is plausible that dietary fibers such as rice bran or ground flax may have similar properties.

Diet

Balanced Whole-Foods Diet

The diet should be high in calories to compensate for the increase in metabolism and should be eaten in the form of small frequent meals. Protein should be supplemented if the patient is nutritionally depleted.[18] Caffeine-containing foods and other stimulants should be avoided.

A whole-foods diet with increased levels of calories, micronutrients, and protein is recommended to meet the increased metabolic needs of the hyperthyroid patient. In mild cases, consumption of large amounts of raw Brassica family foods and raw soy products may be adequately combined with restricted iodine consumption to control symptoms.

Dietary Goitrogens

Some foods contain goitrogenic substances that prevent the utilization of iodine. These compounds are primarily isothiocyanates that are similar in action and structure to propylthiouracil. They are found in such foods as turnips, cabbage, rutabagas, mustard, rapeseeds, cassava root, soybeans, peanuts, pine nuts, and millet. However, these foods are unreliable in the treatment of hyperthyroidism for the following reasons:

- Their goitrogen content is quite low and has minimal beneficial impact on hyperthyroidism.
- Cooking inactivates the goitrogens.
- No substantial documentation exists that these naturally occurring goitrogens interfere with thyroid function to any significant degree when dietary iodine levels are adequate.

An interesting note is that goitrogens are transmitted from cow's milk to humans.[18]

Despite these shortcomings, practitioners may want to use naturally occurring goitrogens in mild cases instead of PTU propylthiouracil and related drugs. In order to achieve clinical results, large amounts of these foods must be consumed in their raw state, and iodine intake must be restricted. The highest levels of isothiocyanates are found in raw soy milk (0.46 to 2.5 mg/dL). In the Brassica family, rutabagas, cabbage, and turnips usually contain the highest levels. However, the quantity varies considerably according to climatic and soil factors. Anecdotally, one half head of raw cabbage per day is the typical prescription. Because iodine is found in kelp and other seaweeds, vegetables grown near the ocean, seafood, iodized salt, and some nutritional supplements, these should be avoided.[24] Great care must be exercised in using this approach because results are inconsistent and delay in effective treatment can harm the patient. If the patient does not respond within a few weeks of treatment, conventional intervention is required.

NUTRITIONAL SUPPLEMENTS

Iodine

Worldwide, iodine deficiency continues to be a problem, but in developed countries iodine excess is more common. Sources of iodine include additives to food products (e.g., salt and iodine used to sterilize pipes in dairies) and in medical products (e.g., povidone/iodine washes, iodine-containing drugs such as amiodarone, radiographic dyes).[25]

The effects of iodine in patients with hyperthyroidism are as follows:

- In large doses, iodine temporarily reduces symptoms by stopping hormone synthesis (Wolff-Chaikoff effect).
- The thyroid can remain suppressed or can eventually resume hormone synthesis at a reduced, former, or even increased rate (escape from Wolff-Chaikoff).[26]
- Excess iodine can trigger hyperthyroidism (Jod-Basedow disease) in a euthyroid person or can trigger an overactive thyroid to return to normal.

From the brief descriptions of these three possibilities, it is clear that, aside from the initial suppression of thyroid function, the action of iodine is unpredictable.

- Iodine intake should be kept on the low end of the normal therapeutic range; that is, 150 to 250 mcg/day for adults.

L-Carnitine

Carnitine is a quaternary amine used for the transport of long-chain fatty acids into the mitochondrial matrix. Carnitine (β-hydroxy/γ-butyrobetaine) was originally isolated from meat extracts in 1905 and its exact chemical structure was determined in 1932. Carnitine is available in several different forms. L-Carnitine is a ubiquitous nutrient in tissues, where it plays an important role in energy metabolism. Carnitine is already known for its important implications for cardiovascular disease, Alzheimer's disease, acquired immunodeficiency syndrome, and a number of other conditions (see Chapter 74).

L-Carnitine has been shown to be an antagonist of thyroid hormone effect in peripheral tissues by inhibiting thyroid hormone entry into the nuclei of human and animal cells.[27] One 6-month randomized double-blinded placebo-controlled study evaluated the use of L-carnitine in iatrogenically induced hyperthyroidism.[28] During this study, 50 women with benign nodular goiter who were already taking a suppressive dose of L-thyroxine were randomly assigned to 5 groups of 10 subjects each. Group 1 was given a placebo for 6 months. Two groups started with the placebo for 2 months and then were prescribed 2 or 4 g/day of carnitine and then returned to the placebo for the last 2 months. The last two groups were started with either 2 or 4 g/day of carnitine for the first 4 months and then given a placebo for the last 2 months. Symptoms of hyperthyroidism, bone mineralization markers, and liver parameters were recorded.

In groups 2 and 3, the symptoms and signs that had worsened while on L-thyroxine plus placebo returned to baseline once the placebo had been substituted with carnitine. In groups 4 and 5, symptoms and signs remained stable or even improved as long as carnitine was given with L-thyroxine, implying that the carnitine effect prevailed over the T_4 effect. For those given supplemental carnitine, liver profiles improved, although cholesterol levels were virtually unaffected. Symptoms and biochemical parameters only worsened in the placebo group.

Two people given carnitine and one person in the placebo group experienced nausea and gastralgia. Neither subject had to

TABLE 175-2 **Medicinal Plants Traditionally Used in the Treatment of Hyperthyroidism**

MEDICINAL PLANT	TRADITIONAL INDICATIONS
Valerian officinalis	Nervine effect
Scutellaria lateriflora	Nervine effect
Cactus grandiflorus	Heart tonic; used with elevated pulse
Iris versicolor	Traditional used for hyperthyroidism
Fucus spp.	To be used with caution, as a high iodine content can improve symptoms at first and then later cause aggravation
Lycopus spp.	Blocks the TSH receptors; blocks peripheral conversion of T_4 to T_3
Lithospermum officinale	Blocks the TSH receptors
Melissa officinalis	Blocks the TSH receptors

TSH, thyroid-stimulating hormone.
Data from Felter HW. The eclectic material medica, pharmacology and therapeutics. Portland, OR: Eclectic Medical Publications, 1985 (first published Cincinnati, 1922); Hoffman D. The new holistic herbal: a herbal celebrating the wholeness of life. Rockport, MA: Element, 1990.

discontinue carnitine administration. Owing to carnitine's extremely low toxicity, the authors of this study recommend considering it for Graves' disease–induced thyrotoxicosis during pregnancy or lactation or in other conditions in which antithyroid drugs may be unwanted, such as liver disease and blood disorders. The form being used must always be L-carnitine alone or L-carnitine bound to either acetic or propionic acid. The D-form of carnitine should never be used (discussed in Chapter 74).

Botanical Medicines

Table 175-2 lists medicinal plants that have traditionally been used in the treatment of hyperthyroidism. Unfortunately, these plants have not been adequately evaluated in clinical studies.

Lycopus Species, Lithospermum officinale, and Melissa officinalis

Aqueous freeze-dried extracts of *Lycopus* species, *Lithospermum officinale*, and *Melissa officinalis* have been studied both in vivo and in vitro, with preliminary results supporting their use in the treatment of Graves' disease. However, additional clinical research is necessary before these plants can be relied on clinically.

Effects noted for these three plants include an ability to inhibit the effects of exogenous TSH on the thyroid glands of rats, block the effects of TSH on the TSH receptor sites located on thyroid membranes, inhibit the peripheral deiodination of T_4 to T_3, and block the effects of antithyroid immunoglobulins on TSH receptors.[29-32]

Eight isolated compounds, mainly oxidation products of derivatives of 3,4-dihydroxycinnamic acid, were found to be responsible for most of these effects. The blocking effects of the isolated compounds of the TSH receptors were reversible, and none of the compounds combined irreversibly, damaged, or altered the TSH receptors in situ.

An alcohol extract of *Lycopus europaeus* administered orally to rats caused a long-lasting decrease in T3 levels, presumably due to reduced peripheral T4 deiodination. A pronounced reduction in TSH was also observed 24 hours later, as were declines in luteinizing hormone and testosterone.[33] Water extracts did not have as strong an effect, explaining the lack of results in some earlier studies. This finding is consistent with the observation that the active constituents are the unoxidized phenolic compounds, which are not present in the aqueous extract.

These findings support the traditional use of these plants for patients with hyperactive thyroids. Unfortunately, there is no research on the clinical use of these plants or documented guidelines for dosage recommendations. Although it is unknown how effective the historic dosage schedules for these plants are, the dosage recommendations from the British Herbal Pharmacopoeia for *Lycopus* species and *M. officinalis* (no mention is made of *L. officinale*) are given as follows.[34]

Calcium

Calcium metabolism is altered in hyperthyroidism, and patients with Graves' disease are more susceptible to osteoporosis than normals.[15]

Natural antithyroid treatments may be beneficial in early, mild cases or to lower dosage requirements of antithyroid drugs. Rarely are they adequate as monotherapies for the significantly hyperthyroid patient.



THERAPEUTIC APPROACH

Acute Graves' disease is not easily treated by naturopathic methods. In severe cases, there is no guarantee that natural treatments will alleviate the symptoms adequately. Thyroid storm is a potentially fatal complication and should be treated aggressively with antithyroid drugs, iodine, or both. In mild cases, natural therapeutics can manage the symptoms well but must be monitored carefully to avoid sudden exacerbation of the illness. Patients will often do well for a time and then relapse. Mild cases should be treated symptomatically and allowed to return to a euthyroid status if possible. If iodine is used, then some sort of ablative treatment should be scheduled, as the risk of escape (with a potential for a return to even more intense symptoms) increases with time.

The allopathic treatment of Graves' disease is unusual in that there are three relatively equal treatments from which to choose. As physicians, we need to do our best to educate patients about the advantages and disadvantages of each treatment option and allow them to decide which treatment best fits their needs.

Importantly, for many patients, decision making is difficult while they are in a thyrotoxic state. For these patients, symptomatic relief must be rendered before a decision is made.

Antithyroid drugs can manage symptoms indefinitely while waiting for a possible return to euthyroid status. If drugs are not well tolerated, then ablative therapies must be considered. Surgery has a higher rate of euthyroid results than radioactive iodine but carries a greater risk of serious complications. Regardless of the treatment selected, supportive treatment can and should be rendered.

Diet

A whole-foods diet with increased levels of calories, micronutrients, and protein is recommended to meet the increased metabolic needs of the hyperthyroid patient. In mild cases, consumption of large amounts of raw Brassica family foods and raw soy products may be adequately combined with restricted iodine consumption to control symptoms.

Supplements

- Fluoride: 3 to 10 mg/day
- L-carnitine: 2 to 4 g/day
- Indole 3 carbinol: 200 to 600 mg/day

Botanical Medicines

- *Lycopus* species, *L. officinale,* or *M. officinalis*
- Dried herb: 1 to 3 g or by infusion three times a day
- Tincture (1:5): 2 to 6 mL three times a day
- Fluid extract (1:1): 1 to 3 mL three times a day

Hydrotherapy

Cold packs are placed over the thyroid three times a day

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CHAPTER 176

Hypoglycemia

Michael T. Murray, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- Blood glucose level at or below 40 to 50 mg/dL
- A normal response curve during the first 2 to 3 hours of a glucose tolerance test (GTT), followed by a decrease of 20 mg or more below the fasting glucose level during the final hours of the test, with symptoms developing during the decrease.

INTRODUCTION

Both low and high blood glucose levels can cause significant physiologic dysfunction. Normally, the body maintains blood sugar levels within a narrow range through the coordinated effort of several glands and their hormones. If these control mechanisms are disrupted, hypoglycemia (low blood sugar) or diabetes (high blood sugar) may result.

The beta cells of the pancreas respond to the rise in blood glucose levels after meals by secreting the hormone insulin, which lowers blood glucose by increasing the rate that glucose is taken up by cells throughout the body. Reductions in blood glucose, as occur during food deprivation or exercise, cause the release of the hormone glucagon by the alpha cells of the pancreas. Glucagon stimulates the release of glucose stored in body tissues as glycogen, especially the liver. Rapidly falling blood sugar levels, anger, fright, and stress may stimulate the release of epinephrine and corticosteroids by the adrenal glands. These hormones provide a quicker breakdown of stored glucose for extra energy during a crisis or increased need.

Americans overstress these control mechanisms through improper diet and lifestyle. As a result, diabetes and hypoglycemia are common diseases.

Hypoglycemia is divided into two main categories: reactive hypoglycemia and fasting hypoglycemia. Reactive hypoglycemia, the most common, is characterized by the development of symptoms of hypoglycemia 3 to 5 hours after a meal and may herald the onset of early type II diabetes. Gastric surgeries may induce this condition,[1] and anorexia nervosa has been a reported to be cause in the literature.[2] Reactive hypoglycemia may also result from the use of oral hypoglycemic drugs. These sulfa drugs (sulfonylureas) appear to stimulate the secretion of additional insulin by the pancreas as well to as enhance the sensitivity of body tissues to insulin. Common examples of this class of drugs are listed in Box 176-1.

Some researchers, however, recommend that for many patients, this syndrome instead be designated idiopathic postprandial syndrome because, although symptoms do exist and are related to rapid drops in blood glucose, the absolute glucose levels are not reliable indicators of the syndrome. Many asymptomatic controls have glucose levels below 50, while many symptomatic patients have normal postprandial glucose levels.[3-5]

Fasting hypoglycemia is rare, because it usually appears only in severe disease states such as pancreatic tumors, extensive liver damage, prolonged starvation, autoantibodies against insulin or its receptor, various cancers, or as a result of excessive exogenous insulin in diabetic patients. Pregnant diabetic women using insulin or oral glycemic medications also have a high incidence of asymptomatic hypoglycemic events.[6]

Hypoglycemia can promote untoward physiologic changes in the body. Insulin-induced hypoglycemia is known to increase the levels of C-reactive protein, a known cardiac risk factor.[7] Because glucose is the primary fuel for the brain, low

levels affect the brain first. Symptoms of hypoglycemia can range from mild to severe, including the following:

- Headache
- Depression, anxiety, irritability, and other psychological disturbances
- Blurred vision
- Excessive sweating
- Mental confusion
- Incoherent speech
- Nocturnal hypoglycemic episodes
- Bizarre behavior
- Convulsions

DIAGNOSTIC CONSIDERATIONS

Clinical hypoglycemia is identified by modified Whipple's criteria consisting of (1) central nervous system symptoms including confusion, aberrant behavior, or coma; (2) a simultaneous blood glucose level equal to or less than 40 mg/dL; and (3) relief of these symptoms by the administration of glucose.[1] The normal fasting blood glucose level is between 65 and 100 mg/dL. A fasting plasma blood glucose measurement greater than 126 mg/dL on two separate occasions is diagnostic of diabetes.[8] Although the most specific criterion for the presence of hypoglycemia is a blood glucose level of 40 mg/dL or less, a blood glucose level below 50 mg/dL should arouse clinical suspicion.[1]

A more functional test of blood sugar control is the oral GTT. It is used in the diagnosis of both reactive hypoglycemia and diabetes, although it is rarely required for the latter. After fasting for at least 12 hours, a baseline blood glucose measurement is made. Then the subject is given a liquid containing glucose to drink. The amount consumed is based on body weight: 1.75 g/kg. Blood sugar levels are measured at 30 minutes, 1 hour, and then hourly for up to 6 hours. Basically blood sugar levels greater than 200 mg/dL indicate diabetes. Levels below 50 mg/dL indicate reactive hypoglycemia. Table 176-1 explains in detail how to interpret the results of a GTT.

The Glucose-Insulin Tolerance Test

Relying on blood sugar levels alone is often not enough to diagnose hypoglycemia, because it is now widely recognized that the signs and symptoms of hypoglycemia can occur in individuals having blood glucose levels well above 50 mg/dL and there is a wide overlap between symptomatic patients and asymptomatic controls.[3] Many of the symptoms linked to hypoglycemia appear to be the result of increases in insulin or epinephrine. Therefore, it has been recommended that insulin or epinephrine (adrenaline) be measured during a GTT because symptoms often correlate better with elevations in these hormones than with glucose levels.[9,10] Several studies have shown that the glucose-insulin tolerance test (G-ITT) leads to a greater sensitivity in the diagnosis of both hypoglycemia and diabetes than the standard GTT.[10,11]

The G-ITT uses a standard 6-hour GTT coupled with measurements of insulin levels. The G-ITT appears to be one of the best diagnostic indicators for faulty sugar metabolism.[11] As many as two thirds of subjects with suspected diabetes or hypoglycemia who have normal GTTs will demonstrate abnormal insulin tolerance tests. Table 176-2 lists the various patterns seen with the G-ITT.

The downside to this test is that it tends to be costly. For example, the G-ITT costs around $200, whereas a standard GTT is usually less than $30.

24-Hour Continuous Glucose Monitoring

Continuous glucose monitors (CGMs) are electronic diagnostic systems that require the insertion of a sensing catheter under the skin of the patient's abdomen. The catheter contains a miniaturized electronic device that measures blood sugar and then sends this information every few seconds to a pager-sized computer module worn on the patient's belt for up to a week. The portable computer module translates and records blood sugar data, which can then be downloaded to a larger computer. A graph showing the average blood sugar reading every 5 minutes (288 blood sugar readings per day) can then be generated and studied in relation to food intake, appetite, food cravings, hypoglycemic symptoms, medication, and exercise. CGMs have been shown to be very useful tools in the diagnosis and monitoring of blood sugar control.[12,13]

Using a CGM, Michael R. Lyon, MD, has discovered that most people with weight problems and insulin resistance go through

BOX 176-1 Oral Hypoglycemic Drugs

- Chlorpropamide (Diabinese)
- Glipizide (Glucotrol)
- Glibenclamide, Glyburide (DiaBeta, Micronase)
- Tolazamide (Tolinase)
- Tolbutamide (Orinase)
- Metformin (Glucophage)
- Thiazolidinediones: Pioglitazone (Actos) or Rosiglitazone (Avandia)
- Acarbose (Precose, Glucobay)
- Glimepiride (Amaryl)
- Gliclazide (Gen-Gliclazide)
- Nateglinide (Starlix)
- Repaglinide (Prandin)

TABLE 176-1 Criteria of Response to the Glucose Tolerance Test

DIAGNOSIS	RESPONSE
Normal	No elevation >200 mg <200 mg at the end of the first hour <140 mg at the end of the second hour Never <20 mg below fasting
Flat	No variation more than ± 20 mg from fasting value
Prediabetic	>140 mg at the end of the second hour
Diabetic	≥200 mg at the end of the second hour
Reactive hypoglycemia	A normal 2- or 3-hour response curve, followed by a decrease of ≥20 mg from the fasting level during the final hours
Probable reactive hypoglycemia	A normal 2- or 3-hour response curve, followed by a decrease of 10-20 mg from the fasting level during the final hours
Flat hypoglycemia	An elevation of >20 mg, followed by a decrease of ≥20 mg below the fasting level
Prediabetic hypoglycemia	A 2-hour response identical to the hypoglycemic prediabetic response but showing a hypoglycemic response during the final 3 hours
Hyperinsulinism	A marked hypoglycemic response with a value of <50 mg during the third, fourth, or fifth hour

their days with remarkably fluctuating blood sugar, or increased glycemic volatility. Rather than the absolute glucose level being the prime determinant of hypoglycemic symptoms, Lyon has found that feelings of hypoglycemia occur when the blood sugar drops rapidly, even when it was above the normal range (i.e., between 70 and 100 mg/dL) (Figure 176-1). In such cases, symptoms of hypoglycemia can range from mild to severe and include such things as food cravings, headache, depression, anxiety, irritability, blurred vision, excessive sweating, and mental confusion.

Rather than referring to these patients as suffering from hypoglycemia, Lyon and Michael T. Murray, ND, propose that they suffer from a new clinical entity they refer to as "elevated glycemic volatility."[63] These authors also believe that such volatility is at the heart of most weight problems. Their data indicate that rapidly fluctuating blood sugar levels are generally related to some degree of insulin resistance and made worse by more than moderate consumption of foods with a high glycemic impact.

TABLE 176-2 **Criteria for the Glucose-Insulin Tolerance Test**

PATTERN	RESPONSE
Pattern 1	Normal fasting insulin 0-30 units. Peak insulin at 0.5-1 hour. The combined insulin values for the second and third hours is <60 units. This pattern is considered normal.
Pattern 2	Normal fasting insulin. Peak at 0.5-1 hour with a "delayed return to normal." Second- and third-hour levels between 60 and 100 units are usually associated with hypoglycemia and are considered borderline for diabetes; values >100 units considered definite diabetes.
Pattern 3	Normal fasting insulin. Definite diabetes.
Pattern 4	High fasting insulin. Definite diabetes.
Pattern 5	Low insulin response. All tested values for insulin < 30. If this response is associated with elevated blood sugar levels, it probably indicates insulin-dependent diabetes ("juvenile pattern").

The Hypoglycemic Index

Another laboratory parameter that can aid in the diagnosis of hypoglycemia, especially in the borderline case, is the so-called hypoglycemic index. This value is determined by calculating the fall in blood glucose levels during the 90-minute period before the lowest point divided by the value of the lowest point. A hypoglycemic index greater than 0.8 usually indicates reactive hypoglycemia.

The Hypoglycemia Questionnaire

In many cases, when all is considered (especially cost to the patient), the most useful measure in the diagnosis of hypoglycemia remains an assessment of symptoms. In general, when symptoms appear 3 to 4 hours after eating and disappear with the ingestion of food, hypoglycemia should be considered. The questionnaire shown in Table 176-3 is an excellent screening method for hypoglycemia.

GENERAL CONSIDERATIONS

In the 1970s, hypoglycemia was a popular "self-diagnosis" for a long list of symptoms; every symptom on the questionnaire in Table 176-3 was linked to hypoglycemia. Although all of these symptoms may be due to hypoglycemia, there are obviously other causes in many cases. The tremendous public interest in hypoglycemia and sugar intake was fueled by a number of popular books like *Sugar Blues,* by William Duffy; *Hope for Hypoglycemia,* by Broda Barnes; and *Sweet and Dangerous,* by John Yudkin. The popularity of these books and the diagnosis of hypoglycemia were met with much skepticism from the medical community. Editorials in the *Journal of the American Medical Association* and the *New England Journal of Medicine* during the 1970s denounced this public interest in hypoglycemia and tried to invalidate the concept.[14,15]

Research in the past 15 years has provided an ever-increasing amount of information concerning the roles that refined carbohydrates and the faulty control of blood sugar play in many disease processes. New terminology and descriptions are now used to

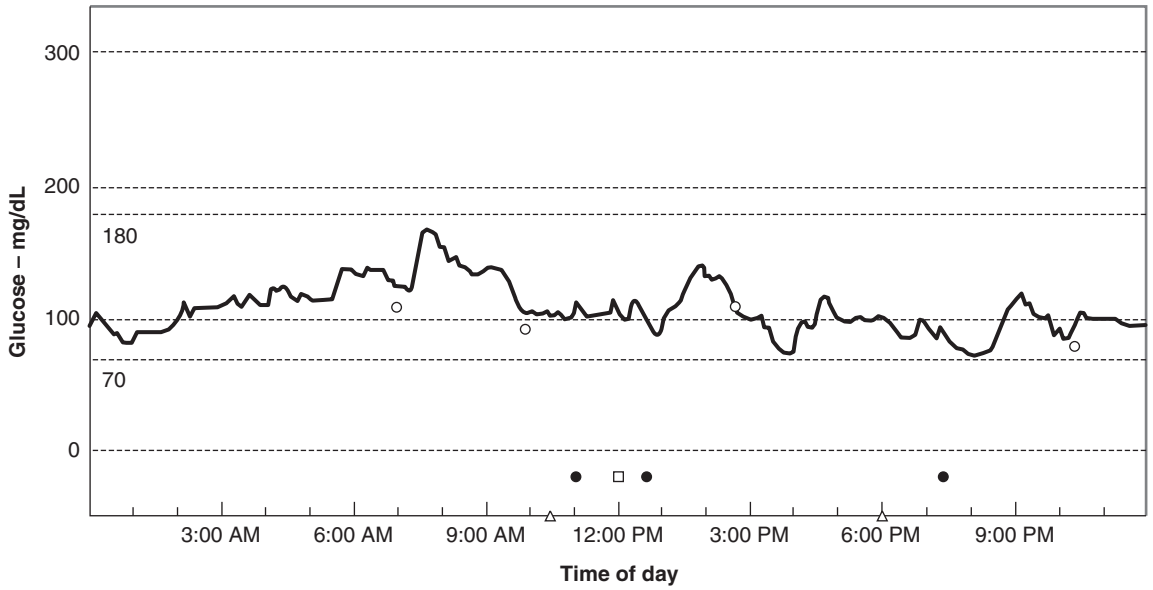


FIGURE 176-1 Blood sugar fluctuation revealed by 24-hour monitoring. Courtesy of Dr. Michael Lyon.

TABLE 176-3 **Hypoglycemia Questionnaire**

	NONE	MILD	MODERATE	SEVERE
Crave sweets	0	1	2	3
Irritable if a meal is missed	0	1	2	3
Feel tired or weak if a meal is missed	0	1	2	3
Dizzy when standing suddenly	0	1	2	3
Frequent headaches	0	1	2	3
Poor memory (forgetful) or concentration	0	1	2	3
Feel tired an hour or so after eating	0	1	2	3
Heart palpitations	0	1	2	3
Feel shaky at times	0	1	2	3
Afternoon fatigue	0	1	2	3
Vision blurs on occasion	0	1	2	3
Depression or mood swings	0	1	2	3
Overweight	0	1	2	3
Frequently anxious or nervous	0	1	2	3

Total Scoring: <5, hypoglycemia not likely a factor; 6-15, hypoglycemia a likely factor; 15, hypoglycemia extremely likely.

describe the complex hormonal fluxes that are largely a result of ingesting too many refined carbohydrates. For example, the term *metabolic syndrome* or *syndrome X* has been introduced to describe a cluster of abnormalities that owe their existence largely to a high intake of refined carbohydrates, leading to the development of hypoglycemia, excessive insulin secretion, and glucose intolerance followed by diminished insulin sensitivity and leading to high blood pressure, elevated cholesterol levels, obesity, and, ultimately, type 2 diabetes. Metabolic syndrome is discussed in greater detail later.

Hypoglycemia, or idiopathic postprandial syndrome, is without question a valid clinical entity. A substantial amount of information indicates that hypoglycemia is caused by an excessive intake of refined carbohydrates.[16,17] Although most medical and health organizations as well as the U.S. government have recommended that no more than 10% of the total caloric intake be derived from refined sugars added to foods, added sugar accounts for roughly 30% of the total calories consumed by most Americans.[18] The average American consumes more than 100 lb of sucrose and 40 lb of high-fructose corn syrup each year. This sugar addiction plays a major role in the high prevalence of ill health and chronic disease in the United States.

Health Impacts of Hypoglycemia

Hypoglycemia and the Brain

The brain depends on glucose as an energy source. When glucose levels are low, as occurs during hypoglycemia, brain dysfunction results in dizziness, headache, clouding of vision, blunted mental acuity, emotional instability, confusion, and abnormal behavior.

The association between hypoglycemia and impaired mental function is well known. What is not as well known is the role that hypoglycemia plays in various psychological disorders. For example, despite numerous studies of depressed individuals showing a high percentage of abnormal glucose or insulin tolerance tests, rarely is hypoglycemia considered and rarely are depressed individuals offered dietary therapy.[19,20] There is no explanation for this oversight among so many physicians, especially because dietary therapy (usually simply eliminating refined carbohydrates from the diet) is occasionally all that is necessary for effective therapy in patients who suffer from depression due to reactive hypoglycemia.

Aggressive and Criminal Behavior

A strong yet controversial link exists between hypoglycemia and aggressive or criminal behavior. Several controlled studies among psychiatric patients and habitually violent and impulsive criminals have shown that reactive hypoglycemia (as determined by an oral GTT) is a common finding.[21,22] Furthermore, during the GTT, abnormal and sometimes emotionally explosive behavior is often observed. In one study, reactive hypoglycemia was shown to induce fire-setting behavior in arsonists.[23]

Several large studies involving more than 6000 inmates in 10 correctional institutions in three states have now evaluated the effect of dietary intervention (i.e., the elimination of refined sugar) on antisocial or aggressive behavior.[24,25]

In the first study, 174 incarcerated juvenile delinquents were placed on a sugar-restricted diet while another 102 offenders were placed on a control diet.[24] During the 2-year study, the incidence of antisocial behavior was reduced by 45% in the treatment group. The most significant changes were in the reduction of assaults (83%), theft (77%), "horseplay" (65%), and refusal to obey orders (55%). Antisocial behavior changed most in those charged with assault, robbery, rape, aggravated assault, auto theft, vandalism, child molestation, arson, and possession of a deadly weapon.

In the largest study, 3999 incarcerated juveniles were studied over a period of 2 years.[25] This study limited the dietary revisions to replacing sugary soft drinks with fruit juices and high-sugar snacks with nonrefined carbohydrate snacks (e.g., replacing a candy bar with popcorn). When the 1121 young men on the sugar-restricted diet were compared with the 884 on the control diet, there were significant differences: suicide attempts were reduced by 100%; the need for restraints to prevent self-injury was reduced by 75%; disruptive behavior was reduced by 42%; and assaults and fights were reduced by 25%. Interestingly, the dietary changes did not seem to affect the behavior of female subjects. This lack of effect seems to indicate that men and women may react to hypoglycemia differently. From an anthropologic and evolutionary view, this makes sense. Low blood sugar levels were undoubtedly an internal signal for men to hunt for food.

The link between hypoglycemia and aggressive behavior also extends to men without a history of criminal activity. In one study, a GTT was given to a group of men who did not have a history of aggressive behavior or hypoglycemia.[17] In these subjects, a significant correlation was found between the tendency to become mildly hypoglycemic and scores on questionnaires used to measure aggression. The results indicate that aggressiveness often coincides with hypoglycemia.

Premenstrual Syndrome

The premenstrual syndrome (PMS) is a recurrent condition of women characterized by troublesome yet often ill-defined symptoms that usually appear 7 to 14 days before menstruation. The syndrome affects about one third of women between 30 and 40 years of age, about 10% of whom may have a significantly debilitating form.

An authority on PMS, Guy Abraham, MD, attempted to clarify the different forms by subdividing PMS into four distinct subgroups (A, C, D, and H).[26] Each subgroup is linked to specific symptoms, hormonal patterns, and metabolic abnormalities (see Chapter 202 for further information).

PMS-C is associated with increased appetite, craving for sweets, headache, fatigue, fainting spells, and heart palpitations. GTTs on PMS-C patients during the 5 to 10 days before their menses typically displayed a flattening of the early part of the curve and reactive hypoglycemia, whereas during other parts of the menstrual cycle the GTT was normal. A flat early part of the GTT curve usually implies excessive secretion of insulin in response to sugar consumption. This appears to be hormonally regulated, but other factors may also be involved.[27] Sodium chloride ingestion enhances the insulin response to sugar ingestion, and decreased magnesium levels in the pancreas can result in the increased secretion of insulin in response to glucose. Regardless of the cause, women with PMS-C appear to be extremely sensitive to hypoglycemia.

Migraine Headaches

Migraine headaches are probably caused by excessive dilation (expansion) of a blood vessel in the head (see Chapter 190). Migraines are a surprisingly common disorder, affecting 15% to 20% of men and 25% to 30% of women at some time in their lives. More than one half of the patients have a family history of the illness. Since 1933, hypoglycemia has been shown to be a common precipitating factor in migraine headaches.[28]

Several studies have found that by eliminating refined sugar from the diets of migraine sufferers with confirmed hypoglycemia, significant improvement may be seen. In one study of 48 migraine sufferers with reactive hypoglycemia, 27 (56%) showed a greater than 75% improvement in symptoms, 17 (35%) showed a greater than 50% improvement, and 4 (8%) showed a greater than 25% improvement.[29]

Atherosclerosis, Intermittent Claudication, and Angina

Substantial evidence indicates that reactive hypoglycemia or impaired glucose tolerance is a significant factor in the development of atherosclerosis. Although a high sugar intake leads to elevations in triglyceride and cholesterol levels, the real culprit may be the elevations of insulin.[30] Abnormal GTTs and elevations in insulin secretion are common findings in patients with heart disease.[31,32]

In addition to playing a role in atherosclerosis, high sugar consumption and reactive hypoglycemia can be a cause of angina and intermittent claudication.[33,34]

Metabolic Syndrome

The term *metabolic syndrome* is used to describe a set of cardiovascular risk factors including glucose or insulin disturbances, high blood cholesterol and triglyceride levels, elevated blood pressure, and android obesity. Other terms to describe this syndrome include *syndrome X, Reaven's syndrome, insulin resistance syndrome*, and *atherothrombogenic syndrome*.[35,36]

The underlying common metabolic denominator in the metabolic syndrome is an elevated insulin level along with insulin resistance. There is little doubt about what contributes to these elevations: an elevated intake of refined carbohydrates. An increased intake of simple sugar leads first to hypoglycemia and later to diabetes. There now exists considerable scientific evidence that the development of type 2 diabetes is preceded by elevations of serum insulin values and insulin insensitivity due to the prolonged consumption of refined sugars and the resulting elevations in insulin eventually lead to type 2 diabetes.[45] In most cases these defects presented themselves decades before the development of diabetes.

Hypoglycemia, increased insulin secretion, metabolic syndrome, and type 2 diabetes can be viewed as a progression of the same illness—maladaptation to the Western diet. The human body was not designed to handle the amount of refined sugar, salt, saturated fats, and other harmful food compounds that many people in the United States and other Western countries feed it. The result is that a metabolic syndrome emerges—elevated insulin levels, obesity, elevated blood cholesterol and triglycerides, and high blood pressure.

THERAPEUTIC CONSIDERATIONS

Dietary Factors

Dietary carbohydrates play a central role in the cause, prevention, and treatment of hypoglycemia. Simple carbohydrates, or sugars, are quickly absorbed by the body, resulting in a rapid elevation in blood sugar and stimulating a corresponding excessive elevation in serum insulin levels. It is thought by some that the assortment of natural, simple sugars in fruits and vegetables has an advantage over sucrose and other refined sugars in that they are balanced by a wide range of nutrients that aid in the utilization of the sugars. However, of greater importance is the fact that in whole, unprocessed foods the sugars are more slowly absorbed, because they are contained within cells and are associated with fiber and other food elements.

Problems with carbohydrates begin when they are refined, which strips them of associated nutrients and increases their rate of absorption. Virtually all of the vitamin and trace mineral content has been removed from white sugar, white breads, pastries, and many breakfast cereals. When high-sugar foods are eaten alone, blood sugar levels rise quickly, producing a strain on blood sugar control. Eating foods high in simple sugars in any form (e.g., sucrose, honey, or maple syrup) is harmful to blood sugar control. Large amounts of fruit juice and even vegetable juice may be a problem for hypoglycemics, as the cell disruption characteristic of juicing increases the percentage of the sugars in the juices.

Currently, more than one half of the carbohydrates consumed in the United States are in the form of sugars added to processed foods as sweetening agents.[18] Patients should be instructed to read food labels carefully for clues to sugar content. They should know that various words are used to describe refined simple carbohydrates; any of the following might appear on the label: *sucrose, glucose, maltose, lactose, fructose, corn syrup,* and *white grape juice concentrate*.

A Closer Look at Simple Carbohydrates

Glucose is not particularly sweet-tasting compared with fructose and sucrose. It is found in abundant amounts in fruits, honey, sweet corn, and most root vegetables. Glucose is also the primary repeating sugar unit of most complex carbohydrates.

Fructose or fruit sugar is the primary carbohydrate in many fruits, maple syrup, and honey. Fructose is very sweet, roughly 1.5 times sweeter than sucrose. Although fructose has the same chemical formula as glucose, its structure is quite different. In order to be used by the body, fructose must be converted to glucose within the liver.

Many physicians have recommended that individuals with diabetes or hypoglycemia avoid fruits and fructose. However, recent

research challenges this. Fructose does not cause a rapid rise in blood sugar levels. Because fructose must be changed to glucose in the liver in order to be used by the body, blood glucose levels do not rise as rapidly with fructose consumption as they do with that of other simple sugars. For example, the ingestion of sucrose results in an immediate elevation in the blood sugar level. Although most diabetic and hypoglycemic individuals cannot tolerate sucrose, most can tolerate moderate amounts of fruits and fructose without loss of blood sugar control. In fact, fructose and fruits are not only much better tolerated than white bread and other refined carbohydrates but they also produce less sharp elevations in blood sugar levels compared with most sources of complex carbohydrates (starch).[37] As a bonus, fructose at concentrations found in most single servings of fruit (e.g., 10 g) has actually been shown to enhance sensitivity to insulin.[38]

Regular fruit consumption also may help to control sugar cravings and promote weight loss in overweight individuals. Although studies have shown aspartame (NutraSweet), glucose, and sucrose to increase the appetite, fructose has actually been shown in several double-blind studies to decrease the calories and fat consumed. Typically, subjects are given food or drink containing an equivalent caloric amount of fructose or other sweetener 30 minutes to 2.5 hours before they are allowed to consume as much food as they want at a dinner buffet. Consistently, subjects receiving the fructose-sweetened food or drink consume substantially fewer calories and fat compared with the groups receiving aspartame, sucrose, or glucose.[39-41]

The Glycemic Index and Glycemic Load

Two helpful methods of categorizing food on the basis of its ability to alter blood sugar are the glycemic index (GI) and the glycemic load (GL).

The GI was developed in 1981 to express the rise of blood glucose after a particular food is eaten.[42] The standard value of 100 is based on the rise seen with the ingestion of glucose. The GI ranges from about 20 for fructose and whole barley, and to about 98 for a baked potato. The insulin response to carbohydrate-containing foods is similar to the rise in blood sugar.

The GI is used as a guideline for dietary recommendations for people with either diabetes or hypoglycemia (see Table 176-4). People with blood sugar problems are advised to avoid foods with high values and choose carbohydrate-containing foods with lower values. However, the GI should not be the only dietary guideline.

For example, high-fat foods like ice cream and sausage may have a low GI, but because a diet high in fat has been shown to impair glucose tolerance, these foods are not good choices for people with hypoglycemia or diabetes.

The GL uses the information the GI provides in a more comprehensive way to assess the impact of carbohydrate consumption.[43] Although the GI reveals how quickly a particular food's carbohydrate content can raise blood glucose levels, it still does not help us to understand how much of the blood sugar–increasing carbohydrate is in a certain food.

The dietary GL is defined as the value of a food's GI divided by 100 and then multiplied by its available carbohydrate content. A GL of 20 or more is considered high, 11 to 19 is considered intermediate, and 10 or less is considered low. The GI of watermelon, for example, is 72, and a typical serving of 120 g has 6 g of available carbohydrate:

$$\text{GL for watermelon} = (72 / 100) \times 6 = 4.32$$

The point of this example is that even though the GI for watermelon is fairly high, its GL is low, indicating that within reasonable serving amounts, it does not adversely stress blood sugar control. For a complete listing of foods and their GI, fiber content, and GL, see Appendix 6.

The GL reinforces the idea that foods containing natural soluble and insoluble fibers as well as whole foods that are minimally processed remain better choices in terms of glycemic influence and insulin response.[44]

Further research indicates that diets with a high GL are directly linked to conditions such as diabetes[45] and coronary heart disease[46] as well as colon,[47] ovarian,[43] and pancreatic[48] cancers.

The Importance of Fiber

Population studies as well as clinical and experimental data show blood sugar disorders to be clearly related to inadequate dietary fiber intake.[18,49] These results indicate that although the intake of refined sugars should be curtailed, the intake of complex carbohydrate sources that are rich in fiber should be increased.

TABLE 176-4 **Glycemic Index of Isocaloric Amounts of Some Common Foods**

	FOOD	GLYCEMIC INDEX
Sugars	Fructose	20
	Glucose	100
	Honey	75
	Maltose	105
	Sucrose	60
Fruits	Apples	39
	Bananas	62
	Orange juice	46
	Oranges	40
	Raisins	64
Vegetables	Beets	64
	Carrot, cooked	36
	Carrot, raw	31
	Potato, baked	98
	Potato (new), boiled	70
Grains	Bran cereal	51
	Bread, white	69
	Bread, whole grain	72
	Corn	59
	Corn flakes	80
	Oatmeal	49
	Pasta	45
	Rice	70
	Rice, puffed	95
	Wheat cereal	67
Legumes	Beans	31
	Lentils	29
	Peas	39
Other foods	Ice cream	36
	Milk	34
	Nuts	13
	Sausages	28

Modified from Truswell AS. Glycaemic index of foods. Eur J Clin Nutr 1992;46(suppl 2):S91-S101.

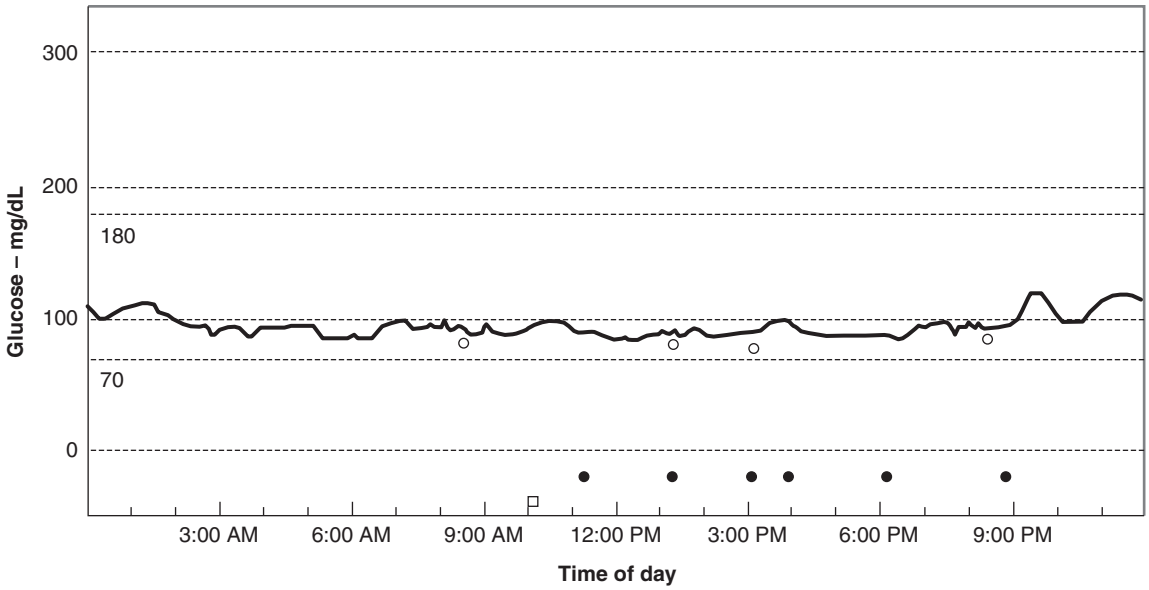


FIGURE 176-2 Blood sugar stabilization from fiber supplementation (same patient as in Figure 176-1). Courtesy of Dr. Michael Lyon.

The term *dietary fiber* refers to the components of the plant cell wall as well as the indigestible residues from plant foods. Different types of fibers possess different actions. The water-soluble forms exert the most beneficial effects on blood sugar control. Included in this class are hemicelluloses, mucilages, gums, and pectins. These types of fiber are capable of the following actions:

- Slowing down the digestion and absorption of carbohydrates, thereby preventing rapid rises in blood sugar
- Increasing cell sensitivity to insulin, thereby preventing the excessive secretion of insulin
- Improving uptake of glucose by the liver and other tissues, thereby preventing a sustained elevation of blood sugar (Figure 176-2)

For a full discussion of the importance of fiber, see Chapter 52.

The majority of fiber in most plant cell walls is water soluble. Particularly good sources of water-soluble fiber are legumes, oat bran, nuts, seeds, psyllium seed husks, pears, apples, and most vegetables. Patients should be advised to consume a large amount of plant food to obtain adequate levels of dietary fiber. A daily intake of 50 g is a healthful goal.

PolyGlycoPlex

Based on their work with CGM, Drs. Lyon and Murray have uncovered many important findings on how to effectively reduce blood sugar volatility. For example, they confirmed earlier work that although a low glycemic diet is very important in reducing blood sugar levels, it has little effect in eliminating blood sugar volatility.[50] They have found that the most effective way to reduce glycemic volatility is a low glycemic diet along with the use of a novel matrix of soluble fibers known as PolyGlycoPlex (PGX). Several double-blind studies have shown a reduction of postprandial hypoglycemia by PGX in a dose-dependent manner, independent of food form.[51-53] The PGX matrix produces a higher level of viscosity, gel-forming properties, and expansion with water compared with any other known fiber. This translates to a significant reduction in the glycemic impact of any food or meal. The typical dosage is 1.5 to 5 g before meals.

Chromium

Chromium is vital to proper blood sugar control, because it functions in the body as a key constituent of the "glucose tolerance factor." Without chromium, insulin's action is blocked and glucose levels are elevated. A chromium deficiency may be an underlying contributing factor to the tremendous number of Americans who have hypoglycemia or diabetes or who are obese.[54] Evidence exists that marginal chromium deficiency is quite common in the United States and may be responsible for many cases of reactive hypoglycemia.[55]

In one double-blind crossover study of eight female patients, 200 mcg of chromium (as chromium chloride) given twice daily for 3 months alleviated hypoglycemic symptoms and the glucose nadir at 2 to 4 hours after a glucose load.[55] In addition, insulin binding improved and the number of insulin receptors increased.[56,57]

Lifestyle Factors

Alcohol

Alcohol consumption severely stresses blood sugar control and is often a contributing factor to hypoglycemia. Alcohol induces reactive hypoglycemia by interfering with normal glucose utilization as well as increasing the secretion of insulin. The resultant drop in blood sugar produces a craving for food, particularly foods that quickly elevate blood sugar, as well as a craving for more alcohol. The increased sugar consumption aggravates the reactive hypoglycemia, particularly in the presence of more alcohol, again due to alcohol-induced impairment of normal glucose utilization and increased secretion of insulin.

Hypoglycemia is an important complication of acute and chronic alcohol abuse. Hypoglycemia aggravates the mental and emotional problems of the alcoholic and the withdrawing alcoholic with such symptoms as the following[58]:

- Sweating
- Tremor
- Rapid heart beat
- Anxiety
- Hunger
- Dizziness
- Headache
- Visual disturbance
- Decreased mental function
- Confusion
- Depression

Although acute alcohol ingestion induces hypoglycemia, in the long run it leads to hyperglycemia and diabetes. Eventually the body becomes insensitive to the augmented insulin release caused by the alcohol. In addition, alcohol itself can cause insulin resistance even in healthy individuals.[59] There is also evidence from large population studies that alcohol intake is strongly correlated with diabetes.[18,60] The higher the alcohol intake, the more likely it is that an individual will have or develop diabetes.

Exercise

An appropriate exercise training program is an important part of a treatment and prevention plan. Regular exercise has been well documented to prevent type 2 diabetes, and it improves many aspects of glucose metabolism including enhancing insulin sensitivity and improving glucose tolerance in those who are already diabetic. Some effects of exercise on blood sugar control may stem from the fact that exercise increases tissue chromium concentrations.[61]

THERAPEUTIC APPROACH

The primary treatment of hypoglycemia is the use of dietary therapy to stabilize blood sugar levels. Reactive hypoglycemia is not a disease; it is simply a complex set of symptoms caused by faulty carbohydrate metabolism induced by an inappropriate diet.

Diet

All simple, processed, and concentrated carbohydrates as well as food choices with a high GL must be avoided. Foods rich in soluble fiber such as legumes and low glycemic vegetables should be consumed regularly. Frequent small meals may be more effective than larger meals further apart in stabilizing blood sugar levels. Alcohol must be avoided, because it can cause hypoglycemia. Further dietary recommendations mirror those in Chapter 161.

Supplements

Many essential nutrients are critical to proper carbohydrate metabolism. Taking a multivitamin-multimineral formula providing at least recommended dietary intake levels appears warranted.

Chromium: 200 to 400 mcg/day
PGX: 1500 to 5000 mg before meals

Exercise

Because the beneficial effects of exercise in improving insulin sensitivity decrease within 3 days after exercise and are no longer evident after 1 week, a sustained program is required.[62] A graded long-term exercise program should be developed that is appropriate to the individual's fitness level and interest; it should elevate the heart rate at least 60% of its maximum for half an hour three times a week.

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CHAPTER 177

Hypothyroidism

Alan Christianson, ND, and Michael T. Murray, ND

DIAGNOSTIC SUMMARY

- Depression
- Difficulty in losing weight
- Dry skin
- Headaches
- Lethargy or fatigue
- Memory problems
- Menstrual problems
- Hyperlipidemia
- Recurrent infections
- Sensitivity to cold
- Thinning of head hair
- Voice changes

GENERAL CONSIDERATIONS

Because the hormones of the thyroid gland are required for mitochondrial metabolism in every cell of the body, a deficiency of thyroid hormones can affect virtually all bodily functions. The degree of severity of symptoms in the adult ranges from mild deficiency states that are not detectable with standard blood tests (hypothyroid syndrome) to severe deficiency states that can be life-threatening (myxedema).

Deficiency of thyroid hormone may be due to lack of stimulation by the pituitary gland, defective hormone synthesis, or impaired cellular conversion of T_4 to T_3. The pituitary gland regulates thyroid activity through the secretion of thyroid-stimulating hormone (TSH). The combination of low thyroid hormone and elevated TSH blood levels usually indicates defective thyroid hormone synthesis, which is defined as *primary hypothyroidism.* When TSH and thyroid hormone levels are both low, the pituitary gland is responsible for the low thyroid function, a situation termed *secondary hypothyroidism.* A final cause is the lack of thyroid hormone-releasing hormone (THRH) from the hypothalamus, called *tertiary hypothyroidism.* Normal blood thyroid hormone and TSH blood levels combined with low functional thyroid activity (as defined by a low basal metabolic rate) suggest cellular hypothyroidism.

Most estimates on the rate of hypothyroidism are based on the levels of thyroid hormones in the blood. This may occur in a large number of people with mild hypothyroidism that has gone undetected. Nonetheless, using blood levels of thyroid hormones as the criteria, it is estimated that between approximately 5% and 10% of the adult population is hypothyroid.[1-4] The Colorado Thyroid Disease Prevalence Study of the year 2000 suggested that no fewer than 10% of the adult population is affected, with the rate exceeding 20% among senior citizens.[5]

Overall, thyroid disease of all types is more common among females. Reports suggest a 8:2 female:male ratio. Hypothyroidism is slightly more prevalent among whites and Mexican Americans (5.7%) than among African Americans (1.7%).[6]

Some writers estimate that 40% of adults would be considered hypothyroid if symptoms and basal body temperature were used for diagnosis.[7,8] It is likely that the true rate of hypothyroidism using these criteria is somewhere near 25% of the adult population and significantly higher among the elderly.

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Symptoms of Hypothyroidism

The earliest stages of hypothyroidism can precede conventionally defined serum abnormalities by several years and present with mild symptoms of fatigue or depression. Advanced stages, which are quite rare at present, can manifest with a life-threatening myxedema coma. The degree of severity of symptoms in the adult ranges from early, mild deficiency states that are not detectable with standard blood tests (hypothyroid syndrome) to severe deficiency states that can be life-threatening (myxedema).

Psychological

The brain appears to be quite sensitive to low levels of thyroid hormone. Depression, along with weakness and fatigue, are usually the first symptoms of hypothyroidism.[9-11] Later, the hypothyroid individual has difficulty concentrating and is extremely forgetful.

Metabolic

A lack of thyroid hormones leads to a general decrease in the rate of utilization of fat, protein, and carbohydrate. Moderate weight gain combined with sensitivity to cold (demonstrated by cold hands or feet) is a common finding.

Cholesterol and triglyceride levels are increased in even the mildest forms of hypothyroidism. This elevation greatly increases the risk of serious cardiovascular disease. Studies have shown an increased rate of heart disease due to atherosclerosis in individuals with hypothyroidism.[12]

Hypothyroidism also leads to increases in capillary permeability and slow lymphatic drainage. Often this results in the swelling of tissue (edema).

Endocrine

Various hormonal symptoms can exist in hypothyroidism. Perhaps the most common are a loss of libido (sexual drive) in men and menstrual abnormalities in women. Women with mild hypothyroidism have prolonged, heavy menstrual bleeding with a shorter menstrual cycle. Infertility may also be a problem. If the hypothyroid woman does become pregnant, she is at greater risk for miscarriage, premature delivery, and stillbirth.

Adrenal dysfunction is a common comorbidity with primary and secondary hypothyroidism. Patients with thyroid antibodies are more likely to possess adrenal cortex antibodies. Furthermore, cortisol secretion can be increased to compensate for low T_3 levels.

Skin, Hair, and Nails

Dry, rough skin covered with fine superficial scales is seen in most hypothyroid individuals, while the hair is coarse, dry, and brittle. Hair loss can be quite severe and is generally diffuse and uniform as opposed to being patchy. The nails become thin and brittle and typically show transverse grooves.

Muscular and Skeletal

Muscle weakness and joint stiffness are predominant features of hypothyroidism.[13] Some individuals with hypothyroidism may also experience muscle and joint pain as well as tenderness.[14]

Cardiovascular

Both overt and subclinical hypothyroidism are thought to predispose the individual to atherosclerosis owing to the increase in cholesterol and triglycerides[9,10,12,15,16] as well as elevated levels of homocysteine and C-reactive protein (CRP).[17] Hypothyroidism can also cause hypertension, reduce cardiac function, and slow the heart rate.

Other Manifestations

Shortness of breath, constipation, and impaired kidney function are some of the other common features of hypothyroidism.

Several diseases have been shown to be associated with low thyroid function, even some of which seem to have no apparent relationship. For example, one study compared the thyroid function of 56 patients suffering from dermatitis herpetiformis with that of 26 control subjects. The patients with dermatitis herpetiformis had significantly increased abnormalities of thyroid function tests (32% vs. 4%), with significant hypothyroidism being the most common abnormality affecting 12 of the 56 patients.[18]

Causes of Hypothyroidism

About 95% of all cases of clinical hypothyroidism are primary. Globally, the most common cause of hypothyroidism is iodine deficiency. The thyroid gland adds iodine to the amino acid tyrosine to create the thyroid hormones. Iodine deficiency leads to hypothyroidism, the development of an enlarged thyroid gland (i.e., a goiter), or both.

Goiters are estimated to affect more than 200 million people worldwide. In all but 4% of these cases, the cause is an iodine deficiency. Iodine deficiency is now quite rare in the United States and other industrialized countries due to the addition of iodine to table salt. Adding iodine to table salt began in Michigan, where in 1924 the goiter rate was an incredible 47%.

Few people in the United States are now considered iodine-deficient, yet some still develop goiters. Prolonged thyrotropin (TSH) elevation can lead to thyrocyte hypertrophy, which can manifest as a goiter. Goiters generally regress as thyrotropin is suppressed but in rare cases may require surgical resection.

Nodules can also form within the gland during or independent of output dysfunction. On palpation, up to 20% of adult patients can be found to have nodules; on random screening by ultrasound, they can be found in up to 50% of the population. The main clinical relevance of nodules is that up to 5% may be cancerous.

A possible cause of goiters or nodules in patients with adequate but marginal iodine intake is the excessive ingestion of dietary or environmental goitrogens. See Nutritional Considerations for details on dietary goitrogens.

Environmental goitrogens include perchlorate, iodine in excess of 1000 mcg/day, fluoride, and mercury. Medications that induce goiters and suppress thyroid function include amiodarone, carbamazepine, lithium, potassium iodine, phenobarbitone, phenytoin, and rifampin.

Goiters can also be the result of Hashimoto's thyroiditis, an autoimmune disorder that is the most frequent cause of clinical hypothyroidism in the United States. In this disease antibodies that bind to the thyroid (specifically against the thyroid peroxidase enzyme, thyroglobulin, and TSH receptors) are formed and prevent the manufacture of sufficient levels of thyroid hormone. In addition to binding to thyroid tissue, these antibodies may also bind to the adrenal glands, pancreas, and acid-producing cells of the stomach (parietal cells).

Hashimoto's thyroiditis is formally a histologic diagnosis, but it can be reasonably assumed to be present with signs of autoimmune thyroid disease. These can include any of the following:

- Serum antibodies against thyroid proteins such as thyrogloblin (TG) or thyroperoxidase (TPO), although 10% to 15% can be antibody-negative.
- Diffuse enlargement of the gland detected by physical examination, ultrasound, or computed tomography.

- Diffuse iodine uptake and glandular enlargement on radioiodine uptake scan.

If a histologic assessment is done via biopsy, fine-needle aspiration, or after thyroidectomy, the typical findings are cellular infiltration of immune cells, especially lymphocytes.

The variables that predict Hashimoto's thyroiditis are family history of thyroid disease of any type and exposure to environmental triggers. Certain toxins are known to be taken up via the sodium iodide symporter and concentrated within the thyroid follicles. Such toxins generate free radicals, which activate immune responses and possibly sensitize immune cells to surrounding thyroid proteins.

Chemicals that are documented to correlate with Hashimoto's disease include:

- Iodine (in excess or when intake increases significantly)
- Perchlorate
- Fluoride
- Lithium
- Mercury
- Bisphenol A
- Teflon

Autoimmune thyroid disease can exist in the absence of serum hypothyroidism, although those with autoimmune thyroid disease progress to hypothyroidism in almost all cases. The presence of Hashimoto's disease raises the risk of having or developing other autoimmune diseases.

Other causes of clinical hypothyroidism include thyroid surgery and ablation and postpartum hypothyroidism, which is a transient form of hypothyroidism, affecting 5% to 10% of women in the United States.

Subclinical Hypothyroidism and Hypothyroidism Syndrome

Classically defined, in subclinical hypothyroidism TSH is elevated while serum thyroid hormone levels are normal. Using this criterion, subclinical hypothyroidism is a relatively common finding in primary care, affecting 2% to 7% of adults.[10] Subclinical hypothyroidism has been shown to be linked to an increased risk for cardiovascular disease.[19]

Thyroid disease in the absence of overt laboratory findings can more accurately be called "hypothyroid syndrome." It can be defined by the following clinical findings:

- The presence of hypothyroid symptoms
- The absence of other explanatory diseases
- Possible functional thyroid abnormalities as found on basal body temperature (BBT) and Achilles' reflex testing

In addition, one or more of the following objective findings will help to confirm the presence of thyroid disease:

- Suboptimal blood levels
- Abnormal antibody studies
- Abnormal findings on ultrasound
- Abnormal findings on fine-needle aspiration of the thyroid

Most patients with hypothyroid syndrome may have early Hashimoto's disease, although some cases can be attributed to impaired thyroid hormone synthesis or conversion related to nutritional deficiencies or environmental toxins.

DIAGNOSTIC CONSIDERATIONS

Before the use of blood measurements, it was common to diagnose hypothyroidism on the basis of BBT (the temperature of the body at rest) and Achilles' reflex time (reflexes are slowed in hypothyroidism). With the advent of sophisticated laboratory measurement of thyroid hormones in the blood, these "functional" tests fell by the wayside. The normal BBT is 97.6° F to 98.2° F. Patients are given instructions for taking BBT as outlined in Appendix 9. Many consider BBT to be an indicator of thyroid status, yet it is affected by many other variables, including adrenal function, body composition, activity level, menstrual status, and immune function. In effect, therefore, it has very little specificity for thyroid function. Furthermore, reliance on BBT as a factor superseding blood levels in determining optimal thyroid dosing can expose patients to dangerous supraphysiologic doses of thyroid hormones. It can, however, be used as a general indicator within the context of a complete clinical evaluation.

It is important to also discuss Wilson's temperature syndrome (WTS), based on the work of Denis Wilson who claims that many people have hypothyroid symptoms yet normal thyroid lab tests due to the excessive conversion of T_4 into rT_3 within the cell membrane, so that lab tests are not reflective of serum T_3 or rT_3. T_4 accounts for 90% of the hormone secretion by the thyroid; however, the form that affects the cells the most is T_3, which cells make from T_4. If the cells cannot convert T_4 to the four times more active T_3, a person can have normal levels of thyroid hormone in the blood yet be thyroid-deficient. Wilson's temperature syndrome designates the presentation of symptomatic hypothyroidism in the absence of blood abnormalities due to deficient peripheral conversion of T_4 to T_3.[20] Unfortunately, there is currently little support for this hypothesis in the medical literature or any way of accurately assessing this conversion, since Wilson states that serum levels of T_3 or rT_3 do not correlate with intracellular levels. The closest known correlate is a phenomenon called euthyroid sick syndrome, which is known to occur during or after severe metabolic stress. With this condition, there are no defects of hypothalamic/pituitary or thyroid function, yet there is a transient elevation of serum rT_3 relative to T_3. It is held that during metabolic crises, the body is able to alter peripheral conversion of T_4 to beneficially slow metabolic processes. This effect is known to last for brief periods, usually 3 weeks or less, and to reverse itself spontaneously.

Wilson claims that by taking ascending and descending doses of compounded sustained release T_3, the positive feedback loop from excess rT_3 is broken and cells are able to form T_3 again as needed. During these cycles, doses of T_3 as high as 100 mcg are routinely used in patients without overt hypothyroidism, exceeding the typical full replacement dose for adults without endogenous thyroid secretion by more than twofold. Unfortunately this protocol carries with it significant risk, and some fatalities have been noted.

Clinical Assessment

A clinical score based on the Colorado Thyroid Disease Prevalence Study has been created to simplify the process of symptom evaluation in suspected hypothyroid patients. In this study of over 25,000 people, it was shown that many patients with significant symptoms did not have clinical hypothyroidism as defined by the overly strict definition of severely elevated TSH and low T_4. Of many symptoms surveyed, those listed in Table 177-1 served as the best predictors of hypothyroidism.

Laboratory Evaluation

When the practitioner is presented with pertinent symptoms and examination findings, testing makes possible confirmation of the diagnosis and refutation of other causes. When clinically indicated, thyroid screening ideally would include a marker of thyroid regulation (TSH), markers of thyroid output (free T_4, free T_3) and markers of thyroid inflammation (thyroid microsomal antibody;

TABLE 177-1 **Accuracy of 12 Symptoms and Signs in the Diagnosis of Primary Hypothyroidism**

	SENSITIVITY (%)	SPECIFICITY (%)	POSITIVE PREDICTIVE VALUE (%)	NEGATIVE PREDICTIVE VALUE (%)	SCORE IF PRESENT
Symptoms					
• Impairment of hearing	22	98	90	53	1
• Diminished sweating	54	86	80	65	1
• Constipation	48	85	76	62	1
• Paraesthesia	52	83	75	63	1
• Hoarseness	34	88	73	57	1
• Weight increase	54	78	71	63	1
• Dry skin	76	64	68	73	1
Physical signs					
• Slow movements	36	99	97	61	1
• Periorbital puffiness	60	96	94	71	1
• Delayed ankle reflex	77	94	92	80	1
• Coarse skin	60	81	76	67	1
• Cold skin	50	80	71	62	1
Sum of all symptoms and signs					12

Data from Zulewski H, Müller B, Exer P, et al: Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls. J Clin Endcrinol Metab 1997; 82: 771-776.

thyroperoxidase antibody; antithyroglobulin antibody). The American Thyroid Association recommends TSH screening every 5 years beginning at age 35.[15]

The diagnosis of hypothyroidism by laboratory methods is primarily based on the results of total T_4, free T_4, T_3, and TSH levels (Table 177-2 lists normal levels). The diagnosis is straightforward in overt cases (Table 177-3). In subclinical cases, the diagnosis is clear but the benefit of treatment in the absence of symptoms is debated. An elevation in TSH with a normal T_4 level is considered subclinical. The accepted normal TSH range is extremely broad, 0.35 to 5.50 mIU/mL. In some conventional circles, treatment is not recommended unless the TSH is greater than 10 mIU/mL. Given the importance of adequate thyroid hormone to human health, our recommendation is more aggressive.

Patients with a combination of subclinical hypothyroidism and objective signs of autoimmune thyroiditis can benefit from TSH reduction. This can be achieved through diet and lifestyle changes and possible thyroid replacement therapy.

THERAPEUTIC CONSIDERATIONS

Figure 177-1 provides an algorithm for managing hypothyroid patients; it combines clinical evaluation, BBT, and laboratory evaluation. Although the conventional diagnostic model may be too restrictive, relying solely on symptoms or BBT to determine who needs thyroid treatment will often lead to many attempts ending in side effects and no benefits. Furthermore, if such measures are used as the sole factors for determining which thyroid patients need dose increases, many will end up on dangerous supraphysiologic doses. Adult patients who have reached full physiologic doses of thyroid (2-2.5 gr) and have TSH scores lower than 1.0 should be considered to have maximal improvement from thyroid treatment. Since superphysiologic doses speed the rate of T_4 degradation, further increases in dosage will not yield any lasting benefit. Higher doses should also be discouraged because a chronically suppressed TSH raises the risk of dementia, atrial fibrillation, and osteoporosis.

TABLE 177-2 **Normal Value of Serum Thyroid Hormone**

T_4	4.8-13.2 mg/dL
Free T_4	0.9-2 ng/dL
T_3	80-220 ng/dL
Thyroid-stimulating hormone	0.35-5.50 mIU/mL

Patients with "hypothyroid syndrome" can be predicted to have a positive clinical response to thyroid treatment when they possess all of the following characteristics:

- Objective signs of early Hashimoto's disease. This would include positive serum antibodies or abnormalities on thyroid anatomy evidenced by examination or ultrasound.
- Pertinent hypothyroid symptoms. These include the highly sensitive symptoms gleaned from the Colorado study delineated earlier.
- Suboptimal thyroid blood levels. TSH scores greater than 2.5 raise the likelihood of Hashimoto's disease and hypothyroid symptoms.[21]

Patients with less sensitive hypothyroid symptoms such as overweight, depression, or poor libido, yet lacking the above three criteria can be predicted to respond poorly to thyroid treatment even if they possess low BBTs or delayed Achilles' tendon reflexes.

Diet/Food Allergy

A clear correlation exists between autoimmune diseases, intestinal permeability, and food allergy. One study of patients with celiac disease revealed that 2% had overt autoimmune thyroid disease. Six months after these patients began a gluten-free diet, their serologic autoantibody markers became undetectable.[22] Because many people, including autoimmune thyroid patients do harbor subclinical allergies to wheat and other foods, an elimination diet, detoxification regimen (see Chapters 15 and 53), or both may be of use to decrease antigen load and strengthen gut integrity and thereby beneficially modify autoantibody activity.

TABLE 177-3 **Laboratory Findings In Thyroid Disease**

DISEASE	PRIMARY HYPOTHYROIDISM	SECONDARY HYPOTHYROIDISM	TERTIARY HYPOTHYROIDISM	PERIPHERAL HYPOTHYROIDISM
THRH	High/normal	High	Low/normal	Normal/high
TSH	High	Normal/low	Low/normal	Normal/high
Free T_4	Low	Low	Low	Normal
Free T_3	Low/normal	Low/normal	Low/normal	Low
Reverse T_3	Normal	Normal	Low/normal	Normal/high

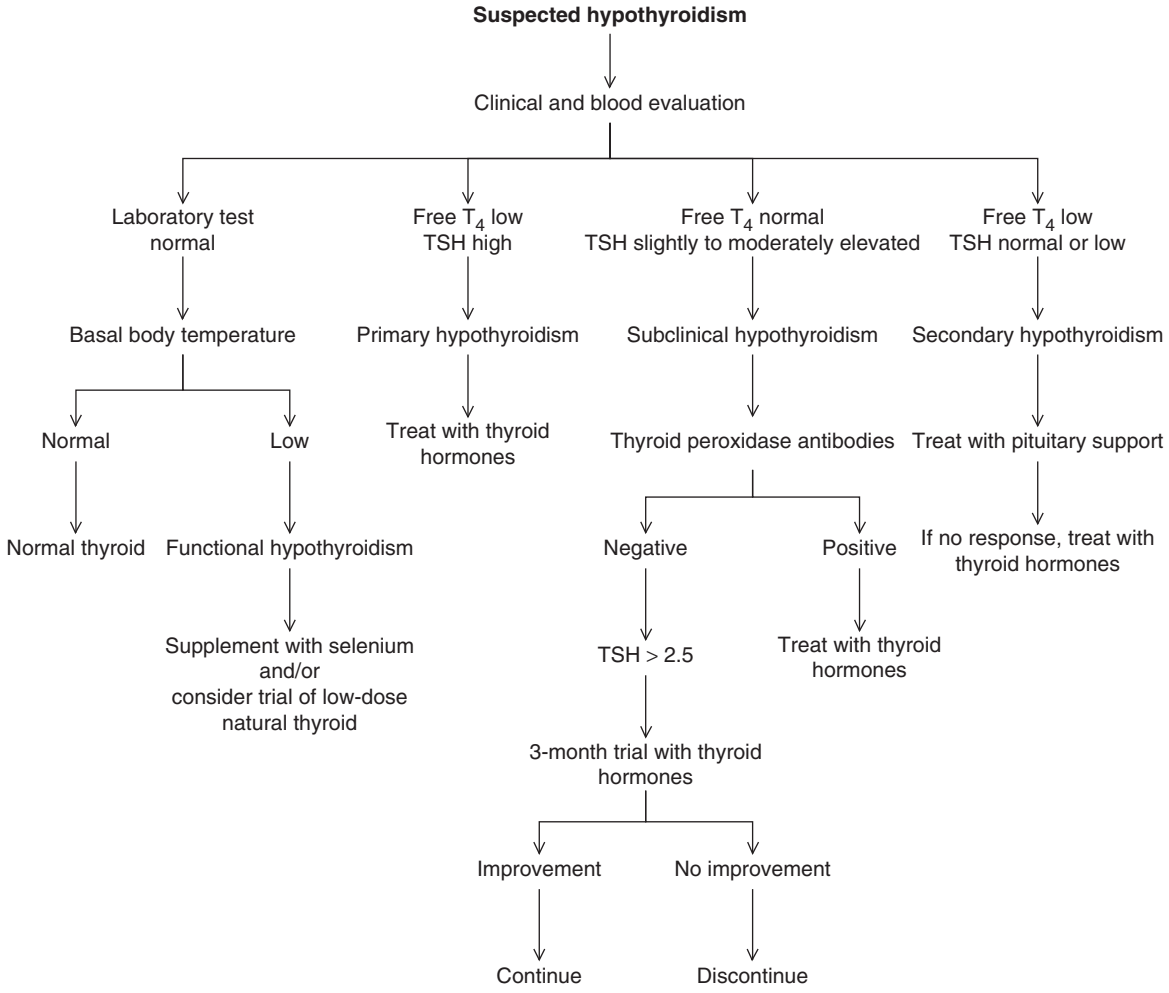


FIGURE 177-1 Hypothyroidism diagnostic flowchart.

Physiologic/Hormonal Considerations

Thyroid-binding globulin (TBG) is a protein made in the liver that transports thyroid hormones, including 75% of circulating T_4. Certain factors may lead to increased TBG levels, including excess estrogen conditions like pregnancy and oral estrogen supplementation regimens from birth control pills and hormone replacement therapy.[23] Tamoxifen therapy for breast cancer[24] and liver diseases also increase TBG levels. High TBG levels can hinder the availability of free thyroid hormone for use in the peripheral tissues, thus contributing to a hypothyroid symptomatology. Depending on the clinical picture, it may be useful to moderate hormonal excesses by decreasing the intake of oral estrogens, changing to nonoral regimens that do not involve a "first pass" through the liver, or helping the liver to more efficiently metabolize these estrogens.

Nutritional Considerations

It is important to support the thyroid gland nutritionally by ensuring an adequate intake of the key nutrients required in the manufacture of thyroid hormone and by avoiding goitrogens.

Iodine, Tyrosine, and Goitrogens

Thyroid hormones are made from iodine and the amino acid tyrosine. The recommended dietary allowance (RDA) for iodine in adults is quite small: 150 mg. The average intake of iodine in the United States is estimated to be more than 600 mg/day. Too much iodine can actually inhibit thyroid gland synthesis. For this reason and because the only role of iodine in the body is to provide for thyroid hormone synthesis, it is recommended that dietary levels or supplementary iodine not exceed 600 mg/day for any length of time.

Deficiencies of iodine intake are rare since the addition of iodine to salt. However, goitrogens can induce an iodine deficiency by combining with the iodine and making it unavailable to the thyroid. These foods are listed later under "Diet". In general, cooking inactivates them. This is not to suggest that these foods should not be eaten but rather that they should not be eaten in excess.

Vitamins and Minerals

Zinc, vitamin E, and vitamin A function together in many body processes, including the manufacture of thyroid hormone. A deficiency of any of these nutrients would result in the production of lower levels of active thyroid hormone. Low zinc levels are common in the elderly, as is hypothyroidism.[25] There may be a correlation. The B vitamins riboflavin (B_2), niacin (B_3), and pyridoxine (B_6) and vitamin C are also necessary for normal thyroid hormone manufacture.

The trace minerals zinc, copper, and selenium are the required cofactors for iodothyronine iodinase, the enzyme that converts T_4 to the far more active T_3. This enzyme has several different forms, each requiring a different trace mineral. Supplementation with zinc (the second most common mineral deficiency) has been shown to reestablish normal thyroid function in hypothyroid patients who were zinc-deficient even though they had normal serum T_4 levels.[26]

Similarly, selenium supplementation may be important, since those living in areas where selenium is deficient have a greater incidence of thyroid disease.[27] Of particular significance is the fact that although a selenium deficiency does not decrease the conversion of T_4 to T_3 in the thyroid or the pituitary, it does result in a great decrease in this conversion in other cells of the body.[28] People with a selenium deficiency have elevated levels of T_4 and TSH. Supplementation with selenium results in a decrease in T_4 and TSH and a normalization of thyroid activity.[29] Moreover, selenium is known to decrease thyroid antibody levels in autoimmune thyroid conditions.[30] Selenium is deficient in the diets of about 50% of the population, which may account for the large number of people with low thyroid activity.[31] This research appears to demonstrate clearly that a selenium deficiency results in low thyroid activity in the cells even though hormone levels are normal or even elevated; it provides some support for Barnes' contentions.

Antioxidant supplementation has been shown to increase thyroid function in rats with methimazole-induced hypothyroidism. Statistically significant results were reported in rats given vitamin C, vitamin E, and *Curcuma longa* (turmeric) extract with decreased abnormal thyroid weight changes, less suppression of T_4 and T_3, and attenuated increases in cholesterol levels.[32] Furthermore, in one animal study, thyroid hormone abnormalities also correlated with decreased glutathione antioxidant status in testicular tissues.[33] There are no human studies to corroborate these findings. However, given the safety and beneficial profile of these supplements, it seems a reasonable approach to consider them in an antiinflammatory, antioxidant treatment regimen.

Exercise

Exercise is particularly important in a treatment program for hypothyroidism. Exercise stimulates thyroid gland secretion and increases tissue sensitivity to thyroid hormone. Many of the health benefits of exercise may be a result of improved thyroid function. These benefits are especially important in overweight hypothyroid individuals who are dieting. A consistent effect of dieting is a decrease in the metabolic rate as the body strives to conserve fuel. Exercise has been shown to prevent the decline in metabolic rate in response to dieting.[34]

Thyroid Hormone Replacement

If nutritional and lifestyle interventions are inadequate to reestablish normal thyroid activity, the prescription of thyroid hormones is necessary. Several thyroid hormone preparations are available, each with advantages and disadvantages. Conventional treatment is administration of oral tetraiodothyronine/levothyroxine sodium (T_4). Levothyroxine preparations are bioidentical to human tetraiodothyronine and readily absorbed orally. The half-life of tetraiodothyronine is roughly 7 days; therefore, once-daily dosing is adequate for steady blood levels. For maximum and consistent absorption, it is best to take thyroid hormones at least one half hour before food and beverages other than water. Morning administration is preferred to mimic the circadian thyroid cycle.

Dosages are titrated to reduce TSH to within its normal range and to elevate T_4 to its normal range. The most common starting dose is 50 mcg (0.05 mg); the most common ending doses range from 88 to 137 mcg for women and 100 to 150 mcg for men.

Some patients who remain clinically hypothyroid may be demonstrated to poorly deiodinate levothyroxine (T_4) into triiodothyronine (T_3). In these cases oral T_3 is given. One is liothyronine (Cytomel). Like T_4, T_3 is well absorbed orally and easily bound by many nutrients. Its half-life is roughly 2 ½ days, so once-daily dosing can still work. Commonly used dosages are 5 or 10 mcg daily.

Although synthetic hormones have become popular, many physicians (particularly naturopathic physicians) still prefer the use of natural desiccated thyroid (NDT) complete with all thyroid hormones, not just thyroxine. Many people in the standard medical community believe that only T_4 replacement is necessary because the body's peripheral tissues will reliably convert T_4 to T_3. However, studies in rats whose thyroids were removed demonstrated that normal tissue levels of T_4 and T_3 were achieved only with an infusion of T_4 and T_3, and not by T_4 alone.[35] The medical literature confirms that physicians recognize many patients treated with desiccated thyroid do tend to feel better.[15] The advantage of NDT is that it provides both T_4 and T_3, as well as T_2 and relevant amino acids and micronutrients (including 0.2% iodine per table). The main drawback often cited by those who prefer thyroxine is that NDT lacks consistency. However, according to the U.S. Pharmacopoeia (USP), these preparations must contain not less than 85% and not more than 115% of the labeled amount of T_4 and not less than 90% and not more than 110% of T_3. The labeled amount is 38 mcg of T_4 and 9 mg T_3 per grain (65 mcg). The equivalencies of the thyroid agents based on clinical response are as follows:

- 100 mcg of T_4 (e.g., Synthroid)
- 20 to 25 mcg of T_3 (e.g., Cytomel)
- 1 grain of desiccated thyroid
- 12.5 mcg of T_3 + 50 mcg of T_4 (e.g.,Thyrolar)

Values for the different forms of thyroid hormones are referred to here as 1 "thyroid unit." Therefore, 0.5 thyroid unit would be equal to 50% of the values shown in the list.

THERAPEUTIC APPROACH

Natural treatment strategies for normalizing thyroid function vary depending on whether there is an autoimmune hypothyroid condition, Wilson's syndrome, or subclinical or clinical hypothyroidism.

Treatments for Autoimmune Hypothyroidism (Hashimoto's Disease)

Thyroid Replacement

The use of thyroid replacement achieves two objectives in the autoimmune hypothyroid patient: the normalization of decreased

thyroid hormone levels and the suppression of thyroid activity, thus decreasing autoimmune processes. Either desiccated or synthetic thyroid replacement may be used in high enough doses in order to decrease TSH to 0.1 or 1.5, the levels found in healthy euthyroid populations. It should be noted that some reports say that TSH values equal to or less than 0.1 mIU/mL may carry a risk of numerous hyperthyroid side effects as well as atrial fibrillation; also that they are associated with bone density losses but not additional fracture.[9]

Desiccated thyroid is thought to be beneficial by stimulating blocking antibodies to antithyroid antibodies and by acting as decoys for thyroid antibodies.[20] Some patients are found to recover from Hashimoto's thyroiditis after an extended treatment time with thyroid hormone and no longer need to be maintained on replacement.[20] Some patients may not benefit from desiccated thyroid, possibly owing to an adverse reaction to antigenic thyroid substances. These patients should promptly be placed on a synthetic thyroid instead. In either case, frequent TSH and antibody tests are essential in order to verify the suppression of thyroid activity and monitor autoimmune activity. One caveat: a common occurrence, often early in Hashimoto's disease, where a hyperthyroid picture is more prevalent. In this case, thyroid replacement may be contraindicated.

Diet/Lifestyle

Food elimination, detoxification, and gut healing options may be useful treatments aimed at ameliorating a possible root factor of antigenic autoimmune activity (see Chapter 15).

Other Recommendations

Dehydroepiandrosterone (DHEA) is a beneficial supplement in the treatment of a number of autoimmune conditions.[36] Although many clinical studies have employed high dosages (100 to 200 mg/day), much lower ones in the physiologic range of 5 to 10 mg/day in women and 10 to 20 mg/day in men may be beneficial and safe. Untoward effects such as hirsutism and acne have been observed in a minority of patients using high doses.[36] Therefore, it may be best to start at a low level and increase slowly while monitoring for DHEA blood levels and clinical symptoms of excess androgens. Because the long-term effects of DHEA administration are unknown, DHEA should be used with caution, particularly in patients at risk for developing hormone-dependent cancers.[37]

Selenium at 200 mg/day is recommend for Hashimoto's autoimmune thyroiditis, especially in those patients who have high titers of antithyroid peroxidase (TPO) antibodies.[30]

Treatments for Nonautoimmune Overt or Subclinical Hypothyroid Disorder

Diet

The diet should be low in raw goitrogens and high in foods rich in the trace minerals needed for thyroid hormone production and activation. Goitrogens to be limited include foods of the genus *Brassica* (such as turnips, cabbage, rutabagas, mustard greens, radishes, horseradishes) as well as cassava root, soybeans, peanuts, pine nuts, and millet. When eaten, these foods should be cooked to break down their goitrogenic constituents. Good sources of iodine include sea fish, sea vegetables (kelp, dulse, arame, hijiki, nori, wakame, kombu), and iodized salt. Good sources of zinc include seafood (especially oysters), beef, oatmeal, chicken, liver, spinach, nuts, and seeds. Copper is found in liver and other organ meats, eggs, yeast, beans, nuts, and seeds. Finally, the best sources of the B vitamins are yeast, whole grains, and liver. The best source of selenium is Brazil nuts, especially those that are unshelled. Organically grown foods should be recommended owing to their higher levels of trace minerals.

Supplements

- Zinc: 20 to 30 mg/day
- Copper: 1 to 2.5 mg/day
- Selenium: 200 to 400 mcg/day
- Vitamin C: 1 to 3 g/day in divided doses
- Vitamin E: 200 to 400 IU/day

Thyroid Hormones

Treatment should begin at levels ranging from 0.5 to 2 thyroid units (see earlier discussion) daily based on the patient's size and serum hormone levels. Reevaluation of basal body temperature, TSH, T_4, T_3, and free T_4 levels 4 to 6 weeks after initiating therapy is recommended, the treatment goal being to normalize basal body temperature as well as serum hormone levels. After stabilization of dosage, periodic evaluations are based on the individual patient's needs or are recommended to be carried out at least once a year.

In the treatment of hypothyroid syndrome, the dosage should be no more than 0.5 thyroid unit daily for at least the first 3 months of treatment.

Thyroid hormone replacement therapy is recommended to be taken on an empty stomach so as to increase absorption. The patient should avoid taking thyroid hormones at the same time as other medications and supplements (especially those containing iron), which may affect absorption. Once-a-day dosage generally produces stable increases in thyroid hormone levels.

The dosage of thyroid hormone during pregnancy will likely have to be increased owing to the effects that estrogens have on increasing serum thyroid hormone–binding globulin, thereby reducing the level of free thyroxine. Careful monitoring is required during pregnancy. Typically dose requirements increase by 30% to 50% during pregnancy and return to prepregnancy levels shortly after delivery.

Exercise/Physical Therapy/Lifestyle

Invigorating activity such as water sports, avoidance of overheated environments, and cold hydrotherapy can stimulate thyroid function.[20]

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CHAPTER 178

Infectious Diarrhea

Peter B. Bongiorno, ND, LAc

DIAGNOSTIC SUMMARY

- Increased bowel movement frequency (usually more than three bowel movements per day)
- Increased stool liquidity
- Abdominal pain
- A sense of fecal urgency
- Fecal incontinence
- Perianal discomfort
- Blood, mucus, or both, possibly present in the stool

GENERAL CONSIDERATIONS

Diarrhea is not only an important clinical entity but has also played a central role in the course of human history. Since the ancient times of Herodotus, the "father of history," diarrhea has had a particularly significant effect on the course of military strategies and consequently on world events. Infectious diarrhea has modified wartime outcomes of the Roman Empire and the Crusades as well as the relatively modern-day military campaigns of Henry V, the Civil War, World War I, and World War II.[1] Walt Whitman, who visited the sick and wounded Union soldiers in Washington, D.C. hospitals, wrote that war consisted of "about 999 parts diarrhea to 1 part glory."[1]

Because there is considerable variation in normal bowel habits, a precise definition of the term *diarrhea* does not exist. Diarrheal disease can be classified into three major clinical syndromes: acute watery diarrhea, bloody diarrhea, and persistent diarrhea. For most patients, any increase in stool mass, stool frequency, or stool fluidity is perceived as diarrhea. For most adults, this consists of a daily stool production in excess of 250 g containing 70% to 95% water. More than 14 L of fluid may be lost daily in severe cases.[2] Low-volume, painful, bloody diarrhea is known as dysentery.

Even today diarrheal illness is a common cause of morbidity and mortality. Infectious agents cause more than 200 million cases of diarrhea in the United States yearly.[3] Although it is a major cause of mortality in developing nations, infectious diarrhea also has significant costs in developed nations in terms of hospitalization and lost time.[4] Intestinal infection is the most common cause of diarrhea worldwide and is responsible for the deaths of 3 to 4 million individuals annually, the majority of whom are preschool-age children.[5] According to the World Health Organization, nearly 2 million children die each year because of diarrheal illness.[1] Despite these alarming statistics, approximately 90% of cases of acute diarrhea are mild and self-limited and respond within 5 days to simple rehydration therapy or antidiarrheal agents.[6]

INFECTIOUS AGENTS AND SYMPTOMS

An increasingly wide variety of viral and bacterial agents are being recognized as causes of serious diarrheal illness.[3] Overall, the causes of infectious diarrhea can be categorized as viral, bacterial, or parasitic. In general, these pathogens create a diarrheal effect by inhibiting intestinal absorption and increasing secretion; in causing inflammation, they promote secretory and exudative diarrheal symptoms.

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Viral Agents

Viruses are important causes of diarrhea. In healthy adults, the clinical manifestation of viral diarrhea is generally an acute, self-limited gastroenteritis. Although at least 25 different bacteria and protozoa can cause an identical clinical syndrome, greater than 75% of diarrhea-associated cases of gastroenteritis are caused by viruses. Viruses are suspected when vomiting is prominent, the incubation period is longer than 14 hours, and the entire illness is over in less than 72 hours. Viral pathogens are likely when there are no warning signs of bacterial infection (such as high fever, bloody diarrhea, severe abdominal pain, more than 6 stools in 24 hours) and there are no epidemiologic clues from the history (i.e., travel, sexual contact, antibiotic use) suggesting an alternative diagnosis.[7]

Rotavirus

Rotavirus is one of the most ubiquitous agents of diarrhea. It can contribute to an acute, dehydrating diarrhea in children and is estimated to cause more than 800,000 annual deaths of young children in developing countries.[8] Rotavirus-associated diarrheal disease is seasonal; in the United States it begins in the autumn in the Southwest and ends in the spring in the Northeast. Rotaviruses are spread via a fecal–oral route that includes person-to-person transmission. Although the precise mechanisms of disease have yet to be fully elucidated, rotaviruses are known to infect the villous enterocytes of the small intestine and cause a watery diarrhea. In addition to diarrhea, patients often have fever and vomiting.[9]

Parvovirus (Norwalk Virus)

Often categorized within the family of the Norwalk virus are the caliciviruses, also referred to as Norwalk-like viruses or small, round-structured viruses. The Centers for Disease Control and Prevention (CDC) estimates that 66% of 13.8 million cases of food-related illnesses are caused by these viruses each year in the United States. This family of viruses is often suspected when acute gastroenteritis sweeps through a semiclosed community (e.g., family, school, residential home, hospital, ship, dormitory).[7] These viruses are transmitted through contaminated food and water or from person to person. Sources of outbreaks have included well water, raspberries, lunch meat, and, in several instances, oysters.[9] Individuals infected by caliciviruses experience nausea/vomiting, diarrhea, abdominal cramping, and headache; low-grade fever, malaise, and myalgias also occur.[9]

Cytomegalovirus

Cytomegalovirus (CMV) is present in a latent state in most people, having been acquired either at birth or through sexual or parenteral exposure. CMV comes out of latency when there is strong allergenic or antigenic stimulation of the immune system. Often those with severe immunodeficiency also have activation and replication of CMV. When CMV becomes active in the bowel wall, gastrointestinal disease may occur. The disease is seen primarily in patients with severe immune deficiency such as acquired immunodeficiency syndrome (AIDS), transplantation, and cancer chemotherapy[7] and is a major cause of diarrhea in these conditions.

Epstein-Barr Virus

By the age of 20 years, almost all adults are infected with Epstein-Barr virus (EBV). This virus infects B cells and then persists for life because these cells proliferate indefinitely. Proliferation is usually controlled by virus-specific cytotoxic T lymphocytes. EBV causes diarrhea mainly in immunocompromised patients.

Bacterial Agents

Escherichia coli

At least four distinct varieties of diarrheogenic *Escherichia coli* exist: enterotoxigenic (ETEC), enterohemorrhagic (EHEC), enteroinvasive (EIEC), and enteroadherent. In North America, the most prominent diarrheogenic *E. coli* is the EHEC serotype, *E. coli* O157:H7.[9] Contaminated ground beef is the most common vehicle of transmission because contaminating bacteria are distributed throughout the meat during grinding and are not killed if hamburgers are undercooked. After an incubation period from 1 to 8 days, typical symptoms include abdominal cramping and diarrhea that can present as mild, moderate, or severe. Early in the disease course, bowel movements may be loose and watery; in time, however, they may contain gross blood. A subset of patients, often children, may develop the severe, life-threatening hemolytic-uremic syndrome, characterized by the clinical triad of hemolytic anemia, renal failure, and thrombocytopenia.[9]

Campylobacter jejuni

Campylobacter is part of the intestinal flora in many mammals. Contaminated and improperly cooked meat contributes significantly to the spread of disease. Unpasteurized dairy products, contaminated water, and other foods also may encourage transmission. Symptoms begin 1 to 7 days after ingestion of the bacteria and consist of fever, headache, and malaise. These may herald the onset of diarrhea and abdominal cramps by 1 to 2 days. The nature of the diarrhea varies from watery to bloody. *Campylobacter* enterocolitis is usually acute and self-limited over 7 to 10 days. Rarely, relapses, complications, severe disease, and death may occur.[9]

Clostridium difficile

C. difficile infection has become the most common cause of infectious diarrhea in hospitalized patients[10] and is most likely to affect the elderly. *Clostridium* can be catalyzed by the use of antibiotics.

Salmonella

The spread of resistant *Salmonella* strains continues to increase worldwide[11] and there are more than 2200 currently known serotypes. Spread chiefly through contaminated food, salmonella enteritidis accounts for 85% of all salmonella infections in the United States. Other prominent salmonella infections include *Salmonella typhi* and *Salmonella paratyphi,* which are responsible for typhoid fever. Nontyphoidal salmonellosis may present as fever, gastroenteritis-related diarrhea, and localized infections of the gastrointestinal tract, endothelial surfaces, pericardium, meninges, lungs, joints, bones, urinary tract, or soft tissues. Typhoidal symptoms include a gradual onset of fever, headache, arthalgias, pharyngitis, constipation, anorexia, and abdominal discomfort.

Shigella

Among the bacterial enteric pathogens, *Shigella* is unique in that ingestion of fewer than 200 organisms and possibly as few as 10 organisms may cause clinically apparent disease. *Shigella*, like other enteric pathogens, may be transmitted through contaminated food and water. However, person-to-person spread and transmission by flies may also occur, because so few organisms are necessary to cause disease.[9] The incubation period is usually 1 to 4 days. Adults present with nonbloody diarrhea with or without fever and possible gripping abdominal pain, urgency, and relief with defecation. As the infection progresses, episodes may increase with the presence of mucus and blood in the stool. Infections often resolve spontaneously in 4 to 8 days for mild cases or 3 to 6 weeks in severe cases.

Yersinia enterocolitica

Yersinia enterocolitica, like *Salmonella* and *Shigella*, is a member of the Enterobacteriaceae family. *Yersinia* species are significantly less frequent causes of bacterial enterocolitis in North America than elsewhere. Pathogenic strains of *Y. enterocolitica* are usually transmitted through fecally contaminated food or water but infrequently are transmitted by contaminated blood products. A 4-day to 7-day incubation period occurs, followed by watery to bloody diarrhea. This organism is invasive and demonstrates a propensity for lymphoid tissues, causing mesenteric lymphadenitis that may be clinically mistaken for acute appendicitis.[9] Disease usually resolves within 1 to 4 weeks, but occasionally complicating septicemia may develop, usually in patients with underlying disease.

Laribacter hong-kongensis[12]

Described and characterized in 2001, *Laribacter hong-kongensis* is a novel genus and species originally isolated from the blood and empyema pus cultures of a cirrhotic patient with bacteremic empyema thoracis. Since then, it has been described in six patients with diarrhea in Hong Kong and Switzerland. Although more extensive epidemiologic studies are necessary, there is reason to consider its role in future studies of diarrheal outbreaks worldwide.

Parasitic Agents

Diarrheal diseases caused by parasites still constitute the greatest single worldwide cause of illness and death. The problem is more severe in underdeveloped countries with poor sanitation, but even in the United States diarrheal diseases are a major cause of sickness and death. Furthermore, the ease and frequency of worldwide travel and increased migration to the United States are resulting in growing numbers of parasitic infections. In addition to normal inhabitants of the gastrointestinal system acting as parasites, there are also significant diarrheal diseases associated with protozoa and helminthes.

Giardia lamblia is the most frequent cause of parasitic enteritis in the United States and should be suspected in cases where history suggests recent hiking and drinking out of streams. Waterborne infection is also important in the developed world, particularly as a result of contamination of domestic water supplies with the cysts of *Giardia intestinalis* and *Cryptosporidium parvum.*[5] Other diarrhea-associated parasites include *Entamoeba histolytica*, *Microsporidium, Isospora belli,* and *Strongyloides* species.

Although the most commonly reported symptoms of parasitic infection are abdominal pain and cramping with concomitant explosive diarrhea, these symptoms do not occur in all cases. In fact, a growing number of individuals are experiencing milder than usual gastrointestinal symptoms due to parasitic infections or symptoms not traditionally considered to be linked to parasitic infections. For example, in some cases of irritable bowel syndrome, indigestion, and poor digestion, parasites may be causing the symptoms. In addition, parasitic infections are often an unsuspected cause of chronic illness and fatigue.

LABORATORY DIAGNOSIS

Numerous laboratory procedures exist for the analysis of patients with diarrhea. Bacterial cultures using selective media, detection of pathogen-specific genes using polymerase chain reaction (PCR), electron microscopic examination and antigen detection for viruses, as well as direct examination with or without using special stains for protozoa are some of the plethora of diagnostic tests available. Despite this wide array, a microbiologic cause is identified in only 50% of patients at best.[12] One hospital survey of more than 30,000 stool specimens sent for testing revealed a specific pathogen in only 5.6% of cases. In descending order, the most commonly identified pathogens were *Campylobacter jejuni*, *Salmonella, Shigella,* and *E. coli* O157:H7.[3]

Confounding this issue, it has been shown that substantial variation exists in the use of stool testing, which typically does not correlate with the clinical characteristics of affected patients.[3,13] One study has identified several important independent variables that may be predictive of positive stool culture in adult patients with a clinical picture of infectious diarrhea. These variables are month of presentation, fever, duration of abdominal pain at presentation, and requirement of intravenous fluid therapy. Surprisingly, this study demonstrated that neither a history of bloody diarrhea nor persistent diarrhea was associated with positive stool culture.[13]

In general, persons with diarrhea should be considered for testing if they are febrile or have bloody stool. When visible blood was present in the stool, more than one third of cases were caused by Shiga toxin–producing *E. coli* O157:H7.[3] Testing for ova and parasites is of low yield in most cases and should be run only when diarrheal illness persists for more than 7 days.[3]

THERAPEUTIC CONSIDERATIONS

Conventional Medicines

Although appropriate in certain cases, the antibiotics and opiates used to treat diarrhea are also well known to have their limitations, as many of these drugs adversely affect gastrointestinal motility; furthermore, increasing numbers of pathogens are proving resistant to antimicrobial agents. Increasing numbers of isolates resistant to antimicrobial agents and the risk of worsened illness (e.g., hemolytic uremic syndrome with Shiga toxin–producing *E. coli* O157:H7) further complicate antimicrobial and antimotility drug use.[3] Additionally, available antiperistaltic or antisecretory drugs to reduce the severity of diarrhea can cause serious side effects in children.[8]

Generally, selective antibiotic treatment is recommended for traveler's diarrhea, *Shigella*, and *Campylobacteria* infection. Bismuth salts (e.g., Pepto-Bismol) can be used for travel abroad in order to coat the intestinal lining and help prevent infection. The role of antibiotic therapy in salmonellosis and *E. coli* O157:H7 infection remains unclear. Avoidance of antimotility agents in bloody diarrhea is emphasized, especially when illness is caused by *E. coli* O157:H7, which could increase the risk of subsequent hemolytic-uremic syndrome. In select at-risk populations, wider use of vaccines, including oral typhoid vaccine and oral cholera vaccine (available only outside the United States) is recommended.[3]

Some newer therapeutic approaches include 5-HT_2 and 5-HT_3 receptor antagonists, calcium-calmodulin antagonists, and alpha-receptor agonists. These may be useful to avoid adverse affects on gastric motilility.[5]

Underlying and Predisposing Factors

Although a pathogenic agent is often responsible for infectious diarrhea, a number of host factors can predispose individuals to experience illness. Poor digestive function, which is often characterized by low stomach acid output or achlorhydria and inadequate pancreatic enzyme output, should be explored in

patients who are susceptible to infectious diarrhea. In these cases, hydrochloric acid and pancreatic enzyme supplementation may be advisable. Immunoglobulin A (IgA) antibodies help discourage epithelial adherence of pathogenic organisms. Depressed levels of secretory IgA can leave the immune system of the gastrointestinal tract feeble and unable to deal with pathogenic infection. Decreased intestinal motility, which can be caused by chronic stress and high sugar intake, can also allow microbes to flourish in an intestinal environment. Recurrent infectious diarrhea may be encouraged by food allergy and sensitivities as well.

The clinician should also be aware that many drugs may actually increase susceptibility to infectious diarrheal illness. Theses include proton pump inhibitors, antifolate drugs, and antibiotics. Hospitalized patients who receive proton pump inhibitors are at increased risk of *C. difficile*–induced diarrhea.[14-16] As in the case of achlorhydria, it is likely that inhibition of upper gastrointestinal digestive acids by proton pump inhibitors may allow pathogens and undigested food to reach the intestines without being properly broken down. Also, antibiotic-associated diarrhea is known to occur with broad-spectrum antibiotics.[17] Antibiotics can disrupt local bowel flora, allowing pathogenic organisms to flourish, and are well-known to leave patients susceptible to diarrhea (see "Probiotics," later).

Hydration/Electrolyte Balance

It is of paramount importance to keep the patient with diarrhea well hydrated and to assure electrolyte balance. This is most crucial in children. Of course rehydration does not treat the diarrhea itself, which will persist until the infection resolves. Signs of dehydration may include decreased or absent urination, decreased skin turgor, and dry tongue. Rehydration using solutions of glucose, sodium, and potassium is appropriate. In cases of severe dehydration with weight loss of more than 10% or unconsciousness, intravenous rehydration is indicated.[18]

Diet

Prevention of infectious diarrhea may be accomplished by avoiding undercooked meat or seafood, unpasteurized milk, or soft cheese.[3] Once the patient has symptoms, traditional use of the "BRAT diet" can usually help decrease gastric motility. The components of this diet are foods that can slow peristalsis and tend to be more binding. These are banana, white rice, apple, plain white toast or bread, and tea.

Evidence indicates that larger, less frequent meals are more taxing to the digestive and absorptive capacities of the gastrointestinal system. In one porcine study, 3-week-old piglets were assigned to one of four dietary regimens and were subsequently all infected with rotavirus, followed 24 hours later with enteropathogenic *E. coli*. The dietary regimen designed to tax the digestive and absorptive capacities of the piglets (a high nutrient intake with a three times a day feeding) significantly produced the most prolonged diarrhea as well as the most advanced colonization of the gut by hemolytic enteropathogenic *E. coli* and persistent shedding of rotavirus. The same nutrient intake divided into 24 equal increments and administered hourly produced a less severe response. The least severe diarrhea was seen in piglets fed one third the nutrient intake either hourly or three times a day.[19]

Traditional dietary preparations for diarrhea such as carrot soup and products based on rice can be useful by having essentially an absorbent power. They have been known to reduce stool output and the duration of diarrhea, although they may not necessarily diminish intestinal loss of water and electrolytes.[18,20]

One study evaluated the effects of green banana and pectin on intestinal permeability in 57 boys with persistent diarrhea. Green banana and pectin contain nondigestible dietary sources of colonic short-chain fatty acids. The patients were given a week's treatment with a rice-based diet containing either cooked green banana, pectin, or a rice diet alone. Intestinal permeability was assessed before and after treatment by giving a lactulose-mannitol (LM) drink and measuring urinary recovery after 5 hours. Treatment with banana significantly reduced lactulose recovery, increased mannitol recovery, and decreased the LM ratio, indicating improvement of permeability. Pectin produced similar results. Permeability changes were associated with a 50% reduction in stool weights, which correlated strongly with the LM ratio.[21] In a study of 154 male infants aged between 1 and 30 months, commonly allergenic soy- and casein-based diets were not helpful in alleviating persistent diarrhea, whereas yogurt and broken-down amino acid formulas were helpful in encouraging a significant reduction in stool output and in the duration of diarrhea.[22] Other studies also suggest, as an adjunctive measure for patients who experience vomiting, the administration of a small amount of glucose.[18]

Supplements

Vitamin A

The administration of vitamin A to children can reduce the incidence of severe diarrhea. One double-blind controlled trial examined 900 children from ages 1 to 5 with acute diarrhea. These young subjects were assigned to receive either 60 mg of vitamin A or a placebo. They were followed up at home on alternate days until they recovered from the diarrheal episode. In all study children, those treated with vitamin A had a significantly lower risk of persistent diarrhea. However, there was no change in the duration or average stool frequency. Interestingly, the group who was not breastfed had a shorter average duration of diarrhea. In these children, the mean number of stools passed after the intervention, the proportion of episodes lasting greater than 14 days, and the percentage of children who passed watery stools on any study day were also significantly lower in those treated with vitamin A.[23]

Folic Acid and Vitamin B_{12}

Studies are beginning to emerge correlating low levels of folic acid and vitamin B_{12} with increased susceptibility to diarrhea. Folic acid deficiency is known to promote malabsorption due to altered structure of the intestinal mucosal cells.[24] Thirteen patients diagnosed with megaloblastic anemia suffering from chronic diarrhea showed significant histologic changes of the ileal mucosa, including inflammation, atrophy, erosion and flattening of the villi, lymphatic ectasia, and focal fibrosis. When given folate and cyanocobalamin supplementation, these patients quickly demonstrated decreased diarrheal episodes as well as intestinal restoration.[25]

Antifolate chemotherapeutic drugs such as methotrexate can contribute to folic acid and vitamin B_{12} deficiencies and can cause or contribute to diarrheal symptomatology. Cancer patients treated with this class of drugs who had lowered folic acid and vitamin B_{12} were found to be more susceptible to subsequent development of serious drug-related toxicities such as myelosuppression, diarrhea, mucosal toxicity, and infection. This suggests that toxicity is related to relative folate deficiency in some cancer patients.[26] In this study, nutritional supplementation led to a marked reduction in toxicity and the abolition of treatment-related deaths without affecting the efficacy of the antineoplastic drugs.

Tangential to the conversation of infectious diarrhea and folic acid, there is a concern for neural tube defects (NTDs) with folic acid and vitamin B_{12} deficiency. It has been suggested that gastrointestinal disturbances such as those caused by diarrhea might negatively affect the availability of these vitamins to the pregnant mother and fetus, thereby increasing the risk of birth defects. In one study evaluating the risk of neural tube defects with periconceptional diarrhea, it was observed that one or more episodes of periconceptional diarrhea were associated with an increased risk of NTD-affected pregnancies compared with no episodes of diarrhea. This association was independent of fever, obesity, maternal age, maternal birthplace, income, prior unproductive pregnancy, and dietary plus multivitamin folate intake.[27] Whether the cause of diarrhea is infectious or of any other origin, it is prudent to ensure proper folic acid and vitamin B_{12} nutrition in women who are trying to conceive, as well as in newly pregnant women.

Folic acid supplementation appears to be without side effects, even at high doses (e.g., 15 mg/day). It has been reported that 8 of 14 healthy human subjects who consumed 15 mg/day of folic acid for 1 month developed abdominal distention, flatulence, nausea, anorexia, sleep disturbances with vivid dreams, malaise, and irritability.[28] This, however, has not been confirmed in a double-blind clinical study[29] and other investigations.[30,31] Vitamin B_{12} is not carcinogenic, teratogenic, or mutagenic. It is considered safe even at 1000 times the recommended daily allowance. However, during such treatment, care should be given to not take large amounts of folic acid, since this may mask the nerve damage associated with vitamin B_{12} deficiency.

Zinc

In recent years the nutritional importance of zinc has been established, as zinc deficiency and its symptoms have been well recognized. Diarrhea has been found to be one of the clinical manifestations of zinc deficiency. Zinc has demonstrated an antimicrobial effect on enteric pathogens such as *S. typhi, Salmonella, E. coli, Enterobacter, Shigella, Staphylococcus albus, Streptococcus pyogenes,* and *Vibrio cholerae*[32,33] and may contribute to the treatment of diarrhea. Zinc absorption occurs throughout the small intestine, not only in the duodenum, jejunum, and ileum. Many illnesses distinguished by chronic diarrhea entail insufficient absorption of zinc. In fact, in some cases of chronic enteropathies in infants, like celiac disease and cystic fibrosis, a deficiency of zinc has been isolated.[34]

Good dietary sources of zinc are meat, fish, and, to a lesser extent, human milk. *Acrodermatitis enteropathica* is a rare but severe disease in which skin lesions, chronic diarrhea, and recurring infections are the main symptoms. The disease is related to the malfunctioning of intestinal absorption of zinc and can be treated by administering pharmacologic doses of zinc orally. The amount of zinc absorbed in the small intestine is influenced by other nutrients: some compounds such as dietary fiber and phytates (which are found in foods including soy, wheat bran, peas, carob, and brown rice) may inhibit this process, whereas picolinic and citric acid facilitate it. Citric acid is thought to be the ligand that accounts for the high level of bioavailability of zinc in human milk.[34]

As a cautionary note, it is theoretically possible that some of the dietary treatments used by practitioners of natural medicine for persistent postenteritis diarrhea—such as elimination of cow's milk and increased fiber and carob powder as well as use of soy formula in infants—can contribute to a scarce supply of zinc and therefore promote the persistence of diarrhea itself.[34] Although these therapeutic approaches are being used, zinc supplementation may be warranted, especially if the patient tends to have diarrheal symptoms.

Glutamine

Glutamine is the most abundant amino acid in the blood. As one of the principal fuels used by the intestinal lining cells, it accounts for 35% of their energy production. Although glutamine is readily available in the diet and synthesized in the body, supplementation improves the energy metabolism of the gastrointestinal mucosa, thus stimulating regeneration.[35] Glutamine prevents intestinal mucosal damage and has been shown to decrease bacterial leakage across the intestines after they are damaged, presumably by stimulating repair.[36] Clearly, glutamine holds promise for enhancing the repair of mucosal injury by a wide range of infections or toxic agents and thus has great potential as a new oral rehydration and nutritional therapeutic for patients with enteric infection, malnutrition, or chemotherapy-induced or radiation-induced enteritis.[36]

Animal models have definitely shown the usefulness of this amino acid in diarrhea. Glutamine has been shown to enhance sodium and water absorption in a rabbit model of cholera and *Cryptosporidium*-infected piglet intestine and has proven effective in a bovine model of *Cryptosporidium* as well. One rat model of cholera toxin–induced diarrhea also showed that alanyl-glutamine (a more stable derivative of glutamine) enhanced water and electrolyte intestinal absorption even better than the traditional glucose solutions.[37]

In one double-blind clinical study of 128 healthy children ages 6 to 24 months old with acute diarrhea, 63 received 0.3 g/kg/day of glutamine while 65 controls received a placebo for 7 days. The average duration of diarrhea in the glutamine-treated group was significantly shorter than that in the placebo group (3.4 days vs 4.57 days, respectively).[38]

Glutamine, even at high doses, is without side effects and is well tolerated.[37] A typical dosage of glutamine is 100 mg three times a day (see Chapter 95 for a more comprehensive discussion of glutamine).

Probiotics

Lactobacillus and Saccharomyces. *Probiotics*, translated as "for life," are bacteria residing in the intestine that are considered beneficial to health. The most important healthful bacteria are *Lactobacillus acidophilus* and *Bifidobacterium bifidum.* Other bacteria (including such beneficial strains as *Lactobacillus casea, Lactobacillus fermentum, Lactobacillus salivores,* and *Lactobacillus brevis*) also become established in the gut (see Chapter 116 for an extensive discussion of these useful clinical agents).

A substantially growing body of scientific evidence has now demonstrated that lactobacilli and fermented foods play a significant role in human health. Probiotics are thought to have a protective effect against acute diarrheal disease and have been shown to be successful in the treatment or prevention of various types of infectious diarrhea including that due to rotavirus, *C. difficile,* and traveler's diarrhea.[4,39,40] Furthermore, studies show that probiotic supplementation may also prevent future nosocomial rotaviral gastroenteritis, thus demonstrating an immune-modulating effect of probiotics,[4,41] possibly by significantly increasing the number of cells secreting IgA. *Lactobacillus* sp. have also shown remarkable ability to inhibit *E. coli* O157:H7 but not *Salmonella* in refrigerated storage.[42] *Lactobacillus* may be considered as a future addition to stored foods used for low immune status and high susceptibility to *E. coli* O157:H7.

Children are especially susceptible to infectious diarrhea and its sequelae. In one double-blind, placebo-controlled study, a standard infant formula was supplemented with the probiotics *Bifidobacteria bifidum* and *Streptococcus thermophilus*. Subjects in

the probiotic group developed diarrhea at a statistically lower rate than those in the control group (7% vs 31%). Additionally, rotavirus shedding was decreased statistically in the probiotic group (10% vs 39%).[40] A second randomized placebo-controlled trial evaluated probiotics in a different but also high-risk population. In this case, 204 undernourished Peruvian children received *Lactobacillus GG (L. GG)* or placebo. Although a difference in rates of diarrhea was observed, where the treated group had statistically fewer episodes of diarrhea, the reduction was minor (from 6 episodes per child per year to 5.2 episodes per child per year). Interestingly, children who were breastfed did not seem to benefit at all, raising the possibility that probiotics provide a similar action as breast milk in the prevention of infection.[43] In a third double-blind study, 81 children aged 1 to 36 months were enrolled in a trial and randomly assigned at admission to receive 6×10^9 CFUs of *L. GG* or placebo twice daily orally for the duration of their hospital stay. The *Lactobacillus*-treated children enjoyed a dramatically reduced risk of nosocomial diarrhea of 6.7%, versus 33.3% in those who were not given the probiotic. Once again, the use of *L. GG* significantly reduced the risk of rotavirus gastroenteritis (2.2% vs 16.7%).[44]

Saccromyces boulardii, also known as *Saccromyces cerevisiae,* is a nonpathogenic probiotic yeast that may be most helpful in diarrhea caused by *C. difficile,* a pathogen most likely to affect the elderly. Although in the conventional medical world vancomycin is the preferred treatment of severe cases, *S. boulardii* alone or in combination with vancomycin has been reported to be an effective therapeutic alternative for recurrent infection.[10] Although it is generally safe, a few case reports have demonstrated that fungemia and sepsis are rare complications of the administration of *S. boulardii* in immunocompromised patients,[45] in whom it may be contraindicated. The daily adult dose is usually 1 g/day in divided doses (500 mg twice a day) for at least 4 weeks.

Corroborating earlier reviews,[46,47] the most recent Cochrane meta-analysis supports the use of probiotics to shorten the duration and reduce stool frequency in acute infectious diarrhea.[48] *L. acidophilus* has been shown to correct the increase of gram-negative bacteria observed following the administration of broad-spectrum antibiotics, as occurs with any acute or chronic diarrhea.[49-54] Similarly, a mixture of *B. bifidum* and *L. acidophilus* inhibited the lowering of fecal flora induced by ampicillin and maintained the equilibrium of the intestinal ecosystem.[52]

Although it is commonly believed that acidophilus supplements are not effective if taken during antibiotic therapy, the research actually supports use of *L. acidophilus* during antibiotic administration.[52,53] Reductions of friendly bacteria or superinfection with antibiotic-resistant flora, or both, may be prevented by administering *L. acidophilus* products during antibiotic therapy. A dose of at least 15 to 20 billion organisms is required. Probiotic supplements should, however, be taken as temporally far away from the antibiotic as possible.

Evidence indicates that the conventional medical world is beginning to take notice of the benefits of giving *Lactobacillus* with antibiotic therapy. In one double-blind, controlled study, the antibiotic containing ampicillin (250 mg) and cloxacillin (250 mg) with or without protected lactobacilli was evaluated in 740 patients undergoing cataract surgery. The incidence of diarrhea in patients receiving antibiotic alone was 13.3%, compared with 0% in patients receiving antibiotic with protected lactobacilli.[17] Although antibiotics should be used judiciously and only in cases where the benefits outweigh the risks, adjunctive therapy may decrease the untoward effects of antibiotic therapy on the gastrointestinal system.

Although many excellent companies provide high-quality probiotic products, it is difficult to sort through all of manufacturers' claims of superiority, and some products have been shown to contain no active *L. acidophilus*.[55] Only high-quality, laboratory-tested probiotics should be used.

Botanical Medicines

Berberine-Containing Plants

Berberine-containing plants include goldenseal *(Hydrastis canadensis),* barberry *(Berberis vulgaris),* Oregon grape *(Berberis aquifolium),* and goldthread *(Coptis chinensis).* Berberine, an alkaloid, has been extensively studied in both experimental and clinical settings for its antibiotic activity. Berberine exhibits a broad spectrum of antibiotic activity, having shown antibiotic activity against bacteria, protozoa, and fungi including *Candida albicans.*[56-62]

Berberine's antibiotic action against some of these pathogens is actually stronger than that of antibiotics commonly used for the disease these pathogens cause. Berberine-containing plants should be considered in infectious processes involving the previously mentioned organisms. Berberine's action in inhibiting *Candida,* as well as pathogenic bacteria, prevents the overgrowth of yeast, which is a common side effect of antibiotic use.

Diarrhea is a common symptom in patients with chronic candidiasis. Berberine has shown remarkable antidiarrheal activity in even the most severe cases. Positive clinical results have been shown with berberine in relieving diarrhea in cases of cholera, amebiasis, giardiasis, and other causes of acute gastrointestinal infection (e.g., due to *E. coli, Shigella, Salmonella,* and *Klebsiella*) and may also relieve the diarrhea seen in patients with chronic candidiasis.[63-69]

The dosage of any berberine-containing plant should be based on berberine content. Because there is a wide range of quality in goldenseal preparations, standardized extracts are preferred. Three-times-a-day dosages are as follows:

- Dried root or as infusion (tea), 2 to 4 g
- Tincture (1:5), 6 to 12 mL (1.5 to 3 tsp)
- Fluid extract (1:1), 2 to 4 mL (0.5 to 1 tsp)
- Solid (powdered dry) extract (4:1 or 8% to 12% alkaloid content), 250 to 500 mg

Note that the dosage recommendations for berberine would be 25 to 50 mg three times a day or a daily dosage of up to 150 mg. This dosage is consistent with the dosage range in the positive clinical studies in patients with gastrointestinal infections. For children, a dosage based on body weight is appropriate. The daily dosage would be the equivalent to 5 to 10 mg of berberine/kg (2.2 lb) body weight.

Because there is a wide range of quality in goldenseal preparations, standardized extracts are preferred. Berberine and berberine-containing plants are generally nontoxic at the recommended dosages; however, berberine-containing plants are not recommended for use during pregnancy, and higher dosages may interfere with B vitamin metabolism.

Potentilla tormentilla (Tormentil Root)

Tormentil root contains more than 15% tannic acid, which makes this plant astringent[70]; it may be useful in treating infectious diarrhea, shorten the duration of rotavirus diarrhea, and decrease the requirement for rehydration solutions.[8] A randomized double-blind placebo-controlled trial was conducted at a children's hospital in St. Petersburg, Russia. In this study, 40 children ranging in age from 3 months to 7 years with rotavirus

diarrhea were divided into two groups: a treatment group consisting of 20 children given 3 drops of tormentil root extract per year of life three times a day until discontinuation of diarrhea or a maximum of 5 days and a control group of 20 children who received a placebo.

The duration of diarrhea in the group treated with tormentil root extract was 60% less than that in the placebo group (3 days, compared with 5 days in the control group). In the treatment group, 8 of 20 (40%) children were diarrhea-free 48 hours after admission to the hospital, compared with 1 of 20 (5%) in the control group. Children in the treatment group also received smaller volumes of parenteral fluids than subjects in the control group.[8] For adults, a reasonable dose is 60 drops of tincture twice daily. Some clinicians find the powdered herb to be more effective in adults at a dosage of 1/4 tsp twice daily.[70]

Allium sativum (Garlic)

Garlic appears to affect DNA and RNA synthesis and is being investigated as an effective antibiotic. In vitro antimicrobial sensitivity tests on *E. coli, Shigella sp, Salmonella sp,* and *Proteus mirabilis,* found significant effects of garlic along with ciprofloxacin and ampicillin. The gram-negative diarrheagenic pathogens from the stool samples were highly sensitive to garlic, whereas ciprofloxacin was most effective against *E. coli*. The differences were inferred to result from genetic differences among the organisms and differences in the modes of action of the antibiotics. Most interestingly, no pathogens were resistant to garlic, which led the authors to conclude it was a promising antimicrobial agent.[71]

Other Antiparasitic Botanicals

A wide variety of botanicals have been used alone or in combination with antiinflammatory and demulcent herbs to specifically stop parasitic infections and heal the digestive tract. Curcumin has been shown to protect against castor oil– and carrageenan-induced diarrhea in rat models.[72] The Brazilian *Ocimum selloi* essential oil produced a significant reduction in the severity and frequency of diarrhea produced by castor oil while also reducing transit time in mice.[73] A Thai herbal formula called Pikutbenjakul—which contains *Piper longum*, *Piper sarmentosum*, *Piper interruptum*, *Plumbago indica,* and *Zingiber officinale*—has shown promise in in vitro work against some *Vibrio* species, *Salmonella*, *Shigella*, *Escherichia coli,* and *Staphylococcus aureus*.[74] Unfortunately, human clinical trials are lacking to corroborate the safety and efficacy of their use. Future studies should evaluate the potential benefits and toxicities of the following antiparasitic herbs: *Artemisia absinthium* (wormwood), *Chenopodium abrosioides* (wormseed), *Curcuma longa* (turmeric), *Phytolacca decandra* (pokeweed, pokeroot), *Juglans* species (black and white walnut), and *Tanacetum vulgare* (tansy).

Homeopathy

A meta-analysis of three double-blind clinical trials of diarrhea found that individualized homeopathic treatment decreases the duration of acute childhood diarrhea. In this review, 242 children ages 6 months to 5 years were analyzed as one group. Children were randomized to receive either an individualized homeopathic medicine or placebo to be taken as a single dose after each unformed stool for 5 days. Parents recorded daily stools on diary cards, and health workers made home visits daily to monitor the children. The duration of diarrhea was defined as the time until there were fewer than three unformed stools per day for 2 consecutive days. A meta-analysis of the effect–size difference of the three studies was also conducted. Combined analysis shows a statistically significant duration of diarrhea of 3.3 days in the homeopathy group versus 4.1 in the placebo group.

Homeopathics commonly included as possible remedies for diarrhea include podophyllum (which is well known for its almost universal application for traveler's diarrhea[75]), aloe, china, mercurius, phosphorus, nux vomica, sulfur, aconite, veratrum album, and arsenicum. Although these results must still be evaluated further with larger-scale studies, given the safety and historical effectiveness of homeopathy, it should be thoroughly considered as part of the natural medicine practitioner's therapeutic choices.

Acupuncture

From a traditional Chinese medicine perspective, diarrhea is generally due to an imbalance of large intestinal regulation as well as deficiency of the spleen and stomach. Although there are variations depending on a particular patient's presentation, the four basic diagnoses are diarrhea due to Cold-Damp, Damp-Heat, Spleen-Yang Depletion, and Kidney Yang deficiency. Typically, diarrhea caused by infectious pathogens falls into the category of Damp-Heat and may present with pain, mucus, and blood in the stool.

A few studies have shown the effect that acupuncture[76-78] and Chinese herbal preparations have on intestinal movement.[79,80] One study demonstrated that intestinal peristalsis was accelerated significantly by acupuncture at the abdomen but suppressed by moxibustion, which is the warming of certain acupuncture points with nearby burning *Artemisia argyi*.[77] Depending on the desired result, the acupuncture practitioner may want to focus on moxa therapy for some cases where slower peristalsis is desired. Two studies measured the influence of electrical stimulation of acupuncture points including ST-36 (Zusanli) and SP-6 (Sanyinjiao) on the myoelectrical activity of the small intestine; as a result, a clear ability of acupuncture to alter intestinal motility was recorded. One of these trials employed 3 Hz of electroacupuncture on the ST-36 (Zusanli) point and demonstrated increased regularity of the gastric myoelectrical system.[78] However, another evaluation did not find acupuncture plus electrostimulation to be effective enough to normalize gastric dysrhythmia after pretreatment with atropine.[81]

Animal research has supported the historical use of acupuncture for infectious diarrhea. The effect of acupuncture was evaluated in the treatment of 32 young pigs with induced enteropathogenic *E. coli* diarrhea. The animals were all inoculated with *E. coli* and then divided into three groups. One group, the controls, remained untreated; a second group was treated with the antibiotic enrofloxacin; and the third group was treated with traditional acupuncture using GV-1 (Jiaochao). Using histopathologic evaluation by hematoxylin-and-eosin stain, severe infiltration of inflammatory cells in the lamina propria was observed in the ascending and descending colon and in the fundic stomach of the untreated control group. Destruction of the fundic gland's architecture and necrotic lesions were also observed. However, in these same anatomic locations, the animals treated with acupuncture or antibiotics maintained a mucosa of the colon and stomach that were relatively similar to those of the normal group.[82] Another corroborating similar study of 34 animals employed Du-20 (Bai-hui), BL-20 (Pishu), CV-12 (ZongWan), and ST-25 (TianShu). This study found no extra benefit from using electrical stimulation.[83]

Many Chinese practitioners find benefit in using acupuncture and Chinese herbs together in order to decrease the side effects associated with Western medicine.[84] One study of Keishi-ka-shakuyaku-to

(Gui-Zhi-Jia-Shao-Yao-Tang) on diarrhea induced by pilocarpine, barium chloride, or castor oil found a significant reduction when the herbal combination was dosed at 1000 mg/kg. This herb may mechanistically act to inhibit excessively accelerated small intestinal movement. Another trial comprised 162 children suffering from chronic protracted diarrhea; it involved randomly dividing them into two groups and observing them clinically. In the Chinese herbal medicine group, Xiang Cheng San was externally applied to the umbilicus of each patient; in a second group, Western drugs were routinely given. The results showed that the therapeutic effects were markedly better in the herbal medicine group.[85] Although no control was used in this experiment, the results are encouraging. A wider variety of patent, granular, and loose herb combinations are used to treat various Chinese diagnoses for infectious diarrhea. Future clinical research will help to elucidate their use.

Finally, complex chronic immune deficiency conditions leave patients quite susceptible to pathogenic infection and are difficult to treat. Diarrhea affects more than 60% of persons living with human immunodeficiency virus (HIV)/AIDS. AIDS patients already on a polypharmaceutical regimen have shown good responses to acupuncture and moxibustion used to alleviate symptoms of diarrhea.[86,87] In one pilot study, 15 HIV-positive men with chronic diarrhea received the same acupuncture/moxibustion treatment for six sessions over a 3-week period. In all subjects, stool frequency was reduced by approximately one episode per day. Stool consistency also improved from baseline to week 3 and week 4 by more than 1 point on Hansen's stool consistency scale. Once again, more studies are necessary, but preliminary results are promising for antidiarrheal therapy that does not require additional pharmaceuticals.

Overall, Chinese medicine modalities have proved to be quite safe. In one 6-year Japanese study, the results of 84 therapists and 65,482 treatments were evaluated. Participants were required to report all adverse events. In total, only 94 (0.14%) adverse events were recorded and none was serious (serious events were considered conditions like pneumothorax, infection, and spinal cord injury). The authors concluded that serious or severe adverse events are rare in standard practice. Although more research is clearly necessary to elucidate the benefits of acupuncture, given the little risk and long history of positive anecdotal evidence, it is certainly worth using.[88] More research on Chinese herbs is also necessary to elucidate the toxicity in those preparations that appear therapeutically beneficial.

THERAPEUTIC APPROACH

Overall, natural treatments can adequately manage most cases of non–life-threatening diarrhea. Importantly, diarrhea itself is an eliminative function used by the body to clear toxins and should not be completely suppressed. Of course, chronic diarrhea and diarrhea that causes extreme or rapid electrolyte and water loss may require conventional interventions. It is imperative to maintain hydration and electrolyte balance. Nowhere is this need more immediate than in children younger than 5 years of age.

Underlying Factors

Addressing underlying factors such as low stomach and pancreatic output and depressed levels of IgA helps decrease the chances of pathogenic infection. When possible, eliminating iatrogenic causes such as proton pump inhibitors and antibiotics also helps prevent recurrences. Diets low in refined sugar are encouraged. Food allergies and intolerances should be assessed in those with recurrent infections. Methods to relieve stress also help encourage proper digestive function.

Proper treatment with either an antibiotic or a natural alternative requires close monitoring by standard laboratory methods (e.g., repeating multiple stool samples 2 weeks after initiation of therapy).

Diet

The BRAT diet may be useful to discourage large volume loss in infectious diarrhea. Green banana and pectin fiber may be a useful part of the BRAT diet. Yogurt may be helpful. Small, frequent meals (hourly, if possible) may be best, with glucose administration in the case of vomiting. Avoidance of soy, casein, and other known allergenic foods may be beneficial.

Nutritional Supplements

Dosages are for adults unless otherwise indicated.

- Vitamin A: 60 mg/day in children and up to 50,000 IU/day for 1 to 2 days for adults with infections. Caution against high doses (above 10,000 IU/day in pregnant women).
- Folic acid: 1 mg/day
- Vitamin B_{12} (methylcobalamin): 600 to 1000 mcg/day
- Zinc picolinate: 30 mg/day
- Glutamine: 100 mg twice a day
- *Lactobacillus sp.* and *Bifidobacteria sp.* 6 to 10 billion CFU of *L. GG* or other high quality probiotic twice a day orally. For prevention of antibiotic-induced diarrhea, a dosage of at least 15 to 20 billion organisms is required. Probiotic supplements should be taken as far away from the antibiotic as possible. In children younger than age 6 experiencing antibiotic-induced diarrhea, the probiotic should be taken every day of the antibiotic dose and continued for 1 week after discontinuing the antibiotic.
- *Saccharomyces boulardi:* specifically to treat *Clostridium difficile,* a daily adult dose of 1 g/day in divided doses (500 mg twice a day) for at least 4 weeks. Can be used adjunctively with vancomycin.

Botanicals

- Berberine: Dosage recommendations for berberine would be 25 to 50 mg three times a day or a daily dosage of up to 150 mg. For children, a dosage based on body weight is appropriate. The daily dosage would be the equivalent to 5 to 10 mg of berberine/kg (2.2 lb) body weight. See earlier discussion for more details.
- Tormentil: 60 drops of tincture twice a day or powdered herb at 1/4 tsp twice a day. In children, 3 drops of tormentil root extract per year of life three times a day until discontinuation of diarrhea or a maximum of 5 days.

Homeopathy

- Typical remedies for diarrhea include podophyllum, aloe, china, mercurius, phosphorus, nux vomica, sulfur, aconite, veratrum album, and arsenicum. Specific choice of remedy should be based on the individual patient and his or her presentation.

Acupuncture

- Acupuncture points may include ST-36 (Zusanli) and SP-6 (Sanyinjiao), Du20 (Bai-hui), BL-20 (Pishu), CV-12 (ZongWan), and ST-25 (TianShu).
- Acupuncture is appropriate stress relief as well as direct treatment of intestinal issues and is excellent for treating HIV/AIDS-related diarrhea.

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CHAPTER 179

Infertility, Female

Leah Hechtman, M Sci Med (RHHG), BHSc (Naturopathy), ND

DIAGNOSTIC SUMMARY

- Inability to conceive a child after 12 months of regular unprotected intercourse (at least twice weekly) with the same male partner and in the absence of male causes.

GENERAL CONSIDERATIONS

Females are believed to contribute to 50% of infertility cases as the primary (30%) and combined (20%) factor. Infertility statistics suggest that 1 in 7 couples in the United States experience this condition. It is defined by a lack of conception after 12 months of regular unprotected intercourse (at least twice weekly) with the same male partner and in the absence of male causes. After 12 months, intervention and treatment are recommended. It is advisable to initiate earlier intervention and treatment for women over 35 years of age. After this time, recommendations are that women should receive a comprehensive review and discussion surrounding natural or assisted conception owing to age-related concerns.

A person's fertility is a reflection of his or her general health and well-being. Because we are genetically constructed to pass on the best information for the next generation, the optimal ages for reproduction are believed to be between 18 and 35 years for a female and 16 and 40 years for a male.

Delaying the decision to have children contributes to the proportion of couples who are involuntarily childless. Demographic[1] and clinical studies[2] have shown that women experience optimal fertility before the age of 30 to 31 years. After the age of 31, the probability of conception declines rapidly, but this can be partly compensated for by continued insemination for additional cycles. In addition, the probability of an adverse pregnancy outcome starts to increase at about the same age.[2]

Thereafter, fertility gradually decreases, with acceleration toward the age of 40 years. In women, fertility remains relatively stable until 30 years of age, generally producing more than 400 pregnancies per 1000 exposed women per year; it then begins to decrease substantially.[3] By 45 years of age, the fertility rate is only 100 pregnancies per 1000 exposed women.[4] Already at the age of 40 to 41 years, half of women will have completely lost their capacity for reproduction. It is generally accepted that reproductive aging is in fact ovarian aging and is related to the decreasing quantity and quality of the pool of follicles preserved in the ovaries.[5]

In order to achieve a normal conception, the following are needed:[3]

- Production of viable sperm with respect to motility, morphology, count, and DNA integrity
- Transport of sperm through the male genital tract and deposition in the female genital tract, usually near the cervix of the uterus during sexual intercourse
- Normal oocyte production (ovulation) by the ovaries
- Transport of sperm and the oocyte within the female genital tract to the site of fertilization in one fallopian tube
- Penetration of sperm into the oocyte, fertilization, development of a preembryo, and its transport to and implantation in the uterus

The reader is directed to Chapter 180, Infertility, Male, for specific information for the male partner. Additionally, Chapter 180 covers the definitions of infertility—primary, secondary, and unexplained.

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TABLE 179-1 **Causes of Female Infertility**

Ovulation disorders (40%)	Aging
	Diminished ovarian reserve
	Endocrine disorder (e.g., hypothalamic amenorrhea, hyperprolactinemia, thyroid disease, adrenal disease)
	Polycystic ovary syndrome
	Premature ovarian failure
	Tobacco use
Tubal factors (30%)	Obstruction (e.g., history of pelvic inflammatory disease, tubal surgery)
Endometriosis (15%)	
Other (approximately 10%)	
Uterine/cervical factors (>3%)	Congenital uterine anomaly
	Fibroids
	Endometrial polyps
	Poor-quality/quantity cervical mucus (caused by smoking, infection); mucous hostility (sperm antibodies)
	Uterine synechiae or adhesions (Asherman's syndrome)

Data from Jose-Miller, A., Boyden, JW, Frey, KA. Infertility. Am Fam Physician 2007;75:849-858.

Fecundity is defined as the couple's chance of conception in a single menstrual cycle. The normal monthly success rate for couples trying to conceive naturally at age 25 is 25%. This figure decreases with increasing age, particularly after 35 years of age for women. It was once believed that a woman's age was the only major contributing factor; however, it is now known that male fertility declines with age concurrent with abnormalities evident in semen parameters.

The probability of a couple's fecundity is calculated to determine the monthly chance a couple has of conceiving a child. It factors in a number of variables and considerations for both the male and female partners. In diagnosing the cause of infertility, it is important to consider all variables as pieces of a couple's reproductive and fertility health. The clinical presentation may suggest either blatant fertility impediments (e.g., genetic abnormality) or each partner may have minor health concerns that, when combined, constitute major impediments to a successful fertility outcome (Table 179-1).

Integrative Infertility Treatment

Assisted Reproductive Technologies and Naturopathy

The statistics suggest that 4.6% of U.S. infants born in 2005 (95% uncertainty range: 2.8% to 7.1%) resulted from ovulation treatments not involving assisted reproductive technologies (ARTs). National ART Surveillance System data indicate that ART treatments currently account for 1.2% of total U.S. live births, 16% of U.S. twins, and 38% of U.S. triplets or higher-order (quadruplets or more) live-born infants.[7] Therefore, the prudent naturopath must be aware of potential interactions and consider each treatment protocol accordingly. It is advisable for clinicians to recommend the following approach to their patients for safe, integrated treatment:

- Prior to an in vitro fertilization (IVF) cycle, a 3- to 4-month preconception program for both partners should be encouraged to ensure appropriate nutritional status and detoxification to optimize successful outcome.
- Any causative or contributing factors that may hinder the success of an IVF cycle should be investigated and eliminated thoroughly.
- Any preexisting health conditions during the preconception window of three to four months must be addressed and treated.
- During an IVF cycle, it is crucial to enable optimal communication between the naturopath and fertility specialist to prevent any interactions. Dietary and lifestyle recommendations should be encouraged; however, nutritional and/or herbal medicine prescriptions must consider potential negative interactions with IVF medications. As such, all prescriptions must be individualized.
- Once IVF has concluded and a successful outcome has been attained, treatment can be modified to support the pregnancy, focusing on miscarriage prevention in the first trimester and then adjusting as the pregnancy continues.

Optimizing Natural Fertility

Natural conception is clearly the ideal scenario for any couple. It is therefore necessary to assess a few key variables including ovulation detection and the timing and frequency of intercourse. Before infertility is diagnosed, current recommendations are to encourage couples to attempt conception for a minimum of 12 months of unprotected appropriately timed intercourse. The time period is reduced in couples where the female is older than 35 years. In these couples, diagnosis of infertility is achieved after 6 months.

A couple's fertility is generally highest in the first few months of unprotected sex and declines gradually thereafter. If no conception occurs within the first 3 months, monthly fecundity decreases substantially among those who continue their efforts to conceive.[8] Therefore, couples who are likely to conceive naturally are likely to do so in a few short cycles. In cases where conception takes longer, other impediments may be present. These may be physical or genetic factors, which may require assistance from ART. However, the cause may simply be a compounding health variable such as a blatant nutritional deficiency. Appropriate investigations, as discussed later on in this chapter, will elucidate the approach required.

Couples should be encouraged to attempt conception during the fertile window. A recently ovulated egg will survive for only a few hours (maximum of 24 hours); however, sperm can survive for up to 5 to 6 days in the presence of fertile-quality cervical fluid. The fertile window is best defined as the 6-day interval ending on the day of ovulation.[9] As estrogen increases in the female in the lead up to ovulation, she produces fertile-quality cervical fluid, which protects the sperm from the acidic pH of the vagina, provides a medium in which it can travel, and provides nutritional sustenance for it to survive on its journey.

A widely held misconception is that frequent ejaculations decrease male fertility. A retrospective study analyzed 9489 men with normal semen quality, sperm concentrations, and motility and found that profiles remained normal even with daily ejaculation.[10] Of more importance is the finding that males with abnormalities such as oligozoospermia, lowered sperm count, and poor motility concerns may be improved with more frequent (daily) ejaculation.[10]

In supporting patients with natural conception, ovulation detection is a key component. Box 179-1 includes the main methods available and highlights their most appropriate application.



DIAGNOSTIC CONSIDERATIONS

Female Reproductive Assessment

A thorough assessment of the female patient is crucial to accurately determine her general and fertility health. Some of these assessments

BOX 179-1 **Ovulation Detection**

Fertility charting incorporates consideration of basal body temperature (waking temperature) and changes in both cervical fluid and cervical position.

Waking temperature is a hindsight measurement that confirms ovulation occurrence. It is only able to assist in *predicting* ovulation once a woman is aware of her cyclic changes. It is used to confirm the luteal shift to progesterone and is beneficial for assessing the lengths of the follicular and luteal phases. It is also used to assess progesterone stability in the luteal phase to support implantation and pregnancy; it can also confirm anovulatory cycles. Progesterone causes the endometrium to support the implantation of a fertilized ovum. It also causes temperature to rise perceptibly, typically 0.4° F/0.2°C. Temperature is best taken immediately on waking after a minimum of 6 hours of unbroken sleep via oral assessment.

Fertile-quality cervical fluid is produced 3 to 5 days prior to ovulation in response to increasing estrogen levels prior to the LH surge. Sperm can theoretically survive for 5 to 6 days in the presence of fertile-quality cervical fluid. The role of cervical fluid is multifaceted; it buffers the pH of the vagina to provide a hospitable environment for sperm survival; provides a medium for sperm to swim in on their journey through the female's reproductive system; provides nutritional supplementation for sperm survival; and acts as a lubricant to increase sexual pleasure and increase frequency of intercourse, thus providing more opportunities for conception. Assessment should be conducted from the vagina (inserting a finger into the vaginal opening and extracting fluid for assessment) rather than relying on toilet paper or underwear changes.

Cervical position assessment is the most controversial of self-assessments, with reproductive specialists often discrediting its value. This is because the position of the cervix is affected by numerous variables, including the timing of bowel movements. The cervical tissue is responsive to fluctuations in estrogen and produces physical and tangible changes when ovulation is approaching. Signs of fertility include a softening, opening of the cervical os, increased wetness from cervical fluid, and a lengthening of the vaginal canal as the cervix shortens away from the vaginal opening. Signs of infertility include a closed os, hardening, shortening, and dryness.

Urine-based ovulation testing detects the LH surge that occurs prior to ovulation, typically occurring 24 to 36 hours before ovulation. Testing can produce false positives and is inadvisable in women with PCOS or other, similar conditions due to LH increases in these populations. Additionally, because sperm require an optimal 2 days' travel time, detection of the LH surge can often be too late to optimize conception. It is therefore advisable to make sure that all variables are synchronistic rather than isolated. Additionally, there are some women whose LH surge is shorter (12 hours or less). This can occur in those with hyperprolactinemia and other conditions that interfere with FSH/LH secretion from the anterior pituitary. In these individuals it is advisable to encourage LH testing twice a day (i.e., morning and night), as they can often "miss" the surge.

Saliva assessment testing and tools base their justification on the premise that with increasing estrogen fluctuations, changes in cervical fluid are synchronistic with other fluid media including saliva. Fertility potential is detected by the presence of a "ferning" pattern in the saliva (viewed by microscopy) suggestive of a synchronicity in cervical fluid changes that enable sperm travel. This method is inappropriate for older patients owing to natural estrogen reductions and is also not optimal for hypothyroid patients because of the relationship between estrogen and thyroid function. Additionally, caution with patients experiencing estrogen displacement, such as those with fibroids and/or endometriosis, is advisable.

may require referral to a fertility specialist, gynecologist, or endocrinologist; however, thorough questioning should be conducted by the naturopath to elucidate a full history and assess causative or contributing factors (Table 179-2). All fertility patients should be screened with the queries in Table 179-3, and stage 1 investigations should be conducted with all fertility patients (Table 179-4).

Complications

Miscarriage

The comprehensive coverage of the topic of miscarriage is beyond the scope of this chapter. Because the incidence is as high as one in four pregnancies,[16] the prudent naturopath should be informed about the background, useful assessments, and treatment approaches to miscarriage as part of the holistic approach to female fertility.

Implantation of the developing embryo into the receptive endometrium is a critical and key event in the establishment of early pregnancy. The unique process of cell adhesion of the trophoblast to the endometrium at the time of implantation and its subsequent invasion into the maternal tissue is dynamically balanced through the expression of specific cell adhesion molecules and endocrine, paracrine, and autocrine signals. The process can be viewed as a series of distinct events, many of which are similar to those of an inflammatory reaction and are greatly influenced by the factors present in the uterine microenvironment, including hormones, growth factors, and inflammatory and proinflammatory cytokines.[17] The secretion of a number of factors achieves modulation of the immunologic response of the trophoblast. Cytokines produced at the fetal-maternal interface play a key role in regulating maternal tolerance to the fetus and successful pregnancy.

Although approximately 25% of all recognized pregnancies result in miscarriage, less than 5% of women will experience two consecutive miscarriages and only 1% experience three or more.[16] Recurrent pregnancy loss is a disease distinct from infertility, defined by two or more failed pregnancies.[18] When the cause is unknown, each pregnancy loss merits careful review to determine whether specific evaluation may be appropriate. Although the general consensus is to evaluate after three or more losses, it is more in keeping with the naturopathic paradigm to review all patients even after the first and more comprehensively after the second or subsequent miscarriage.

The risk of miscarriage is highest immediately after implantation. It is thought that around 50% of all fertilized eggs do not survive, coming away with a normal (or slightly late) period. This is often referred to as an "unnoticed miscarriage" because it is usually not formally acknowledged by the woman, who is never aware of her pregnancy.

In summarizing the possible clinical scenarios, it is useful to group them into three distinct categories:

1. For a healthy, viable pregnancy to initiate and continue successfully, a number of biochemical, anatomic, and molecular events must occur in a systematic and timely manner. Any deviation can disrupt the process and abort the pregnancy.
2. Overlapping clinical continuum of presentation can conflict with or complicate the fertility presentation. Each clinical presentation has the potential to present as infertility (occult implantation failure), subclinical or clinical miscarriage in the first trimester, a fetal loss in the mid-trimester before viability, a premature birth, or as a birth defect presenting at or after term. Each presentation is unique and must be considered holistically and individually.

TABLE 179-2 **Fertility Enquiry**

ASSESSMENT	ELABORATION AND EXPLANATION
Age	What are the ages of the couple?
Fertility history	How long have they been trying to conceive, and have they ever conceived previously (together/separately)? Do they have any idea why they have not been able to conceive?
Sexual history	Potential sexually transmitted disease exposure, symptoms of genital inflammation (e.g., vaginal discharge, dysuria, abdominal pain, fever)
Medical history	Genetic disorders, endocrine disorders, history of pelvic inflammatory disease
Medication history	Hormone therapy, contraceptive pills, psychotropics, NSAIDs
Surgical history	Such as previous reproductive or genitourinary surgery
Contraception	When it was ceased and the likely speed of its reversibility
Fertile times	Whether the couple engage in regular intercourse during fertile times
Lifestyle factors	Diet, exercise, alcohol, smoking cessation, recreational drug use, caffeine, environmental toxin screen
Prior paternity	Previous fertility
Psychosexual issues	Interference with conception
Pubertal development	Poor progression can suggest underlying reproductive issue; initial query regarding age of menarche and secondary sexual characteristics to eliminate Turner's syndrome and the like
Physical examination	Breast formation
	Galactorrhea
	Genitalia (e.g., patency, development, masses, tenderness, discharge)
	Signs of hyperandrogenism (e.g., hirsutism, acne, clitoromegaly)
	Body-mass index and waist:hip ratio to assess weight impact

Modified from Hechtman, L, 2011, Clinical naturopathic medicine. Sydney, Australia: Elsevier; 2011.

TABLE 179-3 **Stage 1 Investigations**

ASSESSMENT	TIMING IN CYCLE	JUSTIFICATION
Follicle stimulating hormone (FSH)	Day 3	Stimulates follicle development. High levels can indicate menopause or declining fertility; query primary ovarian failure. Useful to assess ratio comparative to LH to ensure that hormone status is optimal. Eliminates primary ovarian failure.
Luteinizing hormone (LH)	Day 3 or preovulation (day 13)	Triggers ovulation when surges, excessive levels may indicate PCOS. Useful to assess ratio comparative with FSH to ensure hormone status is optimal.
17-OH Progesterone (P4) (17-hydroxyprogesterone)	Day 21 (7 days postovulation)	Evaluates adequacy of progesterone, confirms ovulation. Eliminates luteal phase defect.
Prolactin (PRL)	Any day	Inhibits ovarian production of estrogen, inhibitory role with progesterone if high, stimulates production of breast milk.
Estradiol (E2)	Day 3	Stimulates egg maturation and endometrial maturation for implantation; responsible for fertile quality cervical fluid.
Testosterone (TT), Free Androgen Index (FAI), androstendione	Any day	Eliminate Polycystic Ovary Syndrome (PCOS) or testosterone dominance.
Specific Hormone Binding Globulin (SHBG)	Any day	Evaluates if concentration of SHBG is affecting the amount of testosterone available to body tissues
Transvaginal ultrasound	Day 7	Evaluates follicle maturation, ovulation, endometrial thickness, and character. General assessment of pelvic organs for diagnosing abnormalities of the uterus and ovaries. Assesses thickness and appearance of endometrium to be followed. Enables antral follicle count.
β-hCG	Any day	Eliminate pregnancy or tumor.
Anti-Mullerian hormone (AMH)	Any day	Assesses ovarian reserve (best when combined with antral follicle count through ultrasound).

TABLE 179-3 **Stage 1 Investigations—cont'd**

ASSESSMENT	TIMING IN CYCLE	JUSTIFICATION
General Health Screen		
CBC, UEC, LFT, iron studies, TSH and urinary iodine (24-hour or morning spot) Serum zinc and copper (including ratio); ceruloplasmin red cell folate, serum vitamin B_{12}, homocysteine, 25[OH]D, Fasting glucose, cholesterol profile, celiac screen, Pap smear	NA	General health assessments to eliminate other abnormalities.
General Pre-pregnancy Screen		
Blood group and agglutinins, infectious disease screening, rubella immunity	NA	General pre-pregnancy assessments.
Cervical Swab and Urinalysis		
Bacterial culture, screen for sexually transmitted infections	NA	Assess for infective pathogen compromising fertility. General urinalysis to eliminate underlying infection or abnormality. Urogenital infections have been found to play a part in the genesis of miscarriage[11] and infertility[13]; however, patients may be unaware of their presence owing to the asymptomatic nature of many infections. Screening for a range of genitourinary infections is necessary in preconception care to detect possible infection and thus barriers to conception. The most common and essential infections that require screening include: Primary genitourinary tract infections: *Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis, Neisseria gonorrhea* Secondary genitourinary tract infections: *Gardnerella vaginalis,* Group B *Streptococcus*, Beta-hemolytic *Streptococcus*, *Staphylococcus aureus, Staphylococcus millerii.*
Other Fertility Assessments		
Waking temperature, cervical fluid assessment, cervical position assessment, ovulation testing (urine), ovulation testing (saliva)	Various	Assessment and interpretation of self-directed assessments (if used). See Box 179-1 for further discussion.
Other Considerations		
Salivary hormone screen, including reproductive and adrenal	NA	Salivary screen provides an advantage over blood levels in yielding significantly greater accuracy for interpretation of findings. The adrenal hormone profile determines adrenal function and may help to determine the presence or extent of acute and/or chronic mental and/or physical stress. Prolonged stress has been shown to have suppressive effects on the fertility of both the male and female. Of importance, it is likely to have a profound impact on gonadotropin release (FSH, LH).
Nutrient and toxic element screening	NA	Assessment of toxic elements including aluminium, arsenic, cadmium, lead, and mercury is crucial so that these can be eliminated as causative or contributing factors. It is widely accepted that excessive exposure to heavy metals has detrimental effects on fertility[14] and must therefore be assessed and remedied during the preconception period.
Environmental screen	NA	Other environmental assessments including those that check for porphyrins, PCBs, chlorinated pesticides, volatile solvents, phthalates, parabens, and other toxins. These should additionally be considered owing to their deranging effects on reproductive function, endocrinology, gamete development, and thus embryologic potential.

Modified from Hechtman, L, 2011, Clinical naturopathic medicine. Sydney, Australia: Elsevier; 2011.

TABLE 179-4 **Stage 2 Investigations**

ASSESSMENT	TIMING IN CYCLE	JUSTIFICATION
Thyroid antibodies and reverse T_3	NA	Indicated if thyroid function appears compromised, ovulation potential is reduced, or patient appears to have implantation issues
Sperm antibodies (serum)	NA	Determines whether antibodies are present against the partner's sperm. If blood results are positive, cervical mucus sperm antibodies may be required.
Laparoscopy, hysteroscopy, and salpingoscopy	Before ovulation	Inspection of uterotubal junctions. Diagnosis and treatment of pelvic diseases (endometriosis) or adhesions. Hysteroscopy complements hysterosalpingography (HSG) in revealing pathology that disturbs the shape of the endometrial cavity, especially intrauterine adhesions, submucosal fibroids, and endometrial polyps. These can be diagnosed with HSG, but hysteroscopy is required to locate the pathology accurately and treat it accordingly.
HSG ± selective salpingogram (if indicated)	Day 7	Vaginal examination and injection of radiographic fluid into the uterus and fallopian tubes on x-ray. Determines if fallopian tubes are clear and uterine cavity is normal.
Clomid challenge test	Day 3, FSH and estradiol Day 10, FSH	Determines ovarian reserve and if pregnancy can occur before assisted reproductive techniques are implemented.
Curettage or endometrial biopsy	Day 26 (just before menses are expected)	Reveals the tissue structure of the endometrium. Estimates normal ovulation owing to timing. Not advised regularly because of risk of scarring.
Other	NA	If all results show no abnormality or if the patient is more than 38 years old, the clinician is advised to consider a number of miscarriage assessments to improve outcome, because a number of these assessments are associated with implantation failure as well as miscarriage (see Table 179-5)

Modified from Hechtman, L, 2011, Clinical naturopathic medicine. Sydney, Australia: Elsevier; 2011.

3. The number of similarities between previous miscarriages (if any) can enable the clinician to ascertain the most definitive scenario and develop and adjust treatment accordingly.
4. As seen in Table 179-5, various conditions can be associated causally or coincidentally with miscarriage.

Classic Causes of Miscarriage

- Genetic/chromosomal: 60% or more of early miscarriages are due to chromosomal abnormalities.
- Age: after age 40, one third of pregnancies end in miscarriage.
- Hormonal abnormalities: luteal phase deficiencies (low progesterone) are the most common cause. This can relate to hyperprolactinemia.
- Metabolic abnormalities: poorly controlled blood sugar levels or diabetes mellitus; polycystic ovary syndrome increases miscarriage risk.
- Uterine abnormalities: distortion of the uterine cavity can account for 15% to 20% of miscarriages.
- Antiphospholipid syndrome: this can account for 3% to 15% of pregnancy losses.
- Thrombophilias: increased risk of thrombosis and consequent increased risk of pregnancy loss, especially in second half of pregnancy.
- Male factors: abnormal sperm DNA (see Chapter 180 for a full discussion).
- Unexplained: no explanation is found in 50% to 75% of couples.

Unexplained Causes of Miscarriage. When the causes of miscarriage are unexplained, the naturopath can provide the most beneficial support and care. A miscarriage, especially a first-trimester loss, can occur for any number of natural biological reasons. A marked deficiency in any nutrient (macro or micro) can theoretically cause a miscarriage. A full discussion of macro- and micronutrients and their relation to pregnancy loss is offered later in this chapter. Additionally, the naturopath's consideration of the patient's general health and comprehensive review of all other factors is invaluable.

THERAPEUTIC CONSIDERATIONS

Supporting Female Fertility

On being asked to consider a patient with infertility, it is crucial for the practitioner to assess several factors initially to determine the best approach to treatment. As in the case of male fertility, naturopathic treatment cannot address all variables, such as genetic factors or overt physical impediments; however, it can attenuate various presentations. In the clinician's initial assessment, the prime objective is assess the patient fairly and holistically. Therefore, consideration should be given to the patient's previous pregnancy, duration of infertility, age of partner, severity of present pathology, and other factors. For example, in the case of a 41-year-old female who has had no prior pregnancies, has been infertile for 2 years, and suffers from endometriosis, it is crucial to initiate integrative care with an REI/fertility specialist, because ART is likely to be required. If this patient had sought consultation 4 years earlier, time constraints would not be as severe and the naturopathic paradigm would possibly be of help. Unfortunately, age is one of the variables that cannot be modified. Similarly, if the couple incorporates donor gametes, the clinician must acknowledge the potential limitations to treatment.

A useful summary to delineate the possible approaches is as follows:

- Treatable conditions: Some patients present with blatant deficiencies or disease processes that require interventions to improve their natural fertility. Most people respond positively to a preconception program focusing on detoxification, which enables conception more readily at the conclusion.
- Untreatable subfertility: Following naturopathic intervention, some infertility factors may not be possible to address or, alternatively, referral for ART/IVF may be required.
- Untreatable female sterility: This can occur in instances of mature patients, genetic disorders, or previous conditions that

TABLE 179-5 **Miscarriage Screen**

ASSESSMENT	JUSTIFICATION	INTERPRETATION
On presentation: at any time in the ovarian (menstrual) cycle		
General health screen including CBC, LFT, UEC, fasting glucose, blood group, and agglutinins	General medical checkup	Various; assess for compounding factors.
Red cell folate, serum vitamin B_{12}	Unsuspected folate deficiency; if low, test fasting serum homocysteine.	Folate supplementation in vitamin B_{12} deficiency masks pernicious anemia and the risk of subacute spinal cord degeneration. RBC and serum are not definitive assessment tools for these nutrients. Additional assessments may be warranted.
Fasting homocysteine	Elevations can correlate with vitamins B_9 and B_{12} findings, presence (or absence) of MTHFR polymorphism and coagulation or vascular abnormalities	Treat as indicated with high doses of vitamins B_6, B_9, and B_{12}. Correlate findings with vitamins B_9 and B_{12} and MTHFR status.
Thyroid function tests (TFTs)	Although mild hypothyroidism is strongly associated with anovulation, even mild hyperthyroidism is strongly associated with miscarriage	It is important to keep all aspects of a TFT well within normal limits: avoid even slightly excessive thyroid replacement in cases of hypothyroidism.
Antithyroglobulin Abs (TG Abs), Thyroid Peroxidase Abs (TPO Abs), TSH receptor Abs	The presence of thyroid antibodies can occur with a normal TFT (especially TPO Abs) and is strongly correlated with a first trimester miscarriage	Miscarriage is increased in the presence of any of the thyroid Abs directly correlating with immune modulation requirements of gestation (i.e., implantation and throughout the first trimester at individual increments).
Fasting plasma glucose	Assess for preclinical diabetes, If raised, assess insulin and HbA1c (± GTT) and assess for PCOS factors	Miscarriage is increased in overt diabetes and PCOS.
Serum testosterone, free androgen index, SHBG, +/– androstendione.	Screen for PCOS. If results are positive, confirm with day 7 ultrasound.	Miscarriage is more likely to occur due to disordered follicular development and oocyte function.
Serum gliadin antibodies (IgG, IgA), serum IgA levels and antibodies to tissue transglutaminase or endomysial antibodies. If the patient is already on a low-gluten or gluten-free diet, referral for celiac gene screen is advisable. Note that it is only 95% accurate and a negative reading is not conclusive.	Asymptomatic celiac disease an occasional (though not unequivocal) cause of unexplained infertility or repeated miscarriage. Underdiagnosed in young adult women (population prevalence 1:250 and satisfies WHO criteria for population screening[20])	Confirmation is via small bowel biopsy needed for diagnosis, however, this will require consumption of gluten for three months. Objective clinical opinion is required to warrant this necessity in the fertility context. Note that missing celiac disease in a woman with otherwise unexplained reproductive dysfunction might prove embarrassing when, later, it manifests more classically. Classic presentation may include marked anemia and/or general nutritional deficiencies
Pregnancy infection screen (rubella, Hep B, Hep C+, HIV, toxoplasmosis, CMV, EBV)	Each infection can correlate with miscarriage eventualities (dependent on each infection and timing in pregnancy)	As indicated with each assessment.
Serum copper, serum zinc, and ceruloplasmin	Wilson's disease, a rare copper storage disorder, can present in young women with repeated miscarriage before other symptoms and signs develop (liver disease, Kayser-Fleischer rings, cerebral dysfunction).[21] Screen for high copper and ceruloplasmin levels; confirm with elevated 24-hour urinary copper excretion (and then liver biopsy). In assessing zinc status, a 1:1 zinc:copper ratio should be observed. Zinc supplementation can then be calculated on an as-required basis.	Population prevalence is ~1:30,000 (in any ethnic group); ATP7B mutant gene carrier frequency is ~1:90; more than 100 mutations are known and affected people are usually compound heterozygotes. Possible mechanism: raised copper levels in uterine secretions compromising mitochondrial function in the conceptus. Additionally, raised copper levels are antagonistic to zinc absorption and will warrant supplementation. Depending on copper reading, treatment with copper-binding agents may be required and has been shown to reverse pregnancy losses.

Continued

Key

General medical or naturopathic referral
Reproductive endocrinology and infertility subspecialist
Research interest in recurrent miscarriage

TABLE 179-5 **Miscarriage Screen—cont'd**

ASSESSMENT	JUSTIFICATION	INTERPRETATION
Prolactin and βHCG	Assess impact of these hormonal levels on pregnancy sustenance and achievement	Address as indicated; typically, hormonal modulation is required to ensure that hormone levels are optimal for each stage of pregnancy (and preconceptually).
Karyotype, peripheral blood (both partners)	Assess for balanced chromosomal translocation in either partner. If an imbalance is detected, couples are prone not only to conceive embryos with unbalanced translocations: their unstable meiotic spindles also make otherwise unremarkable aneuploidies more common.	Referral for genetic counseling to estimate unbalanced chromosomal segregation patterns and initiate PGD if required.
Hysterosalpingogram	To assess tubal patency and fallopian tube structure	Address as relevant
Antinuclear antibody, anticardiolipin antibody (IgM, IgG), lupus inhibitor/ anticoagulant, Immunoglobulin A (IgA)	Screening for the antiphospholipid syndrome, either secondary to SLE or, more commonly but often less aggressively, primary	Lab testing for anticardiolipin antibody is not well standardized and interpretations of isolated elevations are difficult. SLE requires referral to immunologist or rheumatologist. Treatment of definite cases is treated through allopathic means with low-molecular-weight heparin, vaginal progesterone (immunosuppressive locally), corticosteroids, and occasionally plasmapheresis. Naturopathic means include immune modulation, blood coagulation normalization, and dietary modification to support appropriate immune and hematologic systems.
CA-125	Presence does not automatically confirm cancer; however, it can correlate with cancerous conditions, endometriosis, or proliferative disorders	In instances of endometriosis can indicate increased development, poor management, or contributing factors to miscarriage
Anti-TjA antibody (anti-PP1Pk hemolysin)	Rare but well described[22]	Plasmapheresis and immunoglobulin replacement during pregnancy can enable term delivery[23]
Thrombophilia screen	Protein S, protein C, activated protein C (APC) resistance, Anti-thrombin III	Protein S deficiency: second trimester miscarriage increase x 7.4. Protein C deficiency: less convincing APC resistance: first trimester x 2.1, second trimester x 3.317.
Thrombophilia PCR testing (DNA assessments)	Test for Factor V Leiden, prothrombin G20210A, MTHFR C677T and A1298C	Meta-analysis[24] reports the following increased risks of miscarriage with homozygosity: Factor V Leiden: first trimester x 2.1, second trimester x 3.3. Prothrombin G20210: first trimester x 2.3, second trimester x 2.3. MTHFR alleles (increase miscarriage risk with elevated homocysteine): x 4.3 (if controlled with adequate folate may actually protect against miscarriage and intrauterine growth retardation). The naturopathic model also acknowledges the impact of MTHFR on folate metabolism and its subsequent effects on ensuring that DNA replication within each cell (including the cells of the fetus) is consistent. Additionally, folate is responsible for a number of other roles in the body. Therefore, an MTHFR abnormality can correlate with a number of other health concerns regardless of homocysteine status.
Anti Mullerian Hormone (AMH)	Reduced levels may indicate failing ovarian reserve. Increased levels can indicate PCOS.	Interpretation is controversial, however, in instances of reduced AMH, refer to fertility specialist and possibly concurrent ART.

TABLE 179-5 **Miscarriage Screen—cont'd**

ASSESSMENT	JUSTIFICATION	INTERPRETATION
Day 2 of the menstrual cycle		
Serum FSH, LH, estradiol (E2) NB: ovulation tracking over 2 cycles is advisable (E2, LH, and P4)	Reduced oocyte numbers: serum FSH > 11 U/L PCOS: suspected when LH:FSH (U/L) > 2:1. In either case, E2 > 200 pmol/L = more severe. Correlate any findings with a day 7 ultrasound.	Low oocyte numbers: risk of early menopause; IVF may be indicated if also infertile. PCOS: requires additional treatment changes, incidence correlates highly with increased miscarriage risk.
Day 7 of the menstrual cycle (or estimated 1 week prior to ovulation)		
Transvaginal ultrasound		
Uterine assessment	Normal endometrium is > 5 mm thick and echolucent (thick echogenic endometrium means hyperplasia or polyp; if it is thin, consider endometritis). Assess for fibroid or diagnose other uterine abnormalities.	Treat specific to finding (i.e., thin endometrium will require progesterone support; thick endometrium will respond to uterine tonics, such as herbal medicines) and antioxidant regulation. For fibroid-specific treatment, see Chapter 212.
Ovarian assessment	Follicles present in the ovary indicate the typical number of eggs achievable: many peripheral follicles indicate PCOS; few follicles can indicate premenopause (or oopause).	If PCOS, low follicle numbers or endometriotic cyst, specialist management is indicated, possibly including IVF.
Vaginal and cervical swabs and culture (cervical swabs are often indicated for the most accurate interpretation)	Vaginosis, either *Gardneralla vaginalis* or other organismal overgrowth, with loss of *Lactobacillus.* Primary genitourinary infections: *Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis, Neisseria gonorrhoeae* Secondary genitourinary infections: *Gardnerella vaginalis,* group B *Streptococcus,* beta-hemolytic *Streptococcus, Staphylococcus aureus, Staphylococcus millerii*	Urogenital infections have been found to play a part in the genesis of miscarriage[26, 12] and infertility[13]; however, patients may be unaware of their presence due to the asymptomatic nature of many infections. Midtrimester (and later) pregnancy losses can occur after internal cervical os becomes covered by growing sac, at 13 weeks. Vaginal flora modulation is required. Herbal douches, probiotic supplementation, and in some instances, antibiotic treatment.
7 days post ovulation (typically days 21-28)		
Serum progesterone (P4)	Screen for ovulation confirmation	If <35 nmol/L, consider further investigation confirming ovulation. Support progesterone cascades as required.
12 days postovulation (premenstrual phase)		
Premenstrual endometrial biopsy for dating	Check integrated action of almost 2 weeks of progesterone on decidualizing the endometrium; confirm progesterone falling to low level and negative ßhCG day before test. Extremely time-critical investigation: usefulness lost if performed in midluteal phase.	Often deficient stromal decidualization in disorders of ovulation (adjust treatment as indicated if present). A deficiency can also indicate endometrial atrophy (which can be untreatable) or, rarely, a molecular defect: in these two cases, gestational surrogacy may be the only treatment option. Best screen for rare molecular bases for decidualization failure causing implantation failure.
Premenstrual endometrial biopsy for lymphocyte (T-cell) subsets on immunocytochemistry [with adjunct T-cell subsets in blood]	Specialist labs can look for relative abundance of peripheral NK cells (CD57+) versus normal uterine (CD56+) NK cells in relation to T cell numbers[25]	If unfavorable, consider vaginal progesterone during early pregnancy. Relevance of findings is conflictual. Naturopathic treatment measures adapt to module the immune response in relevant instances.

Data from Jansen R., Gee A. Testing for miscarriage. O&G Magazine 2008: 10(2):48-52.

Key: CBC (complete blood count), CMV (Cytomegalovirus), GTT (Glucose Tolerance Test), IVF (In Vitro Fertilization), MTHFR (Methylene Tetra Hydro Folate Reductase), PCOS (Polycystic Ovary Syndrome), PGD (Pre Genetic Diagnosis), RBC (Red Blood Cell), RM (Recurrent Miscarriage), SHBG (Sex Hormone Binding Globulin), SLE (Systemic Lupus Erythematosus), TPO (Thyroid Peroxidase Antibodies), WHO (World Health Organisation).

compromise fertility. Adoption or donor oocytes are the only possibilities for couples in this group who wish to have a family. Donor oocytes may not be an option for all patients.

Naturopathic Preconception Treatment

As in the case of male infertility, during naturopathic preconception treatment, the most optimal approach for females is to encourage a program that correlates with the final stages of gamete development (oocytes). Although women are born with all of their oocytes at birth, there are limited treatment options to remedy the primordial stage of development (unless we can modify potential epigenetic factors). Because the primary follicle development from the primordial follicle takes up to 120 days, preconception care is best prescribed within this time period. Following this treatment approach, we can successfully influence additional stages of oocyte development (secondary → antral → Graafian). By influencing the oocyte's environment during development and the correlating general health of the patient, practitioners are able to positively influence the development of oocytes and address and attenuate related health concerns.

The principles of the preconception approach are to attenuate preexisting conditions; optimize nutritional repletion; detoxify the body from dietary, lifestyle, and environmental perspectives; and encourage a healthy approach to parenting on all levels. It is imperative to acknowledge that nutritional repletion is required throughout the preconception period, and that prescriptions may require higher quantities than typical to optimize the patient's status. Fertility occurs when a person's individual health is optimal. The notion of a healthy body being a fertile one cannot be ignored. As discussed in Chapter 180, the body is primed to pass genetic material only when the environment and conditions are at their best. If survival from an evolutionary perspective is compromised, fertility will be hindered. Everything a person eats, drinks, experiences, or is exposed to can and will influence his or her fertility. True naturopathic fertility supports, acknowledges, and considers absolutely all variables for holistic health. Couples should be encouraged to participate in treatment for 3 to 4 months to properly address all genetic and epigenetic variables.

The concept of preconception care was pioneered by Foresight, the Association for the Promotion of Preconceptual Care. It was established in the United Kingdom in 1978 and is a preconception program that incorporates dietary and lifestyle advice to enhance fertility, thereby increasing chances of a healthy conception. Readers may wish to review this research in more detail for additional information. However, published studies lack sufficient evidence owing to poor study design and delivery (one was provided as a letter to an editor and is referred to as a study); nevertheless, the evidence of successful outcomes cannot be refuted. It is hoped that further investigation into this highly effective approach will be conducted in the future.

If the practitioner is incorporating ART, it is beneficial to inform patients that cotreatment is likely to produce the best outcome. In one study, 65% of couples who had previously undergone multiple IVF cycles were able to conceive within 2 years of a preconception program.[26]

It is important to acknowledge that most fertility patients are incorporating several treatment options concurrently.[27] It is therefore prudent to point out the scope of all treatments and to discuss individual treatment protocols openly so as to foster a collaborative approach and reduce the risk of negative interactions.

Fertility-Damaging Factors

Age. The biggest preventable cause of infertility is undoubtedly a woman's age. Approximately 20% of women wait until after age 35 to begin their families. Several factors have contributed to this trend, including contraception choices, career pathways, marrying at older ages, high divorce rates, financial security, or—most concerning—the fact that many women simply do not realize that their fertility begins to decline in their late twenties, with a rapid decrease from age 35 onward. After 35 years of age, a women's fertility declines rapidly in conjunction with the deteriorating quality of her oocytes (Figure 179-1). She may enter oopause in her thirties, depending on her genetic makeup, thus further reducing the chances of a successful fertility outcome. Regardless of a woman's health, age-related changes cannot be prevented or modified. The age of a woman's oocytes is fixed and, as she ages further, fertility potential undergoes a statistical decline. Although over 95% of healthy couples will conceive within 3 years of trying when the woman is 35 years of age that figure drops to 77% when she reaches age 38. By the age of 41, less than half of the healthy couples will conceive after 3 years of trying.

A number of considerations regarding the effects of age on fertility should be considered. These include the following[3]:

- Ovarian function: As women age, fertility declines owing to normal age-related changes in the ovaries. Women are born with all the oocytes they will ever have, with approximately 300,000 follicles remaining at menarche. They will then lose between 20 to 30 follicles each cycle. Of the oocytes remaining at puberty, it is believed that approximately 360 to 400 of these follicles will

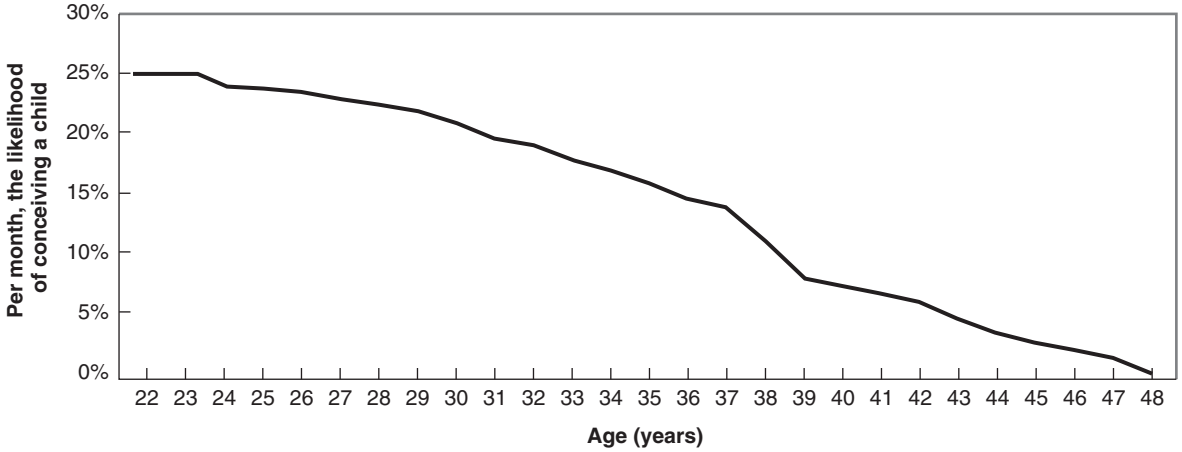


FIGURE 179-1 Impact of age on fertility.

mature over 30 years and be released by the body, with the remainder being lost in each cycle. The rest will undergo atresia, a degenerative process that occurs regardless of whether a woman is pregnant, has normal menstrual cycles, uses birth control, or is undergoing infertility treatment. Smoking appears to accelerate atresia and is linked to earlier menopause.

- Ovarian reserve: Ovarian reserve declines with each cycle. Diminished ovarian reserve is usually age related and occurs because of the natural loss of eggs and decrease in the average quality of the eggs that remain. The remaining eggs become "poor responders" to FSH and LH, thus shortening the menstrual cycles. Young women may also have reduced ovarian reserve because of smoking, a family history of premature menopause, prior ovarian surgery, or even if they have no known risk factors.
- Genetic abnormalities: Aging affects oocyte quality and increases the risk of neonatal genetic abnormalities. As a female ages, her risk for having a child with Down syndrome and total chromosomal abnormalities increase dramatically. At 20 years of age, her risk for producing a Down syndrome child is 1 in 1667 (1 in 526 total risk for any chromosomal abnormalities); at 35 years of age, that risk increases to 1 in 378 (1 in 192). At 45 years of age, the risk increases again to 1 in 30 (1 in 21).[28]
- Miscarriage risk: Older oocytes increase the risk of miscarriage. The risk of miscarriage remains at 10% between 15 and 29 years of age; it then increases to 12% at 30 to 34 years of age and to 18% at 35 to 39 years of age. Thereafter, it escalates significantly to 34% at 40 to 44 years of age and to 53% after the age of 45.[28]

Weight Balance. For optimal conception, women must ensure that their body fat percentage is between 20% and 25% to support fertility and the subsequent health of their child. A body fat percentage below 17% can result in anovulation, with some research suggesting that it can take as long as 2 years before regular conception occurs even after body fat percentage has been corrected.[29] Women with a body-mass index (BMI) below 19 who have irregular or absent menses should be advised to gain weight to improve their chance of conception. Malnutrition can be a relatively simple solution for conception difficulties (provided mental health issues are addressed).

Although anorexia or underweight is a concern, obesity poses a similar and significant risk for infertility. The impact of obesity is much more comprehensive than that of underweight and the necessary treatment is easier to prescribe. The following paragraphs outline the impact of obesity on reproductive function[30]:

- Ovulation potential: Ovulation returns with a relatively modest degree of weight loss from diet and exercise. Approximately 90% of obese women will resume ovulation if they lose more than 5% of their pretreatment weight, and 30% will conceive. In very obese women, these statistics are higher for pregnancy rates than can be expected from a single IVF cycle. This recommendation is crucial and encouraging for obese women wishing to have children.
- IVF outcome: The success rate of ART is reduced in obese women. IVF success rates may be reduced by as much as 25% in obese patients and 50% in very obese patients. IVF centers are very reluctant to perform fertility treatment on women with a BMI greater than 35 and generally recommend a target BMI of 30 before starting treatment.[31]
- Miscarriage: The risk of miscarriage in the first trimester increases from 12% to 15% in normal-weight women under 37 years of age; for women with a BMI above age 35, it increases to 31%. The rate of recurrent miscarriage increases fourfold in obese women.
- Birth defects: Maternal obesity has a detrimental impact on fetal development (e.g., three times the risk of neural tube defects and structural heart defects). Folic acid supplementation is less effective in preventing neural tube defects, so high-dose supplementation is required for obese women (it is always beneficial to calculate nutrient requirements based on the patient's presenting weight, using Clark's rule).
- Pregnancy complications: Pregnancy complications are more common in obese women (gestational diabetes is six times more common); and pregnancy-induced hypertensive diseases are more common (specifically, gestational hypertension and preeclampsia). Complications increase the risk of premature delivery and/or the need for cesarean section. Babies born to obese women have heavier birth weights (fetal macrosomia), which increases the risk of traumatic vaginal delivery. Additionally, there is a higher complication rate for cesarean and vaginal deliveries in obese women (e.g., excessive blood loss, thromboembolic disease, and postoperative infection).
- Pregnancy outcomes: Increasing BMI increases the risk of stillbirth (twice the risk vs. normal-weight women).
- The newborn: Maternal obesity carries long-term risks for the newborn infant (e.g., increased risk of being overweight as an adult and the likelihood that these children will have weight-related diseases in adulthood).

Immunologic Considerations. Although this topic is beyond the scope of this chapter, the immunologic considerations associated with successful conception and a healthy birth are worthy of review. Because optimal production of gametes requires a healthy immune response, any deviation from "normal" can significantly affect the outcome. In females, any immunologic aspect that can affect general health, conception, implantation, and the maintenance of pregnancy can cause problems. A number of miscarriage factors (including implantation factors) relate to autoimmune diseases. Therefore stabilizing and modulating the immune response is a key objective of treatment. The immune system must "switch itself off" at conception, implantation, and a number of key stages in the first trimester. Therefore consideration of these variables is crucial.

Environmental Factors. Increased industrialization and the use of agricultural chemicals has contributed to an increased exposure to thousands of chemicals now associated with a negative impact on male and female fertility. Exposure to environmental toxins such as radiation, heavy metals, and chemicals can cause oxidative stress and damage to DNA, leading to a negative impact to female fertility.

A comprehensive discussion of the effects of environmental factors is provided in Chapter 180. The reader is specifically directed to the discussion regarding estrogen exposure and general environmental pollutants. Specific considerations for women should acknowledge the impact of substances more commonly associated with females, including makeup, fragrances, hair dyes, nail polishes, and other beauty products. All of these can have a negative impact on reproductive function and hormone cascades. It is therefore prudent to reduce such exposures as much as possible, specifically within the preconception window and during first trimester, when embryogenesis and placentogenesis is paramount.

Of greater concern is the fact that gestational exposure to carcinogens, endocrine disruptors, and other toxins has been shown to affect more than one generation in some cases. Most studies unfortunately have not investigated effects beyond the third (F2) generation. Further studies are required in this intriguing area of genetics, especially because the F2 generation may have experienced the exposure directly. Chemicals known to induce phenotypic effects in unexposed generations include alloxan,[32] cyclophosphamide,[33] orthoaminoasotoluol,[34] benzpyrene,[35] diethylstilbestrol,[36]

and vinclozolin.[37] The underlying mechanisms are not known and in most cases inherited genetic lesions cannot be ruled out, especially in cases of mutagens (e.g., cyclophosphamide). As time progresses, it is likely that these chemicals will induce greater damage to subsequent generations due to their cumulative effects and earlier generational impact.

A full discussion on potential environmental impacts is provided in Chapter 35.

Sleep Irregularities. Shift work is associated with negative effects on the regularity of the menstrual cycle, reproductive function, and also increases the risk of an adverse pregnancy outcome. In one study, the effect of shift work on nurses (all less than 40 years of age) was reviewed; the investigators evaluated sleep, menstrual function, pregnancy outcome, and reproductive function. It was found that 53% of the women studied noted menstrual changes owing to shift work, changes that clearly could affect fertility.[38] It is therefore essential that women wishing to achieve pregnancy normalize their cycles and find a way to optimize and regulate their sleep patterns.

Lifestyle

Smoking. Both active and passive cigarette smoking is known to have a significant effect on both pregnancy rates and long-term ovarian function. Additionally, smokers are more likely to have a premature menopause, thus making smoking one of the most readily avoidable causes of infertility. Smoking appears to reduce fertility by having a direct effect on the uterus, oocytes, and embryos by increasing the thickness of the zona pellucida.[39] It becomes difficult for the sperm to penetrate the increased thickness of the zona pellucid. Overall, research indicates that smoking can age oocytes prematurely by as much as 10 years. Considering that the average age for conception is 30 years and the average age at which fertility begins to decline steeply is 38 years, it appears prudent to recommend immediate smoking cessation coupled with systematic antioxidant therapy.

On review of the research, smoking has been shown to decrease ovarian vascularization and reduce oocyte maturation.[40] It is linked with premature ovarian aging (premature menopause) and an increased risk of miscarriage.[41] It is important to note that smoking, either current or historical, is strongly correlated with negative effects on the health of the oocytes. A trial comprising 14,779 women between the ages of 18 and 23 years showed that current smokers and ex-smokers had an increased risk of menstrual symptoms and miscarriage compared with women who had never smoked.[42] Of more importance, it was found that women who smoked 20 or more cigarettes a day and for the longest periods were most at risk. Additionally, those who started smoking at a younger age had the worst outcome.

A recent Cochrane review found that active and passive smoking reduced fertility and decreased the chance of a healthy live birth in both fertile and infertile populations.[43] Additionally, a number of meta-analyses have proved that smokers perform poorly in IVF/ART procedures as compared with their nonsmoking counterparts.[44,45]

Caffeine. Patients should be encouraged to avoid caffeine during the preconception period and during pregnancy. Caffeine has been shown to increase time to conception[46-48] and has also been linked with endometriosis and an increased risk of spontaneous abortion.[49] Caffeine has been shown to increase dopamine production, which in turn stimulates progesterone secretion, thus inhibiting the production of prolactin (owing to the antagonistic and regulatory interrelationship between progesterone and prolactin). Any prolactin abnormality, either excess or deficiency, can affect a woman's fertility negatively. According to several studies, as little as one caffeinated beverage a day can lead to a temporary reduction in conception.[50,51] Owing to its prolactin-modulating effects, caffeine appears to increase early follicular estrogen levels.[52] Caffeine is also likely to interfere with adrenal function and associated cortisol secretion. In addition, caffeine's diuretic effects increase the loss of nutrients that are beneficial to fertility. It is important to note that quantity of coffee has a direct correlation with pregnancy rates. Women who drink less than one cup of coffee a day are twice as likely to conceive compared with moderate coffee drinkers.[47]

Alcohol. A review of the literature regarding alcohol intake and female fertility indicates that there are many factors that can affect each woman uniquely. There are strong associations with alcohol intake and miscarriage[53]; excessive alcohol consumption is associated with hyperprolactinemia[54]; adverse effects on oocyte retrieval and lower chance of subsequent pregnancy in IVF[55]; and a minimum of 50% reduction in conception can be seen with intake as low as one drink per week during a menstrual cycle.[56] Additionally, research suggests that alcohol produces negative effects on blastocyst development and implantation; increases estrogen levels, causing a subsequent reduction in FSH secretion and suppressing folliculogenesis, thus leading to anovulation and infertility.[57]

It is advisable to recommend the cessation of alcohol intake during the preconception period. Conclusive evidence exists regarding fetal abnormalities and associated alcohol intake during pregnancy. This evidence can often be sufficient to motivate patients. Because detoxification is encouraged during the preconception period, the avoidance of alcohol is recommended.

Marijuana. As discussed in Chapter 180, marijuana contains cannabinoids, which have been shown to impair signaling pathways, alter hormonal regulation, and interfere with the timing of implantation.[58] Additionally, it is believed to cause ovulatory abnormalities and to disrupt ovarian function.[59] Furthermore, marijuana has been shown to have harmful effects on the developing fetus.[60] Therefore avoidance is strongly recommended.

NUTRITIONAL CONSIDERATIONS

The Fertility Diet

There are countless papers documenting dietary modifications to support and improve a woman's fertility. Specifically, research suggests that dietary modulation improves ovulation, conception, and the birth of a healthy child.

The strongest evidence in favor of dietary modification to support fertility can be seen in the prospective study developed from the information ascertained from the Nurses' Health Study II.[61] Of importance, the information acquired was from 2 years prior to the report of infertility in this study, thus enabling a preconception interpretation. Information included dietary and lifestyle characteristics (body weight, physical activity) and medical health factors. In this intriguing study the participants were followed for 8 years. The "high-fertility diet" thus characterized includes the following:

- Lower intakes of trans fatty acids and greater intake of monounsaturated fats[62]
- Lower intake of animal protein and greater intake of vegetable protein[63]
- Higher intake of high-fiber, low-glycemic carbohydrates
- Preference for high-fat dairy products (because this has been found to reduce the risk of anovulatory infertility by more than 50%, in contrast to low-fat dairy, which reduced the risk of successful conception by only 11%)
- Higher dietary sources of nonheme iron

- Higher frequency of multivitamin use
- More likely to consume coffee, tea, and alcohol
- More likely to be physically active (vigorous activity for 30 minutes or more daily)
- Less likely to smoke
- Less likely to have long menstrual cycles
- More likely to be a recent user of the oral contraceptive pill
- Weight balance: BMI between 20 and 25

Researchers concluded that these components of a fertility diet are conducive to the most successful outcome. When these approaches are combined with the control of body weight and increased physical activity, the majority of infertility problems involving ovulation may be prevented.

In another trial, researchers noted that the Mediterranean diet increased the chance of a successful pregnancy in those undergoing IVF/intracytoplasmic sperm injection (ICSI). It was found that the high content of B vitamins (especially vitamin B_6) combined with the high intake of vegetable oils may be the mechanism responsible for this positive outcome.[64]

L-Arginine

Arginine is a precursor of nitric oxide synthesis and is required for angiogenesis, embryogenesis, fertility generally, and hormone secretion.[65] Additionally, it is required for the replication of cells, making it essential for oocyte development and embryo formation.

One paper[66] produced notable results. The specific population were "poor responders"—women who had failed to achieve an adequate number of mature follicles and/or adequate serum estradiol levels following gonadotrophin stimulation. This trial indicated that arginine supplementation (oral at 16 g/day) improved ovarian response, endometrial receptivity, and pregnancy rates. The women were divided into two groups: (1) flareup gonadotrophin-releasing hormone analog (GnRHa) plus elevated pure follicle stimulating hormone (pFSH) (n = 17) or (2) flareup GnRHa plus elevated pFSH plus oral L-arginine (n = 17). Results indicated that group 2 (the arginine group) demonstrated a lower cancellation rate, increased number of oocytes on collection, and increased embryo quality and transfer compared with the control group. Additionally, 3 of 17 women in the arginine group conceived, whereas none in the control group did so.

The literature regarding arginine and fertility outcome is impressive, however, although the trial showed very promising results, it assessed only a small sample of women, too small to allow definitive conclusions. Further research into the potential of this promising adjunct during ART procedures is recommended.

L-Carnitine

Similarly to its role in male reproductive function, L-carnitine plays a vital role in fatty acid metabolism. It is derived from the amino acids lysine and/or methionine and works synergistically with coenzyme Q10. It is essential in the transport of fatty acids into the mitochondria; a deficiency results in a decrease in fatty acid concentrations in the mitochondria and reduced energy production. Prescriptions must use the L form and not the DL form to ensure effectiveness and safety. The mitochondria are crucial components of oocyte development, acceptance of the spermatozoa, and subsequent embryogenesis. It is the mRNA within the oocyte that requires the power of the mitochondria to allow conception to occur. Therefore, the prescription of carnitine is specifically indicated in women who are experiencing implantation issues and/or presenting with aging oocytes.

In mouse studies, carnitine has been found to exert a protective effect on mouse oocytes, reducing damage to the oocyte's cytoskeleton and also mitigating embryo apoptosis induced by incubation in the peritoneal fluid of patients with endometriosis.[67] Although peritoneal fluid has a strong impact on endometriosis, it helps to regulate endometrial lining production and implantation factors. As such, human studies are lacking, the prescription of carnitine for patients experiencing endometriosis and/or implantation failure due to endometrial factors is recommended.

Antioxidants

Compared with male fertility, there is little evidence supporting the use of specific antioxidants. However, the consensus remains that the use of antioxidants combined with a good diet improves fertility in women.[27] One Cochrane review assessed the use of vitamin supplementation in the prevention of miscarriage. It concluded that patients given any type of vitamin therapy, compared with controls, would be significantly less likely to develop preeclampsia and more likely to have multiple pregnancies.[68] Therefore, it is highly likely that any vitamin prescription, provided that it is prescribed holistically and effectively, will have a positive effect on female fertility.

Transgenerational epigenetic effects include both the physiological and behavioral (intellectual) transfer of information across generations. Although in most cases the underlying molecular mechanisms are not understood, modification of the chromosomes that pass to the next generation through gametes is sometimes involved; this is called transgenerational epigenetic inheritance.

The oocyte, a highly sensitive structure, is highly vulnerable to its external environment and external influences. Every female is born with all of her oocytes. As such, they are thus exposed to everything she experiences throughout her entire life. Additionally, from an epigenetic perspective, a woman's oocytes are also exposed to everything to which her mother and even her maternal grandmother were exposed.

Oxidative stress has a detrimental effect on female fertility by increasing time to conception; decreasing fertilization rates; decreasing oocyte penetration function and viability; decreasing implantation; and increasing loss of implantation.[69]

The oocyte requires a regular antioxidant supply to continue to reduce oxidative damage both from current circumstances and historical (or transgenerational) exposure. During conception, the mRNA is responsible for using antioxidant reserves to address any DNA fragmentation or oxidation from both the sperm and the oocyte. The very act of conception and the subsequent travel of the embryo through the fallopian tubes prior to implantation generates free radical damage. Because oxidative stress has been shown to hinder optimal fertility,[70,71] it is imperative to provide sufficient support for the oocyte so that conception and implantation can occur.

Alpha Lipoic Acid

In both its lipid- and water-soluble forms, alpha lipoic acid is a powerful antioxidant found in virtually all cells of the human body, scavenging free radicals implicated in oxidative stress. It assists in the chelation of heavy metals, thus minimizing the risk of cellular damage and regenerating other antioxidants, including vitamins C and E, coenzyme Q10, and glutathione.[72]

Vitamin A

Vitamin A is a powerful antioxidant that assists in cellular growth and differentiation, both crucial for embryogenesis and placentogenesis.[73] It is required for gene expression and cellular differentiation in organogenesis and embryonic development[74] as well as for immunity, regulatory functions, the integrity of epithelial tissue,

and the health of the cilia in the fallopian tubes. It has a direct relationship with zinc, and the deficiency of zinc has been linked with infertility, miscarriage, and the development of cleft palate. It is a cofactor of 3 β-dehydrogenase in steroidogenesis (specifically for estrogen production) and deficiencies may result in impaired enzyme activity.[75] Additionally, low concentrations of vitamin A are associated with anovulation,[76] and plasma levels have been observed to be decreased in women suffering from habitual miscarriage.[77]

Supplementation during pregnancy is inadvisable due to the potential for malformation and congenital abnormalities. However, supplementation in the preconception period is strongly advised. Owing to its lipid-solubility and the liver's high storage capacity, it is advisable to keep prescriptions below 10,000 IU/day. It is also important to note that cross-placental transfer occurs primarily with lipid-soluble nutrients. Therefore, cessation of vitamin A supplementation is advisable as a cautionary measure immediately prior to conception attempts.

An alternative is to prescribe carotenoids (beta-carotene), owing to their lower toxic potential. An additional benefit is that they have a role in ovarian oocyte and follicular maturation and function.[78] However, 15% to 25% of whites are unable to convert beta-carotene to vitamin A, so it is not a substitute for vitamin A (see also Chapters 69 and 135).

Coenzyme Q10

Coenzyme Q10, also known as ubiquinone (ubidecarenone) or ubiquinol, is an endogenous enzyme involved in intracellular adenosine triphosphate (ATP) production; it serves as a cofactor in oxidative stress respiration for the citric acid cycle and the electron transport chain.[79] It is a fat-soluble antioxidant and free radical scavenger found in every cell in the body and plays a vital role in all energy-dependent processes. It is required in the maintenance of cell membrane integrity and cell functioning and is therefore specifically important for all new cells in the body and the development of cells in their maturation process. It is endogenously produced from tyrosine in a 17-step process that requires riboflavin (B_2), niacinamide (B_3), pantothenic acid (B_5), pyridoxine (B_6), cobalamin (B_{12}), folic acid (B_9), vitamin C, tetrahydrobiopterin, and trace elements as cofactors. Therefore, an ample supply of these key nutrients is essential for the production of this enzyme. Additionally, it can be expected that patients with thyroid irregularities (both hyper- and hypothyroid) would require additional coenzyme Q10 owing to its reliance in tyrosine as an initial building block.

Unfortunately research is lacking, because there are no specific trials highlighting the therapeutic application of coenzyme Q10 concurrent with the assessment of reproductive outcome. However, there are countless papers supporting its inclusion in culture media used in an IVF setting, and it is considered a crucial component to mimic various reproductive fluids incorporated in natural conception. In the clinical setting, its role can be extrapolated fairly conclusively; therefore, its use should certainly be considered, because its clinical and therapeutic effectiveness are irrefutable. Because dietary sources are poor choices for optimal effect, supplementation is essential. In choosing supplements, it is essential to select the ubiquinol form, as it is the active antioxidant.

Specifically in the context of female fertility, coenzyme Q10 can be seen to support mitochondrial function and to have positive applications for maturing oocytes, which are at greater risk of oxidative damage. Oxidative damage is typically seen in the zona pellucida of the oocyte, thus preventing the acrosome reaction with sperm (fertilization). Receptivity of the zona pellucida is strongly correlated with the antioxidant status of the oocyte, and coenzyme Q10 is believed to be the most specific antioxidant for this application. Understandably, requirements for coenzyme Q10 will be greater for more mature oocytes (women above 35 years of age) or women undergoing ART procedures owing to the increased oxidative effect on the oocyte of such procedures.

Vitamin C

Vitamin C is the body's primary water-soluble antioxidant. It is protective against free radicals, protects folic acid and vitamin E from oxidation, and has been shown to improve fertility outcomes in women with luteal-phase defects.[80] The ovary is considered the primary site of ascorbic acid accumulation, because the midcycle change of retention and excretion of ascorbic acid is one of the main markers of ovulation. In the literature, vitamin C is seen to be crucial for collagen biosynthesis and its positive effect on the growth and repair of the ovarian follicle and the development of the corpus luteum[81]; it may also facilitate luteal steroidogenesis. It is necessary for the maturation of the preovulatory follicle and reduces the risk of preeclampsia when prescribed concurrently with vitamin E. Deficiency increases the risk of miscarriage, spontaneous rupture of membranes, and brain tumors in the offspring.

Vitamin C is best co-prescribed with bioflavonoids, which provide the additional benefits of strengthening capillaries, preventing miscarriage, and preventing breakthrough bleeding during the pregnancy.

Vitamin E

Vitamin E is a powerful lipid-soluble antioxidant that is essential for fertility and reproduction. It is a plant-derived fat-soluble vitamin that exists in eight different isomers. Alpha-tocopherol is the most biologically active form for conception and is the focus in nutrition research. It has been shown to maintain the health of the ovaries[82]; help PMS sufferers, including relief of affective and physical symptoms[83]; relieve benign breast disease[84]; and ameliorate menstrual migraine,[85] indicating effects in the regulation of hormonal activity. The literature suggests that it may be of benefit in infertile women by reducing scar formation (especially keloid scarring when applied topically).[86] This may make it particularly useful to those suffering from endometriosis and or complicated reproductive conditions such as Asherman's syndrome. Additionally, one study found that women suffering from infertility and endometriosis had lower levels of vitamin E and increased lipid peroxidation.[87] This was confirmed by another study indicating that levels of vitamin E were low in infertile patients as compared with controls. This research suggests that the antioxidant capacity was compromised in infertile women and may cause subsequent risk of oxidative damage.[88]

Selenium

Selenium is a powerful antioxidant with marked immune-modulating properties. Supplementation appears to reduce the risk of miscarriage, especially in association with thyroid autoantibodies.[89] Supplementation has been suggested as a powerful supportive nutrient to regulate and control thyroid autoimmunity, specifically thyroid peroxidase (TPO) antibodies.[89] Selenium is essential in thyroid hormone synthesis because several of the enzymes involved are selenoproteins.[90] Selenium also plays a role in the immune system and the coagulation system.[91,92]

In a double-blind randomized clinical trial, selenium substitution decreased TPO antibody levels in euthyroid subjects and increased quality of life.[92] In another trial it also decreased TPO antibody levels in hypothyroid patients treated with T_4 substitution.[93] Specifically in this specialized population, lowered selenium levels have been

observed in the hair of women with recurrent miscarriage as compared with controls who have had successful pregnancies[91]; decreased serum selenium has also been observed in women who suffered from miscarriage in the first trimester as well as recurrent miscarriage.[94]

Zinc

More than 200 enzymes require zinc for their activity; these include the enzymes required for the production of the nucleic acids in DNA and RNA.[95] Zinc has specific antioxidant properties required for the reproductive system and protects the oocytes from free radicals and reactive oxygen species.[96] It enables reproduction, ovulation, fertilization, and the development of the oocyte.[97,98] Deficiency may result in altered synthesis/secretion of follicle-stimulating hormone or luteinizing hormone,[99] because it has been reported to have a role in the synthesis, transport, and peripheral action of hormones. Low zinc status is associated with low circulating concentrations of several hormones.[100]

Deficiency may produce symptoms such as abnormal ovarian development, increased risk of miscarriage, or increased risk of teratogenicity.[101] It is considered to be the single most important nutrient for preconception and pregnancy and is frequently disrupted with the use of an oral contraceptive pill or a copper intrauterine device. In animal trials, low zinc levels were associated with impaired ovulation and a larger number of deteriorated oocytes[97]; in such circumstances supplementation may be beneficial. Caution is advised, as an excessive intake of zinc can be detrimental[102]; doses should be calculated on the basis of assessments and clinical findings.

In the preconception period, zinc supplementation used to enhance fertility will further support a healthy pregnancy and subsequent healthy birth. Poor maternal zinc status is associated with a number of adverse pregnancy outcomes including low birth weight, premature delivery, complications of labor and delivery, and congenital anomalies in the offspring.[103] Additionally, requirements increase during pregnancy, because marginal zinc deficiency has been shown to be prevalent during this time.[104] Monitoring is crucial, because as suboptimal levels are associated with growth retardation in the fetus.[104] In one study, supplementation of 25 mg from at least 19 weeks' gestation resulted in a significantly greater birth weight.[105] Additionally, a meta-analysis of supplementation trials indicates that zinc supplementation produced a 14% reduction in premature deliveries.[106]

B-Complex Vitamins

It is imperative to take the B-group vitamins in a stable, combined formulation owing to their interrelation and interdependence in a number of key reactions in the body. Their synergy of effect can be seen in countless scenarios; however, some patients may require additional key B vitamins such as folate for methylenetetrahydrofolate reductase (MTHFR), polymorphisms, or vitamin B_6 in instances of luteal-phase defects or progesterone insufficiency.

Deficiencies of this group of vitamins have been associated with a number of fertility problems, including fetal abnormalities such as neural tube defects,[107] neonatal or perinatal death, low birth weight, and miscarriage.[108,109] It is important to consider that alcohol, carbohydrate-rich diets, and the oral contraceptive pill increase the body's requirements for B vitamins. Therefore, any couple wanting to optimize their fertility may require additional B vitamins to prepare themselves for conception. Acknowledging that stress also increases requirements for B vitamins and that stress has been identified as playing a major role in couples who are have difficulty conceiving, the importance of adequate B-vitamin intake is further emphasized.

Vitamin B_1 (Thiamine)

In animal models, vitamin B_1 has been shown to stabilize the membranes of newly generated neuronal cells during embryogenesis concurrent with slowing cell death. Additionally, it has been shown to be involved in the plasma membrane transformation of uterine epithelial cells during pregnancy.[110] It plays a key role in reproductive function, with deficiency associated with altered cellular differentiation and proliferation and interference with hormonal processes, thus increasing the risk of miscarriage.[111] Additionally, when taken preconceptually in combination with vitamins B_3 and B_6, it has been shown to contribute to the prevention of oral facial clefts.[112]

Vitamin B_2 (Riboflavin)

Vitamin B_2 is crucial for energy production, antioxidant defense, and numerous enzyme systems that rely on the presence of B vitamins. Insufficient levels can lead to altered estrogen and progesterone levels, often causing irregular menstruation. Supplementation often addresses irregularities such as general menstrual difficulties, irregular menses, PMS, and infertility.[113]

Vitamin B_2 is essential for the development of the fetus; according to animal studies, deficiency appears to affect embryonic growth and cardiac development. Therefore, supplementation has been encouraged to prevent these complications.[114] Low dietary intake has also been associated with low birth weight[115] and has been shown in one study to increase the risk of congenital heart defects in the offspring of mothers who did not take vitamin supplements in the periconceptual period or consume sufficient dietary saturated fatty acids.[116]

Vitamin B_6 (Pyridoxine)

Vitamin B_6 is required for the metabolism of amino acids, lipids, pathways of gluconeogenesis, and synthesis of neurotransmitters during the periconception period.[73] It is required for the synthesis of prostaglandins; it also plays a key role in conjunction with vitamins B_9 and B_{12} in their regulation of homocysteine, which, when elevated, has been linked to infertility and recurrent spontaneous miscarriage.[117,118] Additionally, elevated homocysteine concentrations in follicular fluid are also associated with poor oocyte and embryo qualities in patients with polycystic ovary syndrome (PCOS) who are undergoing assisted reproduction,[119] thus further supporting the B-vitamin combination.

In addition, vitamin B_6 helps to reduce elevated prolactin levels, support luteal-phase defects by increasing progesterone secretion, increase the influx of magnesium into the myometrium, improve the absorption of zinc, and prevent preeclampsia, toxemia, and infarction of the placenta. Serum levels are often low in hyperemesis gravidarum, and a deficiency may be associated with a higher incidence of gestational diabetes.

Vitamin B_9 (Folic Acid)

Folic acid is required for healthy DNA and RNA synthesis, optimal protein synthesis, and the regulation of gene expression.[120] Deficiency can be corrected with supplementation, which is recommended for at least 3 months for any woman planning pregnancy.[121] The primary justification for its preconceptual prescription is to prevent neural tube defects; however, it must be supplemented for the first 28 days of gestation to achieve this goal.[122] Therefore, a preconceptual prescription for 3 months prior to conception is the safest option, because most women are unaware of their pregnancy status until it is confirmed after a minimum of 14 days.

Supplementation of folic acid is associated with a decreased incidence of ovulatory infertility[61,123] and has been identified as being

important for oocyte quality and maturation.[98] Inadequate folate results in elevated homocysteine and alters DNA methylation negatively, influencing oocyte and early embryo quality.[124] Inadequate B-vitamin status and raised concentrations of homocysteine are also associated with early loss of pregnancy, as evidenced by a systematic review, which found that folate deficiency–induced hyperhomocysteinemia posed a risk for placenta-mediated diseases such as preeclampsia, spontaneous abortion, and placental abruption.[125]

Vitamin B_{12} (Cyanocobalamin)

It is common for women to take folate in isolation and not acknowledge its co-partner, in all chemical reactions, vitamin B_{12}. Vitamins B_9 and B_{12} work together to ensure that the replication of DNA and RNA in all cells is uniform and regulated. In one longitudinal study, it was noted that although folate levels decreased slightly during pregnancy and remained decreased for up to 6 weeks postdelivery, vitamin B_{12} progressively declined during pregnancy and reached marginal or deficient levels in some individuals.[126] Clinicians are reminded that supplementation of either vitamin B_9 or B_{12} in isolation can cause a rebound anemia of the other nutrient and that pernicious anemia can be masked with supplementation of one vitamin in isolation, as evident on the basis of red cell indices. Furthermore, low maternal levels of vitamin B_{12} have been associated with a threefold risk of neural tube defects,[127] again confirming its combined role with folate.

Vitamin B_{12} deficiency has been linked to infertility and recurrent spontaneous miscarriage.[128] Moreover, pregnancy has been shown to occur following correction of this deficiency.[128] In addition, it is prudent to acknowledge the collaborative role of vitamin B_{12} in cases of elevated homocysteine levels.

Vitamin D

The Third National Health and Nutrition Examination Survey (NHANES III) reported a prevalence of vitamin D deficiency of between 25% and 57% among adults.[129] It is important to note that the accepted levels of this vitamin in this analysis are below what naturopaths would consider a safe, therapeutic level for optimal health. Therefore, it can be hypothesized that the deficiency percentage is actually much higher. Each week a new paper emerges highlighting an additional application for this crucial vitamin. Its main functions include calcium homeostasis; modeling and remodeling of bone (supporting the skeletal health of both mother and child); immune activation; cell differentiation, proliferation, and growth; and many others.

In the context of female fertility, the active form of vitamin D, 1-25-dihydroxyvitamin D3, has been shown to regulate the transcription and function of genes associated with placental invasion, normal implantation, and angiogenesis.[130] Vitamin D is a powerful immune modulator and therefore an effective prescription for those who experience autoimmune conditions that affect fertilization, implantation, and an increased risk of miscarriage. This is because of vitamin D receptors found in cells involved in the immune response. Specifically in fertilization, it is believed to have receptors on the zona pellucida of the oocyte as well as in the head of the sperm. Researchers have theorized that the acrosome reaction with the zona pellucida is enabled by an adequate vitamin D status. Additionally, this vitamin appears to be involved in the acceptance of the sperm by the oocyte, whereby the vitamin D receptors act as gatekeepers to enable immune regulation and thus prevent rejection.

Maternal vitamin D deficiency has also been suggested to be an independent risk factor for preeclampsia, and a number of animal studies highlight the fact that vitamin D deficiency is associated with infertility.[131]

Calcium

Calcium is an important nutrient for conception, embryogenesis, and gestation. It is required for oocyte maturation, fertilization,[132] and bone formation of both mother and child. It has also been shown to exhibit a protective effect against preeclampsia. A Cochrane review emphasized that calcium supplementation appeared to almost halve the risk of preeclampsia,[133] which supports the prescription of calcium for all preconceptual women whose dietary intake is inadequate.[134]

Iodine

Iodine deficiency has increased in the past two decades owing to changes in the dairy industry. The primary supplementation for most people consisted of their dairy intake owing to iodine solutions used to clean the dairy equipment.[135] This practice has been modified, so that today chloride and bromide solutions are used instead.

Adequate dietary intake of iodine preconceptually is imperative because it can minimize the risk of thyroid-related disorders and/or mental retardation in the infant, defects that are commonly seen in the offspring of deficient mothers. Additionally, low iodine has been shown to negatively affect the development of the central nervous system in the fetus and can hinder conception owing to its role as a nutrient donator for the T_3 and T_4 hormones that regulate thyroid function and thus ovulation.

Maturing oocytes are highly dependent on healthy thyroid hormone levels for optimal reproductive function[136]; deficiency may result in a spectrum of disorders, including miscarriage, stillbirth, mental retardation, and cretinism (deaf mutism and spasticity).[137,138] Additionally, thyroid autoimmunity is significantly higher among infertile women than among fertile women and increases the rate of miscarriage.[139] Therefore, iodine can help to supply building blocks for thyroid hormones that are compromised by the autoimmune process.

Subclinical hypothyroidism may be associated with ovulatory dysfunction and adverse pregnancy outcomes; it is therefore crucial to assess thyroid (and iodine) status for both infertile males and females, because correction of this condition can reverse or prevent infertility.[140] In one study, 4980 women (462 of whom were pregnant) were tested for iodine status. Repeated miscarriage and stillbirth were associated with higher levels of deficiency, which increased the risk of reproductive failure.[141]

As early as 1939, Kemp[142] acknowledged a link between a deficiency of iodine and stillbirth of unknown origin. In the late 1970s, Potter et al[143] discussed the decline in stillbirth rates following iodine supplementation, highlighting the positive relationship that ensued between iodine (when taken at the correct dose) and a reduced incidence of stillbirth. Current research[144] indicates that 2000 babies continue to be stillborn every year. In spite of advances in technology, the cause of one third of these deaths is unknown.

It is recognized that a diagnosis of hypothyroidism based on thyroid stimulating hormone (TSH) values in isolation may not suffice to diagnose mild to moderate iodine deficiency in the pregnant woman.[145] It is therefore prudent to assess the urinary iodine status of each patient either as a morning spot urine test, 24-hour urinary excretion test, or iodine:creatinine ratio, as recommended by the World Health Organization.[146,146a]

Iron

Iron is required for the formation of red blood cells, subsequent transport of oxygen to the tissues via hemoglobin, nucleic acid metabolism as well as being involved in numerous enzyme systems within the body.[73] Because there may be a risk of hemochromatosis, it is imperative that all patients be assessed thoroughly prior to prescription to ensure that their health is prioritized. If supplementation

is needed, patients should address this deficiency in the preconceptual period to help prevent iron deficiency during the pregnancy.[134] Results from the Nurses' Health Study II suggest that women who consume iron supplements have a significantly lower risk of ovulatory infertility than women who do not.[147]

In one paper, iron supplements up to 40 mg or more were shown to reduce the risk of ovulatory infertility by up to 60% and to improve the chances of conception compared with women who did not take iron supplements.[147] The link between iron deficiency and infertility has been confirmed by a number of other papers.[148] Therefore, practitioners should study the patient's iron profile and ensure that all components are within the normal range, aiming to achieve serum ferritin stores of 80 ng/mL prior to conception, and saturation of greater than 30%. It is imperative to assess a full iron study profile, because ferritin can be elevated due to inflammatory processes in the body and give a false sense of iron repletion. This is especially important because some women are unable to take iron supplements during the first trimester owing to their tendency to aggravate nausea.

Magnesium

Magnesium is involved in numerous reactions in the body relevant to fertility, including cell signaling and energy production. Women experiencing spontaneous abortion have been observed to have lower plasma magnesium levels than healthy controls,[149] and those experiencing associated stress regarding their fertility will benefit from both magnesium and B vitamin supplementation. Stress is associated with impaired fertility, including miscarriage and failed pregnancy outcomes.[150]

Essential Fatty Acids (EFAs)

Women undergoing preconception care are encouraged to consume a diet rich in essential fatty acids,[134] because omega-3 fatty acids are required to maintain the lipid bylayer in all cell membranes and to serve as precursors for prostaglandin synthesis. Specifically in the prevention of miscarriage, omega-3 fatty acids (4 g/day providing 795 mg of docosahexaenoic acid and 1190 mg of eicosapentaenoic acid) have been found to improve the velocity of blood flow in the uterine arteries in women with recurrent miscarriage due to impaired uterine perfusion.[151]

Supplementation with omega-3 fatty acids has been shown to improve endometrial function. In vitro studies of decidualized cells have identified a decrease in prostaglandin production by up to 80%, indicating that prescription is beneficial for all women but most importantly those suffering from endometriosis or endometrial insufficiency.[152] Additionally, supplementation is believed to assist in reducing spontaneous preterm births associated with intrauterine inflammation.[153]

Probiotics

Alterations in the microflora of the vagina and subsequent genital and intrauterine infections[154] have been linked to reproductive failure and adverse pregnancy outcomes such as preterm labor, miscarriage, and spontaneous preterm birth.[154-156] In one study, during the first half of pregnancy, women with altered vaginal flora of bacterial origin were four times more likely to have a spontaneous preterm birth compared with the overall preterm birth rate.[157]

Botanical Medicines

Cimicifuga racemosa (Black Cohosh)

Cimicafuga racemosa (now known as Actaea racemosa) has historically been described by the eclectics as a uteroovarian tonic for "pains of a dull aching character; dragging pains in the womb, with sense of soreness; the dull tensive pains incident to reproductive disorders of the female, as well as the annoying pains accompanying pregnancy; false pains; after pains."[158] Its modern clinical application focuses heavily on mitigating menopausal complaints and regulating the estrogen cascade specifically in this life stage; however, its potential benefits are far broader, and it shows promise in assisting fertility. In one trial, women who were not responding to clomiphene citrate were divided randomly into two groups, both of which received clomiphene. However, one group was also given 120 mg of *C. racemosa*. Results showed that pregnancy rates were higher in the *C. racemosa* plus clomiphene group compared with the group that received clomiphene is isolation.[159]

Alchemilla vulgaris (Lady's Mantle)

Unfortunately there is little research on this valuable herb. It has a strong clinical and traditional use as a therapeutic astringent, which makes it an effective prescription for patients experiencing menorrhagia or frequent early miscarriage. Its tannin content supports the antihemorrhagic property, and *A. vulgaris* has traditionally been prescribed to halt bleeding and heal wounds (internal or external).[160] *A. vulgaris* is used to treat female reproductive problems including menstrual disorders, to prevent miscarriage, and as an aid to conception.[161]

Angelica sinensis (Dang Guai)

A. sinensis is a traditional Chinese herbal medicine with a gentle warming action. It is believed to nourish the blood, restore the body's natural balance, and serve as a female tonic for a number of gynecologic conditions, including amenorrhea. It appears to contain components that can increase uterine tone and relax the uterine musculature. The two active constituents most associated with this function include ligustilide[162] (an essential oil component) and ferulic acid.[163] Like many other herbal medicines, it is supported by a long history of use and clinical efficacy. In the absence of human studies, animal experiments have demonstrated that compounds in *A. sinensis* also regulate prostaglandin synthesis and can regulate experimentally induced inflammatory responses due to prostaglandin release.[164] Additionally, thromboxane A2, which increases blood viscosity and promotes blood clotting, appears to be regulated by this herb.[165] These mechanisms may explain its strong reputation as a blood tonic. *A. sinensis* is specifically prescribed for women with compromised fertility who also have blood disorders, menorrhagia, and reproductive inflammatory responses such as those present in endometriosis. It is important to remember that the very process of fertilization and implantation is a marked inflammatory event, which may explain the efficacy of *A. sinensis* as an antimiscarriage herbal medicine serving to promote and sustain conception.

A. sinensis is known to have spasmolytic effects on the uterus, specifically in the treatment of dysmenorrhea. It appears to normalize uterine activity and ease pelvic blood flow, which relieves pelvic congestion and pain. Traditionally it has been combined with *Paeonia lactiflora*[166] and *Ligusticum wallichii*[163] for menstrual pain that is aggravated by the cold. Modern herbalists extrapolate that usage to suggest that *A. sinensis* is a relaxing blood mover that can improve circulation to the uterus and thus assist in normalizing the endometrial lining and supporting implantation.

Asparagus racemosa (Shatavari)

A. racemosa is an Ayurvedic botanical renowned for is effects on the female reproductive system; it has been used for this purpose since the sixteenth century. *A. racemosa* is believed to function as an aphrodisiac, promoting strength and enhancing sexual appetite while preventing miscarriage and supporting healthy fertility. The roots were traditionally boiled in milk and consumed with sugar owing to their ability to promote libido and to increase *ojas* (which

can be likened to the naturopathic version of "vital force"). In Western herbal medicine, Shatavari is primarily prescribed as a female reproductive herb; in animal studies, it has been observed to exert estrogenic effects.[167] Unfortunately, few well-blinded human clinical studies are to be found in the literature; however, in Ayurveda, this herb has been used safely over long periods of time, even during pregnancy and lactation.[168]

Chamaelirium luteum (False Unicorn Root)

An important herbal medicine for reproductive disorders, *C. luteum* is a restricted herb owing to its threatened status from excessive wild crafting. Therefore, practitioners are encouraged to prescribe other herbal medicines containing similar steroidal saponins, such as *Dioscorea villosa* (wild yam) and to prescribe *C. luteum* if the clinical objective is not achieved. Additionally, the combination of *A. racemosa* (Shatavari) and *D. villosa* (wild yam) may be an even better choice owing to the synergistic action of these herbs.

Chamaelirium luteum has a strong traditional application as an antimiscarriage herbal medicine. It is undoubtedly one of the most effective herbal medicines for this purpose. The rhizomes appear to function as a uterine tonic and, since the time of the eclectics, have been prescribed to remedy any imbalance or symptom in the female reproductive tract. King's dispensatory documents the use of *C. luteum* for treating repeated and successive miscarriages, and Ellingwood[169] highlights its use for uterine displacement, particularly where there is threatened abortion, saying that it should be combined with *Viburnum prunifolium* to optimize this effect. It has a strong traditional application in the regulation of ovarian function and is particularly indicated to assist in the regulation of menstrual issues experienced in the first half of the cycle.[170] Additionally, it is described as an ovarian amphoteric because of its ability to regulate and normalize ovarian function.[170] Unfortunately, its precise mechanism of action is unknown; however, researchers have determined that it contains steroidal saponins, which are converted through digestion into the sapogenin diosgenin. This constituent has been shown to produce effects on ovarian function via its action on the hypothalamic-pituitary axis.

Paeonia lactiflora (White Peony)

Paeonia lactiflora has long been used in traditional Chinese medicine for its effects on the female reproductive system. In Chinese medicine, *P. lactiflora* is used in a formulation known as Dang-Gui-Shao-Yao-San, a combination of medicinal herbs used for the treatment of ovulatory disorders and thus to promote a good fertility outcome. Another formulation, Unkei-to (a traditional Japanese herbal medicine consisting of Shakuyaku [*Paeonia radix*, *Paeonia lactiflora Pallas*] and Keihi [*Cinnamomi cortex*, *Cinnamomum cassia Blume*]) demonstrates stimulatory effects on the ovulatory process and human granulosa cells in vitro.[171] This formulation has been found to promote steroidogenesis, cytokine secretion, 17 beta-estradiol secretion, and progesterone secretion in highly luteinized granulosa cells obtained from IVF patients.

Tribulus terrestris (Tribulus)

Tribulus terrestris is generally thought of as a male tonic; however, it is used extensively in Western herbal medicine for the treatment of female reproductive disorders, including infertility.

A common clinical use of Tribulus involves its FSH-stimulating properties at the start of the menstrual cycle in initiating ovulation and improving conception rates. Most of the substantiating evidence for this claim, although clinically relevant, lacks research substantiation.

In a clinical context, one can expect to see a marked increase in cervical fluid within a few days of taking the prescription. This increase precedes ovulation and supports conception outcome markedly. It is especially beneficial for patients who have delayed or absent ovulation, because it regulates the ratio of follicle stimulating hormone to luteinizing hormone. Patients are generally more aware of their increased fertility, libido, and release of cervical fluid. This has a positive effect on their mood and confidence in their fertility.

Most papers and documentation refer back to a poorly designed study by Tabakova et al,[172] who conducted a nonrandomized trial in 51 women with endocrine sterility to assess the effect of Tribestan (standardized Tribulus extract) on infertility. Although the results of this study were encouraging, larger studies of better design are needed in order to evaluate the effectiveness of Tribestan in treating female infertility. Subjects took Tribestan, 1 to 2 tablets (250 mg per tablet) by mouth three times daily, either on days 5 to 14 of the cycle (schedule I), or days 1 to 12 of the cycle (schedule II) for the first 3 months. After a washout period, the patients were treated with Tribestan, 1 to 2 tablets by mouth three times daily days 1 to 12 of the cycle, plus either Stimovul, 1 to 2 tablets daily on days 5 to 14 of the cycle, or clomiphen citrate 1 to 2 tablets daily on days 5 to 9 of the cycle. The authors found that 67% of the patients treated with Tribestan had normalized ovulation with or without pregnancy. When compared with other drugs, Tribestan was inferior to Stimovul alone. Of 36 patients, 20 went on to receive combination treatment.

Vitex agnus castus (Chaste Tree)

V. agnus castus, one of the best-known adjuncts to fertility treatment, is beneficial for anovulatory cycles, hyperprolactinemia, hypothalamic dysfunction, hypothalmic-pituitary-ovarian (HPO) axis modulation, and promoting a regular and normal menstrual cycle. It is well known for its beneficial effects in premenstrual syndrome (PMS), and numerous trials have been undertaken in multiple countries to evaluate its effectiveness. It has been proved to alleviate symptoms associated with latent hyperprolactinemia, whereby it is characterized by lower-than-normal progesterone secretion and normal to mildly elevated prolactin levels. These characteristics are believed to cause a number of menstrual disorders including typical PMS symptoms, altered menstrual cycle lengths, and amenorrhea. Causative factors appear to relate to an alteration in the hypothalamic pituitary axis. *V. agnus castus* has been shown to correct menstrual irregularities[173] including amenorrhea,[174] specifically when caused by latent hyperprolactinemia, owing to its ability to inhibit prolactin secretion.[175] This is achieved by competitively binding to dopamine D2 and opioid receptors, suggesting a dopaminergic effect.[176]

An uncontrolled study using a blend of *V. agnus castus* combined with green tea extract and nutrients (L-arginine; vitamins E, B_6, and B_{12}; folate; as well as iron, magnesium, zinc, and selenium) administered to 30 women who had been unsuccessful in their attempt to conceive despite trying for 6 to 36 months also observed beneficial results.[177] After 5 months of treatment, 5 women out of 15 in the treatment group were pregnant (33% vs. 0%, $P < 0.01$). Four of the five women had healthy live births.

A randomized double-blind controlled trial of *V. agnus castus* compared with placebo was shown to improve hormone levels, facilitate the recurrence of menstruation in women with amenorrhea, and ameliorate pregnancy outcome in women with fertility problems.[178] Women were given a registered product called Mastodynon and results were impressive. In those with amenorrhea or luteal-phase insufficiency, pregnancy occurred in the active group more than twice as often as in the placebo group, with minimal side effects.

Another study used a preparation containing *V. agnus castus* as well as other botanicals.[179] Ninety-six women with secondary

amenorrhea, luteal insufficiency, or idiopathic infertility received either the *Vitex* combination or placebo over three menstrual cycles. Of these women, 15 went on to conceive (7 with amenorrhea, 4 with idiopathic infertility, and 4 with luteal insufficiency).

THERAPEUTIC APPROACH

General Measures

- Avoid exposure to free radicals.
- Identify and eliminate exposure to environmental hazards including pesticides, solvents, heavy metals, and other toxins
- Use effective stress-reduction techniques and employ psychological counseling if needed.
- Avoid cigarette smoking, alcohol, and recreational drugs
- Avoid douches, vaginal sprays, scented tampons, or other feminine products that change the pH of the vagina and disturb vaginal microecology.
- Ensure that weight is within a healthy body-mass index (20%-25%).
- Avoid medications that affect the quality of cervical fluid, including antihistamines, some cough mixtures, dicyclomine, progesterone (taken prior to or at ovulation), propantheline, tamoxifen and others.
- Avoid all personal lubricants (unless sperm-friendly types are chosen), because several studies show that some common lubricants kill sperm as effectively as contraceptive jellies do.[180-192]

Diet

- Encourage the principles of the fertility diet.
- Avoid dietary sources of free radicals, saturated fats, hydrogenated oils, trans fatty acids, and cottonseed oil.
- Increase consumption of good dietary sources of antioxidant vitamins, carotenes, and flavonoids (dark vegetables and fruits) as well as essential fatty acids (nuts and seeds).
- Recommend daily consumption of 8 to 12 servings of vegetables and 1 to 2 servings of fresh fruits.
- Optimize protein intake from both vegetarian and organic animal sources.
- Ensure that hydration requirements are met using a 30 mL/2.2 lb (1 kg) formula to calculate requirements individually and optimize hydration and renal function.
- Eliminate caffeine, alcohol, sugar, and artificial substances (preservatives, colorings, additives).
- Encourage sufficient essential fatty acid intake in the form of half a cup of raw nuts or seeds, cold-pressed oils, and sustainably farmed fish (from organic sources).

Nutritional Supplements

Supplementation is best achieved incorporating the repletion model (as previously discussed). A comprehensive summary of all nutrients is listed in Table 179-6 however, an individualized prescription based on a thorough assessment is advisable to accurately determine the most essential supplements required.

Botanical Medicines

Cimicifuga racemosa (black cohosh)

- Fluid extract (1:2): 2 to 4 mL (0.5 to 1 tsp) three times daily
- Extracts equivalent to dry herbal medicine: 42.25 mg/day

Alchemilla vulgaris (lady's mantle)

- Fluid extract (1:1): 40 to 85 mL/day

TABLE 179-6 **Summary of Nutrient Considerations to Promote Fertility**

Vitamin A[a]	3000-5000 IU/day
Vitamin B_1 (thiamine)	50-100 mg/day
Vitamin B_2 (riboflavin)	50 mg/day
Vitamin B_3 (niacin)	50-200 mg/day
Vitamin B_5 (pantothenic acid)	50-200 mg/day
Vitamin B_6 (pyridoxine)	50-250 mg/day
Vitamin B_9 (folic acid)	800-5000 mcg (dependent on MTHFR status and homocysteine levels)
Vitamin B_{12} (cyanocobalamin)	800-5000 mcg (reflecting vitamin B_9 with a 1:1 ratio where possible)
Vitamin C	1000-4000 mg/day in divided doses
Vitamin D3[b]	1000-5000 IU/day (decrease to 1,000 IU/d in summer and 2,000 IU/d in winter when repleted)
Vitamin E (mixed tocopherols and tocotrienols)	500-1000 IU/day
Vitamin K[c]	2-75 mg/day
Beta carotene	10-30 mg/day
Coenzyme Q10	100-300 mg/day in divided doses
Calcium	1000-1500 mg/day
Chromium[d]	100-1000 mcg/day
Copper[e]	2-4 mg/day
Iodine[f]	200-400 mcg/day (decrease to 200 mcg/day when repleted)
Iron[g]	10-100 mg/day
Magnesium	500-1000 mg/day
Selenium	150-300 mcg/day
Zinc	40-80 mg/day (decrease to 25 mg/day when repleted)
Total omega-3 essential fatty acids	1000-5000 mg/day
Docosahexaenoic acid (DHA)	400-700 mg/day
Eicosapentaenoic acid (EPA)	800-1000 mg/day
Total omega-6 essential fatty acids	1000-2000 mg/day
Evening primrose oil	1000-1500 mg/day
L-Arginine	3000-10,000 mg/day
L-Carnitine	1000-4000 mg/day
Probiotics (mixed strains)	$25\text{-}50 \times 10^9$/day

[a]Retinol equivalents are now used: 1 mcg RE = 1 mcg retinol = 6 mcg beta-carotene = 12 mcg other carotenoids. Avoid during pregnancy. Ensure that prescription is based on need due to fat solubility and potential for placental transfer in second trimester. Monitor dose carefully. Alternatively, beta-carotene may be a more appropriate prescription.
[b]Prescribe based on pathology results.
[c]Consider prescription in instances of coagulation disorders. Monitor closely to ensure no drug interaction is present.
[d]Dose dependent on blood sugar level control and weight requirements. Calculate based on patient's weight.
[e]Avoid in instances of Wilson's disease (assess prior to prescription) and ensure that prescription is recommended only when zinc:copper ratio is considered.
[f]Assessment prior to prescription is essential to determine dose. Should only be conducted when thyroid function values can be reviewed.
[g]Prescription must have pathology interpretation prior to recommendation to determine required dosage.

Angelica sinensis (dang gui)

- Fluid extract (1:1): 2 to 4 mL (0.5 to 1 tsp) three times a day

Asparagus racemosa (Shatavari)

- Fluid extract (1:1): 2 to 4 mL (0.5 to 1 tsp) three times a day

Paeonia lactiflora (white peony)

- Fluid extract (1:1): 2 to 4 mL (0.5 to 1 tsp) three times a day

Tribulus terrestris (Tribulus)

- Standardized extract, equivalent to dried herb (aerial parts of leaf), standardized to contain furostanol saponins as protodioscin 12.22 mg/1 g, 9 to 36 g per day.

Vitex agnus castus (chaste berry)

- The usual dosage of chaste berry extract (often standardized to contain 0.5% agnuside) in tablet or capsule form is 175 to 225 mg per day. If using the liquid extract, the typical dosage is 2 to 4 mL (1/2 to 1 tsp) per day.

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CHAPTER 180

Infertility, Male

Michael T. Murray, ND, and Leah Hechtman, M Sci Med (RHHG), BHSc (Naturopathy), ND

DIAGNOSTIC SUMMARY

- Inability to conceive a child after 12 months of regular unprotected intercourse (at least twice weekly) with the same female partner and in the absence of female causes.
- Sperm abnormalities confirmed by two properly performed semen analyses of sperm count, morphology, motility, or other aspects.

GENERAL CONSIDERATIONS

Infertility affects about 7.3 million women and their partners in the United States, which equates to approximately 12% of the reproductive-age population.[1] One out of seven couples will experience difficulty conceiving. Infertility affects men and women equally, with approximately one third of cases being due to male factors, one third to female factors, and the remaining one third to joint issues. In the United States, it is estimated that about 6% of men between the ages of 15 and 50 years are infertile.[2]

Throughout the world there has been a recent and dramatic decline in fertility that appears to be unrelated to the socioeconomic status of any given country; however, deferred childbearing and improved contraception are undoubtedly major factors. Population growth is below the replacement rate in several countries—such as Sri Lanka, Denmark, and Spain—where there have been no obvious increases in abortion rates or contraceptive use. This loss of fertility has affected Denmark to the point where approximately 7% of all newborn babies are now being conceived by assisted methods.[3] In the United States, some patients will require assisted reproductive technologies (ARTs) in order to conceive. Statistics indicate that in vitro fertilization (IVF) and similar treatments account for less than 3% of infertility services and approximately 0.07% of U.S. health care costs.

As a general rule, it is considered that 3 out of 5 couples conceive within 6 months of trying; 1 in 4 take between 6 months and a year. For the rest, conception takes more than a year, indicating that there may be a problem. Therefore, we can define primary infertility as existing when pregnancy has never occurred despite regular unprotected intercourse for a year or more. Secondary infertility is defined as existing if, despite having achieved a pregnancy in the past (which may or may not have resulted in the birth of a child), a couple is unable to conceive again after a year or more of regular unprotected intercourse.

Unexplained infertility occurs in approximately 5% to 10% of couples trying to conceive. Generally, assessments reveal limited information and find no apparent cause for infertility. The effort to determine whether unexplained infertility is a true diagnosis is often complicated by poor investigation or the lack of current assessment strategies. The naturopath can often elucidate answers in these situations by taking a holistic view in assessing the patients and thus producing positive outcomes.

Most causes of male infertility reflect abnormal sperm counts, morphology, or motility. Although it takes only one sperm to fertilize an egg, a male ejects nearly 200 million sperm in an average ejaculate. Because of the natural barriers in the female reproductive tract, only about 40 sperm ever reach the vicinity of an egg. There is a strong correlation between the number of sperm in an ejaculate and fertility.

Fertility is a reflection of general health and well-being and can also indicate latent or undiagnosed genetic abnormalities or other etiologic considerations.

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TABLE 180-1 **Semen Terminology**[5]

Aspermia	An absence of semen despite male orgasm
Azoospermia	A complete absence of sperm (spermatozoa) in the semen.
Oligozoospermia	Reduced number of normal motile sperm cells (spermatozoa) in the ejaculate (compared with *azoospermia*, which means no sperm in the ejaculate). It includes laborious terms such as *asthenozoospermia, teratozoospermia, and oligoasthenoteratozoospermia*
Teratozoospermia	Sperm with abnormal morphology
Necrospermia	Death of sperm
Oligoasthenoteratozoospermia	An unnecessarily long name that indicates low count, weak motility, and abnormal morphology

These considerations are many and varied; thus, a comprehensive, holistic review is essential. An overview of the causes of male infertility is given in Table 180-1.

- A smooth, oval head that is 5 to 6 µm long and 2.5 to 3.5 µm around (smaller than the point of a needle)
 - A well-defined cap (acrosome) that covers 40% to 70% of the sperm head
 - No visible defect of neck, midpiece, or tail
 - No fluid droplets in the sperm head that are bigger than half of the sperm head's size[4]

If a sperm deviates from normal, it is defined by the terminology given in Table 180-1.

SPERMATOGENESIS

In healthy young men, sperm are produced by repeated divisions of cells in small, coiled tubules within the testes at an average rate of approximately 100 million per day. Each spermatogenic cycle consists of six stages, and approximately five cycles are required to produce one mature sperm. From the beginning of division of the stem cell to the appearance of mature sperm in the semen takes between 72 and 76 days. Therefore, anything that the male experiences during spermatogenesis can affect mature sperm regardless of his health at the time of examination. Factors to consider would include illness, toxicity, trauma, nutritional status, and others.

The sperm spend 2 to 10 days passing through the epididymis, during which time they mature and become capable of swimming and penetrating oocytes. At the beginning of ejaculation, sperm are transported from the tail of the epididymis via the vas deferens to the urethra. The seminal vesicles, prostate gland, and Cowper's glands secrete most of the volume of semen; these secretions help deliver the sperm during ejaculation. The volume of liquid coming from the two epididymides is less than 5% of the total semen volume. Approximately 60% of the semen volume comes from the seminal vesicles and 30% from the prostate gland. The average semen volume for healthy men ejaculating every 2 days is 3 mL; the average sperm concentration is 85 million/mL (more specifics are given later). During ejaculation, the sperm and prostatic fluid are usually ejected first and the seminal vesicle fluid follows. The seminal vesicle fluid coagulates, giving the semen a lumpy, gel-like appearance. Liquefaction occurs after 20 minutes or so, when the gel disappears.

DIAGNOSTIC CONSIDERATIONS

Andrology Assessments

Semen Analysis

In a fertility context, the semen analysis forms the primary basis of assessment. It provides the clinician with a snapshot of the male's fertility and reflects his general health in the preceding 72 to 76 days.

An individual's semen quality can vary considerably between samples, even in males with normal semen parameters. In interpreting the assessment, it is imperative that the clinician acknowledge the important fact that a diagnosis is not achieved until an abnormality is confirmed by two separate investigations. As a result, at least two and occasionally three semen analyses are needed, each several weeks apart, in order to gain an accurate picture of an individual's *average* semen quality. It is well recognized that sperm count can be adversely affected by illness, especially fevers, which may temporarily suppress sperm count in normal males for several months. In this case, the semen analysis should of course be delayed. Additionally, general recommendations such as in-clinic collection (versus at-home collection), careful consideration of laboratory guidelines (abstinence timing, lubricant usage), and the standard of the andrology laboratory facility must be considered in reviewing results. Table 180-2 outlines the World Health Organization's (WHO's) guidelines for assessing a semen analysis.

In 2010, the WHO released updated guidelines for semen analysis. The fourth edition (released in 1999, with a review in 2003) had presented a more positive picture of male fertility. The 2010 guidelines suggest that, overall, male fertility is declining. (Note that all andrology laboratories have adopted the new guidelines. The greatest difference can be denoted by reviewing morphology, owing to differing criteria and percentage scales.)

A semen analysis can be conducted by a number of assessments, including the following:

- General semen analysis (SA): To assess motility, morphology, concentration, volume, appearance, and so forth.
- Sperm chromatin integrity test: To determine the level of DNA damage to sperm
- Immunobead test: To assess for antibodies against sperm
- Semen culture: To assess for infection
- Retrograde ejaculatory testing: To assess for retrograde semen flow or obstruction if semen analysis yields an extremely low count
- Trial wash: To assess sperm factors and determine whether IVF or intracytoplasmic sperm injection (ICSI) is more appropriate, conducted prior to IVF and/or ICSI procedures
- MESA/TESE/PESE (microsurgical epididymal sperm aspiration/testicular sperm extraction/percutaneous epididymal sperm aspiration): To extract sperm from the testicles by a specialized procedure when sperm count is low/absent or if ejaculation is not possible

Male Reproductive Assessment

A thorough assessment of the male patient is crucial to accurately determine his general and fertility health. Some of these assessments may require referral to a fertility specialist, urologist, or endocrinologist; however, thorough questioning should be conducted by the naturopath to elucidate a full history and assess causative or contributing factors. Tables 180-3 through 180-6 highlight the most relevant assessments required in a fertility workup.

TABLE 180-2 **Interpretation of Semen Analysis**

SEMEN PARAMETER	LOWEST REFERENCE (REFERENCE RANGE)	INTERPRETATION AND TREATMENT OBJECTIVE
Standard Components of a Semen Analysis		
Abstinence	Parameters are defined based on abstinence of 3 days.	It is essential to ensure that males ejaculate and then count the required 3 days' abstinence.
Collection method	*Optimal collection is via masturbation; however, specialized condoms can be provided for males with religious restrictions. Additionally, standard lubricants can interfere with the accuracy of the reading and must be avoided. Andrology laboratories are able to supply alternatives.*	
Specimen	Semen sample must be complete.	Incomplete samples are frequent and will distort readings. Assessment can be determined only by reviewing a full sample owing to variations in prostatic secretion vs. epididymal involvement.
Analysis time	*Sample must be analyzed within 60 min and is best collected in the clinic environment to prevent complications.*	
Appearance	Nil debris, nil clumping, or viscosity changes, liquefaction complete.	Debris, clumping, viscosity, or liquefaction issues can suggest systemic congestion, poor hydration, poor elimination, or immune reactions (clumping especially). It can also indicate poor ejaculation frequency.
pH	>7.2 (7.2-7.8)	pH control is essential for sperm survival. An abnormally high or low semen pH can kill sperm or affect their ability to move or to penetrate an egg. The pH of the sample will be affected if there was a delay between sample collection and analysis. If the pH is <7.0 and the sample is azoospermic, there may be an obstruction of the ejaculatory ducts or bilateral congenital absence of the vas deferens (CBAVD). pH irregularities can relate to dietary intake and hydration level. Very acidic samples can indicate obstruction and require referral.
Volume	>1.5 mL (1.4-1.7 mL)	Volume can be affected by the period of abstinence (3 days are recommended), incomplete ejaculation, and retrograde ejaculation. It generally indicates dehydration; treatment should consist of hydration calculation based on weight and energy expenditure.
Concentration		
Sperm concentration	> 15 million/mL (12-16 million/mL)	Concentration can be affected by a number of factors, including: • Incomplete collection of the sample • Health status of the individual • Obstruction • Genetic condition The finding of no sperm in the ejaculate suggests either an absence of sperm production or obstruction to sperm outflow. It is most important that an azoospermic semen sample be spun down to carefully examine whether the ejaculate contains even a few sperm. The naturopathic approach considers defects in internal processes and hormonal pathways as potential hindrances to an optimal count. Nutritional deficiencies are essential, and interferences with pathways for spermatogenesis require exploration.
Total sperm count	>39 million per ejaculate (33-46 million per ejaculate)	
Motility		
Total motility	40% (38%-42%) (>25% rapid, >40% progressive, >50% motile)	Sperm must be able to move forward (or "swim") through cervical mucus to reach an egg. A high percentage of sperm that cannot swim properly may impair a man's ability to father a child. There are other important conditions that predominantly affect sperm motility, such as sperm autoimmunity, a condition that accounts for about 6% of male infertility. No movement (immotile sperm) may be due to structural problems in the sperm's tail or to death of sperm. The percentage of sperm that are alive (sperm vitality) is noted because this declines in association with genital tract infections and disorders of sperm transport through the genital tract. The proportion of live sperm is assessed if total motility is <50%. Low motility and high vitality could indicate a disturbance of the motility apparatus. If >75% of sperm are dead, immobilizing antisperm antibodies might be present and testing is encouraged. Poor motility can often indicate autoimmune processes; infection; lack of mitochondrial energy to propel the sperm; or medication, alcohol or other toxins that affect semen quality.
Progressive rating	>3	
Progressive motility	>32% (31%-34%) with forward movement	
Vitality	>58% (55%-63%) live	

Continued

TABLE 180-2 **Interpretation of Semen Analysis—cont'd**

SEMEN PARAMETER	LOWEST REFERENCE (REFERENCE RANGE)	INTERPRETATION AND TREATMENT OBJECTIVE
Morphology		
Sperm morphology	4% (3%-4%) normal forms (Tygerberg criteria) Note: A trial wash can provide specificities of morphologic abnormalities (i.e., head, neck, tail).	Sperm shape is an important predictive indicator of the sperm's fertilizing ability. Morphology is performed on Pap-stained sperm using the Strict Tygerburg criteria of assessment. These criteria have a strong correlation with the presence of abnormalities and clinical pregnancies and accept only sperm that are normal in every way. Morphology is often a direct reflection of generalized toxicity, because semen is a by-product of the body and is a major eliminatory channel. Detoxification, avoidance of environmental toxins, and immaculate dietary practices are essential. Key nutrients in sperm structure must be considered, including protein, essential fatty acids (DHA), all antioxidants including coenzyme Q10, zinc, vitamins C and E, and selenium.
Teratozoospermia index (TZI)	<1.64 TZI	
Specialized Additions to a Semen Analysis		
Immune factors		
Peroxidase-positive leukocytes	<1.0 million/mL	The presence of white blood cells or bacteria indicates the presence of a genitourinary infection. Ascertaining the type of infection is the primary objective, with subsequent targeted treatment to eradicate it. It is essential to assess the female partner to prevent cross-infection. Antibodies attach to the surface of the sperm and reduce their life span, impairing their motility and ability to penetrate the partner's cervical mucus. Antibodies located on the sperm head may prevent the sperm from fertilizing the egg. Abstinence or a barrier method until the immune system is regulated is essential, along with concurrent autoimmune treatment with herbal medicines, dietary modifications, lifestyle modifications, and nutritional supplementation.
Semen culture	Negative	
Mixed antiglobulin reaction (MAR) test (motile sperm with bound particles)	<50%	
Immunobead test (motile spermatozoa with bound beads)	<50% sperm with adherent particles	
GAM or isotype	>20% positive >50% pathologically significant (except tail tip binding)	
Sperm DNA Damage		
SCIT (sperm chromatin integrity test)	DNA Fragmentation Index (DFI): • Excellent DNA integrity (<15%) • Good DNA integrity (15%-24%) • Fair DNA integrity (25%-29%) • Poor DNA integrity (>29%) High green stain (HG): • Normal (<15%) • Abnormal (15%-100%)	Various methods have been developed to measure strand breaks in sperm DNA in situ. Currently, there are four major tests of sperm DNA fragmentation, including the Comet, Tunel, SCIT (Sperm Chromatin Integrity Test) and the Acridine Orange Test (AOT). DNA fragmentation can be attributed to various pathologic conditions including cryptorchidism, cancer, varicocele, fever, age, infection, leukocytospermia, and others. Many environmental conditions can also affect DNA fragmentation, such as chemotherapy, radiation, prescribed medicines, air pollution, smoking, pesticides, chemicals, heat and ART preparation protocols. Research indicates that sperm with high levels of DNA fragmentation have a lower probability of producing a successful pregnancy. Samples with a DNA fragmentation level greater than 29% are likely to have significantly reduced fertility potential, including a significant reduction in term pregnancies and an increased miscarriage rate. Sperm that appears to be normal by traditional semen analysis parameters may have extensive DNA fragmentation. It is normal for up to 1:5 sperm (20%) to have some DNA fragmentation. Mature sperm are protected from damage, because 85% of the chromosome are bound by protamines into a condensed, compact structure. If more than 20% of sperm have DNA damage, there is an increased risk of infertility, poor oocyte fertilization, defective/impaired embryo development, increased probability of implantation failure, miscarriage and recurrent miscarriage (up to 3-4 times higher) and genetic disease or childhood cancer in the next generation.

TABLE 180-2 **Interpretation of Semen Analysis—cont'd**

SEMEN PARAMETER	LOWEST REFERENCE (REFERENCE RANGE)	INTERPRETATION AND TREATMENT OBJECTIVE
		Reasons for testing include unexplained infertility, low fertility rates, poor embryo quality, implantation failure post-IVF, recurrent miscarriage, exposure to environmental toxins, abnormal semen analysis, and in males above 45 years of age. Once male germ cells have completed meiosis, they lose their capacity for DNA repair, discard their cytoplasm (containing the defensive enzymes that protect most cell types from oxidative stress), and eventually become separated from the Sertoli cells that have nursed and protected them throughout their differentiation into spermatozoa. In this isolated state spermatozoa must spend a week or so journeying through the male reproductive tract and, uniquely in our species, a further period (up to 3 or 4 days) in the female tract waiting for an egg. During this period of isolation, sperm DNA is vulnerable to damage by both xenobiotics and electromagnetic radiation. Such DNA damage is associated with male infertility; its aberrant repair in the fertilized egg may result in mutations in the embryo with the potential to either induce abortion or impair the health and fertility of the offspring.[134,135] Treatment consists of environmental review and modification as well as exceptionally high doses of antioxidant prescription.
Other		
Seminal zinc	>2.4 mol per ejaculate	Low levels suggest that supplementation is required.
Seminal fructose	>13 mol per ejaculate	Normal levels are 300 mg/100 mL ejaculate. Absence may indicate that the man was born without seminal vesicles or may have a blockage of seminal vesicles. Referral is essential for further investigation.
Seminal neutral glucosidase	>20 mU per ejaculate	Alpha-glucosidase is a normal constituent of human semen produced mainly in the epididymis. It is significantly correlated with sperm count. Its activity is low in cases of epididymal obstruction.

Data from World Health Organization. *WHO Laboratory Manual for the Examination and Processing of Human Semen,* 5th ed. Geneva, Switzerland: 2010, cited in Hechtman L. *Clinical Naturopathic Medicine.* Chatswood, Australia: Elsevier Australia.

TABLE 180-3 **Fertility Inquiry**

ASSESSMENT	ELABORATION AND EXPLANATION
Age	What ages are the couple?
Fertility history	How long have they been trying to conceive, and have they ever conceived previously (together/separately)? Do they have any idea why they have not been able to conceive?
Sexual history	STI screen: Potential sexually transmitted disease exposure, symptoms of genital inflammation (e.g., urethral discharge, dysuria)
Medication history	Such as sulfasalazine (Azulfidine), methotrexate, colchicine, cimetidine (Tagamet), spironolactone (Aldactone)
Surgical history	Such as previous genitourinary surgery
Contraception	When it was ceased and the likely speed of its reversibility
Fertile times	Whether the couple engage in regular intercourse during fertile times
Lifestyle factors	Diet, exercise, alcohol, smoking cessation, recreational drug use, environmental toxin screen
Prior paternity	Previous fertility
Psychosexual issues (erectile, ejaculatory)	Interference with conception
Pubertal development	Poor progression suggests underlying reproductive issue
A history of undescended testes	Risk factor for infertility and testicular cancer
Previous genital infection (STI) or trauma	Risk of testis damage or obstructive azoospermia
Symptoms of androgen deficiency	Indicative of hypogonadism
Previous inguinal, genital, or pelvic surgery	Testicular vascular impairments, damage to vasa, ejaculatory ducts, ejaculation mechanisms
Medications, drug use	Transient or permanent damage to spermatogenesis
General health (diet, exercise, smoking)	General health screen

Modified from Hechtman L. *Clinical Naturopathic Medicine.* Chatswood, Australia: Elsevier Australia, 2011.

TABLE 180-4 **Physical Examination**

ASSESSMENT	ELABORATION AND EXPLANATION
General examination	Acute/chronic illness, nutritional status
Genital examination	Assess for varicocele, testicular size, and other genital factors Testes: Small testes suggest spermatogenic failure Presence of vas deferens: may be congenitally absent Epididymides: thickening or cysts may suggest previous infection and resultant obstructive problems Varicoceles: detected when standing, coughing, or performing Vaslsalva maneuver Penis: assessed for abnormalities (e.g., Peyronie's disease) that may interfere with intercourse
Degree of virilization assessment	Assess for signs of virility Signs of androgen deficiency (e.g., increased body fat, decreased muscle mass, decreased facial and body hair, small testes, Tanner stage <5)
Prostate examination	Assess if history suggests prostatitis or a sexually transmitted infection

Modified from Hechtman L. *Clinical Naturopathic Medicine.* Chatswood, Australia: Elsevier Australia, 2011.

TABLE 180-5 **Endocrinologic Assessments**

ASSESSMENT	JUSTIFICATION FOR ASSESSMENT
Follicle stimulating hormone (FSH)	Assessment to ensure that hormonal status is optimal to eliminate hormonal abnormalities
Progesterone (P4)	Testosterone
Prolactin (PRL)	Testosterone is often normal (8-27 nmol/L) even in men with significant spermatogenic defects. Some men with severe testicular problems display a fall in testosterone levels and rise in serum LH. These men should undergo evaluation for androgen deficiency. The finding of low serum testosterone and low LH suggests a hypothalamic–pituitary problem (e.g., prolactinoma; serum prolactin levels required).
Luteinizing hormone (LH)	FSH
Total testosterone, free testosterone	Elevated levels are seen when spermatogenesis is poor (primary in testicular failure); in normal men, the upper reference value is approximately 8 IU/L. In azoospermic men, 14 IU/L strongly suggests spermatogenic failure, 5 IU/L suggests obstructive azoospermia; a testis biopsy may be required to confirm that diagnosis.
Sex hormone–binding globulin (SHBG)	Evaluates if concentration of SHBG is affecting the amount of testosterone available to body tissues.
DHEA-S, cortisol	Additional hormone levels should be reviewed on an individual basis, including a full adrenal profile if the impact of stress is considered relevant.

Modified from Hechtman L. *Clinical Naturopathic Medicine.* Chatswood, Australia: Elsevier Australia, 2011.

THERAPEUTIC CONSIDERATIONS

When the naturopath is presented with a male patient complaining of infertility, the first step is to determine whether he has been given a thorough, comprehensive assessment. Assessment results can help to determine whether the issue can be effectively treated, because genetic factors or overt physical impediments will require additional interventions.

- *Treatable conditions:* One in eight infertile men has a treatable condition that can be overcome, so that natural conception may become possible.
- *Untreatable subfertility:* Three quarters of infertile men have sperm present in the semen, but in lower numbers than normal. In these cases the problem cannot be solved without intervention. These men are often defined as subfertile, since pregnancies may occur but at lower rates than usual. On average, more months of trying are needed to achieve conception, or conception may simply not occur. Following naturopathic intervention, it may be possible to address infertility factors or, alternatively, offer a referral for ARTs/IVF.
- *Untreatable male sterility:* About one in nine infertile men has no sperm in his semen or testes and cannot be treated. Sperm-producing cells in the testes either have not developed or have been irreversibly destroyed. Adoption or donor insemination are the only possibilities for couples in this group who wish to have families.

In treating males for infertility, the optimal approach is to adopt a preconception program for both prospective parents. Preconception treatment adheres to the philosophy that the final stages of gamete production can be modified and influenced. The final stages of spermatogenesis last between 72 and 76 days. By influencing the environment to which sperm are exposed and optimizing the general well-being of the host, practitioners may be able to influence sperm development positively and to address and deal with related health concerns.

Of importance, acknowledging and addressing nutritional status throughout this developmental stage can significantly influence the prospective outcome. The concept of nutrient repletion is highly applicable within a fertility context. Optimal fertility is best achieved when prime health is realized. The repletion model indicates that prescriptions are required for a minimum of 3 months to properly address any deficiencies present and to ensure that all nutrients are used within each required pathway in the body. For example, zinc is involved in hundreds of pathways, including those that affect reproductive health and function. To rectify all possible deficiencies, sufficient zinc supplementation at a repletion dose (typically higher than in general prescriptions) for an extended time (at least 3 months) can enable optimal correction. At lower doses or doses of insufficient duration, zinc treatment may address only those health concerns that have the highest priority (i.e., immune function vs. sperm production).

TABLE 180-6 **Other Assessments**

ASSESSMENT	JUSTIFICATION
General Health Assessments	
FBC, blood type Standard blood chemistries 25[OH]D3 Fasting glucose Cholesterol profile General sexually transmitted infection (STI) screen	General health assessments to eliminate other abnormalities
TSH and urinary iodine (24-hour or morning spot)	Query thyroid function and iodine status
Urinalysis/swab	
Infection screen	General urinalysis to eliminate underlying infection or abnormality. Urogenital infections have been found to play a part in the genesis of miscarriage[136,137] and infertility.[138] Most patients are unaware of their presence owing to the asymptomatic nature of these infections. The most common infections that require screening include *Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis,* and *Neisseria gonorrhoeae.*
Advanced Fertility Assessments	
Karyotyping and subsequent genetic testing	Advanced fertility assessments if previous results show no abnormality or if infertility remains unexplained. WHO guidelines suggest that peripheral blood karyotyping analysis can be diagnostically helpful. Abnormal genotype may be present in up to 12% of azoospermic men and 4% of oligospermic men. Cystic fibrosis screening is recommended for azoospermia if due to CBAVD. Optional screening for Y-chromosome microdeletion if sperm count is <5 million/mL.
Scrotal (testicular) ultrasonography	History of undescended testes or concern regarding testicular cancer.
Transrectal ultrasonography	If ejaculatory duct obstruction suspected.
MTHFR C677T MTHFR 1298C Prothrombin G20210A Factor V Lieden Selenium assay Fasting homocysteine	Indicated in instances of miscarriage, unexplained infertility, marked sperm abnormalities, or implantation issues.
Other Considerations	
Nutrient and toxic element screening	Assessments of toxic elements, including aluminum, arsenic, cadmium, lead, and mercury are crucial so as to eliminate them as causative or contributing factors. It is widely accepted that excessive exposure to heavy metals has a detrimental effects on fertility[139,140] and must therefore be assessed and remedied during the preconception period.
Environmental impact	Other environmental assessments, including those that assess porphyrins, PCBs, chlorinated pesticides, volatile solvents, phthalates, parabens, and other toxins. These should additionally be considered due to their deranging effects on reproductive function, endocrinology, gamete development, and thus embryologic potential.

Modified from Hechtman L. *Clinical Naturopathic Medicine.* Chatswood, Australia: Elsevier Australia, 2011.

Within the naturopathic framework it is crucial to naturally support and attenuate all coexisting health conditions. Therefore, treatment should be structured to acknowledge all health concerns; that is, to optimize the general health of the male patient as an underlying position.

Finally, it is always important to acknowledge that the most favorable fertility occurs when the individual's health is optimal. The body is primed to pass on genetic material only when the environment and other conditions are at their best. If survival from an evolutionary perspective is compromised, fertility will be hindered. Everything a person eats, drinks, experiences, or is exposed to can and will influence fertility. True naturopathic supports of fertility acknowledge and consider absolutely all variables of holistic health. Couples should be encouraged to participate in treatment for 3 to 4 months to properly address all genetic and epigenetic variables affecting the gamete.

Improving Sperm-Controlling and Sperm-Damaging Factors

The first step in improving sperm counts, morphology, and function is controlling factors that can damage or impair sperm formation. These include the following:

- Scrotal temperature
- Estrogen and xenoestrogen exposure
- Heavy metals
- Radiation

- Cigarettes, alcohol, and illicit drugs
- Obesity
- Infection

Scrotal Temperature

The scrotal sac normally keeps the testes at a temperature of between 94° F and 96° F. At temperatures above 96° F, sperm production is greatly inhibited or stopped completely. Typically, the mean scrotal temperature of infertile men is significantly higher than that of fertile men. A reduction in the scrotal temperature in infertile men is often enough to make them fertile. This is best achieved by having them avoid tight-fitting underwear, tight jeans, and hot tubs.

In addition, the following exercise or exercise equipment can raise scrotal temperature, especially if a man is wearing synthetic fabrics, exceptionally tight shorts, or tight bikini underwear: rowing machines, simulated cross-country ski machines, treadmills, and jogging. After exercising, a man should allow his testicles to hang free to allow them to recover from heat buildup.

Infertile men should wear boxer-type underwear and periodically apply a cold shower or ice to the scrotum. They can also choose to use a device called a testicular hypothermia device or "testicle cooler" to reduce scrotal temperatures. The testicle cooler looks like a jock strap from which long, thin tubes have been extended. The tubes are attached to a small fluid reservoir filled with cold water that attaches to a belt around the waist. The fluid reservoir is also a pump that causes the water to circulate. When the water reaches the surface of the scrotum, it evaporates and keeps the scrotum cool. Because of evaporation, the reservoir must be filled every 6 hours or so. It is recommended that the testicle cooler be worn daily during waking hours. Most users claim that it is fairly comfortable and easy to conceal.[15]

Increased scrotal temperature can be due to the presence of a varicocele. A large varicocele can lead to scrotal temperatures high enough to inhibit sperm production and motility. Surgical repair may be necessary, but scrotal cooling should be tried first.

Estrogen and Xenoestrogen Exposure

According to experts on the impact of the environment and diet on fetal development, we now live in an environment that can be viewed as "a virtual sea of estrogens."[16,17] Increased exposure to environmental estrogens and other environmental pollutants during fetal development as well as during the reproductive years is suggested to be a major cause of the tremendous rise in the incidence of disorders of development and function of the male sexual system[18] (see Box 180-1).

One can best view the relationship between estrogens and male sexual development by examining the effects of the synthetic estrogen diethylstilbestrol (DES). Between 1945 and 1971, several million women were treated with DES. By 1970, the side effects of DES became better known. DES is now recognized to have led to substantial increases in the number of men suffering from developmental problems of the reproductive tract as well as decreased semen volume and sperm count.[16] Apart from having been used in humans, DES and other synthetic estrogens were used for 20 to 30 years in the livestock industry to fatten the animals and make them grow faster.

Although most synthetic estrogens like DES are now outlawed, many animals, both livestock and poultry, are still hormonally manipulated, especially dairy cows. Cow's milk contains substantial amounts of estrogen because of modern farming techniques. The rise in dairy consumption since the 1940s inversely parallels the drop in sperm counts. Avoidance of hormone-fed animal products, including milk products, is important for male sexual vitality, especially in men with low sperm counts or low testosterone levels.

There are reports that estrogens have been detected in drinking water.[17,19] Presumably they are recycled from excreted synthetic estrogens (birth control pills) at water treatment plants. These estrogens may be harmful to male sexual vitality because they are more potent—they do not bind to sex hormone–binding globulin (SHBG). Purified or spring water may be a suitable option to prevent exposure. It is also important to ensure that bottled water is avoided owing to the bisphenol A content of plastic bottles.

Other sources of estrogen in the environment (food, water, and air) can weaken male sexual vitality. For example, many of the chemicals with which we have contaminated our environment in the past 50 years are weakly estrogenic. Most of these chemicals, like polychlorinated biphenyls (PCBs), dioxin, and dichlorodiphenyltrichloroethane (DDT), are resistant to biodegradation and are recycled in our environment until they find a safe haven in our bodies. For example, even though DDT has been banned for nearly 30 years, it is still often found in the soil and in root vegetables such as carrots and potatoes. These toxic chemicals are known to interfere with spermatogenesis, but their effects during sexual development may be even more important.

All of the estrogenic factors previously discussed are thought to have their greatest impact during fetal development. On the basis of animal studies, these estrogens inhibit multiplication of the Sertoli cells. The number of Sertoli cells is directly proportional to the number of sperm that can be produced, because each Sertoli cell can support only a fixed number of germ cells that will develop

BOX 180-1 Compounds that Exert Estrogenic Activity

- Alkylphenols (intermediate chemicals used in the manufacture of other chemicals)
- Atrazine (weed killer)
- 4-Methylbenzylidene camphor (4-MBC) (sunscreen lotions)
- Butylated hydroxyanisole, BHA (food preservative)
- Bisphenol A (monomer for polycarbonate plastic and epoxy resin; antioxidant in plasticizers)
- Dichlorodiphenyldichloroethylene (one of the breakdown products of DDT)
- Dieldrin (banned insecticide)
- DDT (banned insecticide)
- Endosulfan (widely banned insecticide)
- Erythrosine, FD&C Red No. 3
- Ethinylestradiol (released into the environment as a xenoestrogen)
- Heptachlor (restricted insecticide)
- Lindane, hexachlorocyclohexane (restricted insecticide)
- Metalloestrogens (a class of inorganic xenoestrogens)
- Methoxychlor (banned insecticide)
- Nonylphenol and derivatives (industrial surfactants; emulsifiers for emulsion polymerization; laboratory detergents; pesticides)
- Pentachlorophenol (restricted general biocide and wood preservative)
- Polychlorinated biphenyls, PCBs (banned; formerly used in electrical oils, lubricants, adhesives, paints)
- Parabens (lotions)
- Phenosulfothiazine (a red dye)
- Phthalates (plasticizers)
- DEHP (plasticizer for PVC)
- Propyl gallate (used to protect oils and fats in products from oxidation)

into sperm. Sertoli cell multiplication occurs primarily during fetal life and before puberty and is controlled by follicle-stimulating hormone (FSH). In animal studies, estrogens administered early in life have been found to inhibit FSH secretion, resulting in a reduced number of Sertoli cells and, in adult life, diminished sperm counts.

One example of the impairment of male sexual development by environmental estrogens is the ability of vinclozolin, a fungicide used in the wine industry, to disrupt the fertility of male rats.[20] Alarmingly, just one exposure of a pregnant female rat to this fungicide was found to disrupt spermatogenesis in more than 90% of the male offspring for at least four generations via an effect exclusively transmitted through the male germ line.

Environmental toxins are also linked to increasing testicular cancer rates, testicular dysgenesis syndrome (TDS), cryptorchidism, and hypospadias.[3,21] Whether the outcome is impaired spermatogenesis, TDS, testicular cancer, or any other disturbance may depend on the timing and nature of the xenobiotic attack and the genetic background on which these factors are acting. As such, a determination of the outcome will have to take into account the patient's polymorphism profile for proteins involved in detoxification, such as the cytochrome P450s and glutathione-*S*-transferases. The bottom line is that the environmental impact on spermatogenesis cannot be underestimated. Industrial growth since the end of World War II has introduced many complex chemicals into the environment that are novel to biological detoxification systems. Some of these molecules are reproductive toxicants, capable of impairing fertility and inducing developmental abnormalities in the embryo, including errors in normal sexual differentiation.

The power of reproductive toxicants that target the germ line lies in their capacity to generate damage that can be passed down the generations via genetic or epigenetic means. A prime example is the effect of paternal smoking. Men who smoke heavily generate spermatozoa that may have high levels of DNA damage, largely as a result of oxidative stress. One of the consequences of this DNA damage is that the children of such men exhibit an increased incidence of childhood cancer.[22] Although we have traditionally focused on the ability of cigarette smoke to induce lung cancer, a far more sinister effect is its ability to induce DNA damage in the germ line and thereby influence the health and well-being of future generations.

It is therefore advisable to discourage exposure to cigarette smoke in all male fertility patients and, in those with suspected heavy exposure, to initiate further investigations and specialized treatments to chelate and support detoxification.

Exposure Route

Environmental toxins may exert their genetic or epigenetic effects on the germ line via several potential routes of exposure:

1. Women may be exposed to xenobiotics during pregnancy, thereby disrupting the normal differentiation of the germ line in the fetus.
2. Women exposed to toxicants may transmit xenobiotics to their offspring via breast milk.
3. Because of acquired toxicity, men may contribute adverse effects on the integrity of DNA in the male germ line. Toxicologic studies in animal models reporting infertility, abortion, and birth defects as a result of male exposure to xenobiotics demonstrate that such associations are possible.[9] Epidemiologic studies suggest that they are clinically significant.[3,21]

For a full discussion of potential environmental effects, see Chapter 35, "Environmental Medicine."

Assessment

It is advisable to thoroughly assess all presenting patients for exposure to environmental toxins and, depending on the results, to offer appropriate treatment. Specific areas to consider include the following:

1. Full occupational exposure review
2. Nonoccupational exposure
 - The area in which the couple lives
 - Age of the couple's home
 - Ages of carpet, floor coverings, floorboards
 - Renovations—when, what, and how
 - Type of heating/AC
 - Use of indoor or outdoor pesticides
 - Attached garage
 - Blinds, curtains
 - Cleaning products
 - Pool/spa/sauna
 - Pets—type, medicines, foods
 - Food sources
 - Water source
 - Others

It is best to recommend the avoidance of other exposures, such as those from renovation materials, cleaning products, personal toiletries, new furniture, new carpet or cabinets, plastics, gas, chemical gases, and many others. Organic, environmentally sound, sustainable practices are generally the safest.

For men who work in occupations that may affect fertility, it is important to wear protective clothing and follow all occupational health and safety guidelines.

Heavy Metals

Sperm are also particularly susceptible to the damaging effects of heavy metals such as lead, cadmium, arsenic, and mercury.[18]A hair mineral analysis for heavy metals should be performed on all men with reduced sperm counts to rule out heavy metals as a cause.

Radiation

Cell phones operate at 400- and 2000-MHz frequency bands and emit radiofrequency electromagnetic waves (EMWs).[23] Cordless phones must be considered in this context as well; these use the 900-MHz, 1.9-GHz, 2.4-GHz, and 5.8-GHz bands. Reports of potential adverse effects of radiofrequency EMWs on the brain, heart, endocrine system, and DNA in humans and animals are commonly found in the literature. Specifically from a fertility context, they have also been implicated in DNA strand breaks.[24] The relationship between cell phone use and male infertility remains unclear. Harmful EMWs emitted from cell phones may interfere with normal spermatogenesis and result in a significant decrease in sperm quality. Specific findings pertaining to sperm motility in humans have also been noted.[25,26]

In one observational study,[27] the use of cell phones decreased semen quality by decreasing the sperm count as well as the sperms' motility, viability, and normal morphology. This decrease in sperm parameters was dependent on the duration of daily exposure to cell phones and independent of initial semen quality. Of greatest importance was that sperm count, viability, and morphology declined as cell phone use increased. Specifically, use of the cell phone for more than 4 hours a day caused a 25% drop in the number of sperm produced, and only 20% of these looked normal.

It is therefore prudent to discourage cell phone use and recommend that male patients refrain as much as possible from storing cell phones in their pockets, owing to increased genital exposure to the frequency bands.

Cigarettes, Alcohol, and Illicit Drugs

Lifestyle exposures including cigarette smoke, alcohol, and caffeine have all been studied in relation to male reproductive health. Over the years the focus has primarily been on semen quality and/or fertility. More recently, the literature evaluating direct adverse effects of lifestyle exposures on sperm, chromosomes, and chromatin has grown owing to concern that induced damage could be transmitted to offspring, causing transgenerational health effects.

Cigarette Smoking. A common source of oxidants is cigarette smoking, which is associated with decreased sperm counts and sperm motility as well as a higher frequency of abnormal sperm.[28] Cigarette smoking, as well as the increase in environmental pollution, is thought to be a major contributor to the diminution in sperm counts seen in many industrialized nations over the past few decades.

Although passive and active smoking is known to lead to a number of health concerns, male patients are often complacent about its impact. However, heavy smokers have been shown to produce more than 20% less sperm. Cigarette smoking accelerates DNA damage of the sperm, and smoking cessation is the quickest treatment strategy to reverse such damage and thus affect sperm morphology parameters positively. When the sperm enters the oocyte during conception, the mRNA within the oocyte attempts to defragment the DNA and provide antioxidant support so as to improve sperm quality. It is important to note that the improvements to sperm occur prior to any oocyte maintenance. It is only once the sperm has been positively addressed that the mRNA and any antioxidant potential within the oocyte can address any oocyte deficiency, oxidative process, or DNA (or chromosomal) abnormality. When the male partner is a heavy smoker, it often means that there are simply insufficient reserves to repair the damage for both gametes; as a result, the oocyte fails, causing either fertilization deficits, a lack of implantation, or abnormalities in the embryo, thus initiating an early miscarriage or negative effects on the long-term health and fertility of the subsequent child.[29] The female's surveillance does not typically allow the compromised embryo to grow beyond early miscarriage, because the chance of a healthy birth is then unlikely. Therefore, this highly pertinent clinical discussion can motivate most male patients to take responsibility for their oxidative processes and commit to smoking cessation.

A recent systematic Cochrane review found that in *both* fertile and infertile populations, active and passive smoking is associated with reduced fertility and a decreased chance of producing a healthy, live infant. In males, cigarette smoking has been observed to impair sperm respiration, thus affecting the sperms' mitochondrial function[30] as well as causing a reduction in sperm motility and semen quality.[31] It is therefore strongly recommended that all males cease both passive and active smoking for at least the preconception period and ideally beyond it.

Alcohol Intake. Excessive alcohol consumption in men is strongly associated with diminished sperm function; however, comprehensive research in this area is limited. Researchers acknowledge the impact; however, conclusive data are scarce. From a naturopathic viewpoint, however, it is important to encourage avoidance for a number of reasons, including effects on the liver and detoxification as well as on endocrinology (especially estrogen pathways), calorie consumption, hyperglycemic effects, and others. It is prudent to recommend alcohol avoidance in the preconception period so as to ensure optimal functioning of the male body and subsequent positive effects on sperm parameters. It is of prime importance to recommend abstinence from binge drinking and regular heavy drinking.

Marijuana and Other Recreational Drugs. The effects of marijuana and other recreational drugs are difficult to determine because their use is illegal. Nevertheless, the use of such drugs generally should be discouraged, particularly because they have well-documented harmful effects on the developing fetus.[32] A known fertility toxicant, marijuana contains constituents known as cannabinoids, which have been shown to impair signaling pathways, alter hormonal regulation, and complicate timing issues during embryo implantation.[33] In males, cannabinoids have been found to inhibit the mitochondrial respiration of sperm,[34] reduce testosterone production,[33] decrease sperm motility, compromise sperm morphology, and decrease sperm function, specifically capacitation and acrosome reactions.[35]

Obesity

Obese men are known to have lower sperm counts (up to 50%), reduced sperm motility, reduced spermatogenesis, increased DNA fragmentation in sperm, and increased levels of erectile dysfunction. Additionally, extra-abdominal weight can increase scrotal temperature. Hormonal changes are primarily responsible for such changes in obese men. The levels of total and free testosterone are reduced in obese men in proportion to the level of obesity. Estrogen is increased owing to the peripheral aromatization of androgens in adipose tissue. The estrogens produced have a negative feedback effect on gonadotropin production, thereby reducing FSH. This reduction in FSH further reduces testosterone production and spermatogenesis. Additionally, increased body fat and a sedentary lifestyle are associated with raised testicular temperature, which further adversely affects spermatogenesis.[36]

Infections and Infertility

Infections in the male genitourinary tract—including infections of the epididymis, seminal vesicles, prostate, bladder, and urethra—are thought to play a major role in many cases of infertility.[37] The exact extent of this role is largely unknown because of the lack of suitable diagnostic criteria coupled with the asymptomatic nature of many infections. The presence of antisperm antibodies or high levels of debris in the semen sample are considered to be good indicators of chronic infection in the absence of other clinical findings.

A wide number of bacteria, viruses, and other organisms can infect the male genitourinary system. Table 180-6 offers a list of the more common potential causative agents.

NUTRITIONAL CONSIDERATIONS

A single sperm comprises the key nutritional ingredients (see Figure 180-1).

Diet

The dietary guidelines in Chapter 44 provide sound guidance for improving fertility. In particular, it is important to eat the right types of fats. Surrounding the entire sperm is a "shield" of essential fatty acids protecting its structure, enabling continuity of movement, and safeguarding the integrity of the precious genetic material within. The male's dietary intake must be assessed so as to ensure that all trans, rancid, and oxidized fats and excessive saturated fats are avoided. It is recommended to prescribe sufficient essential fatty acids from both supplemental and dietary sources. The presence of essential fatty acids ensures that sperm are kept fluid and flexible, which regulates the acrosome reaction, sperm-oocyte fusion, and sperm-oocyte fertilization.[38]

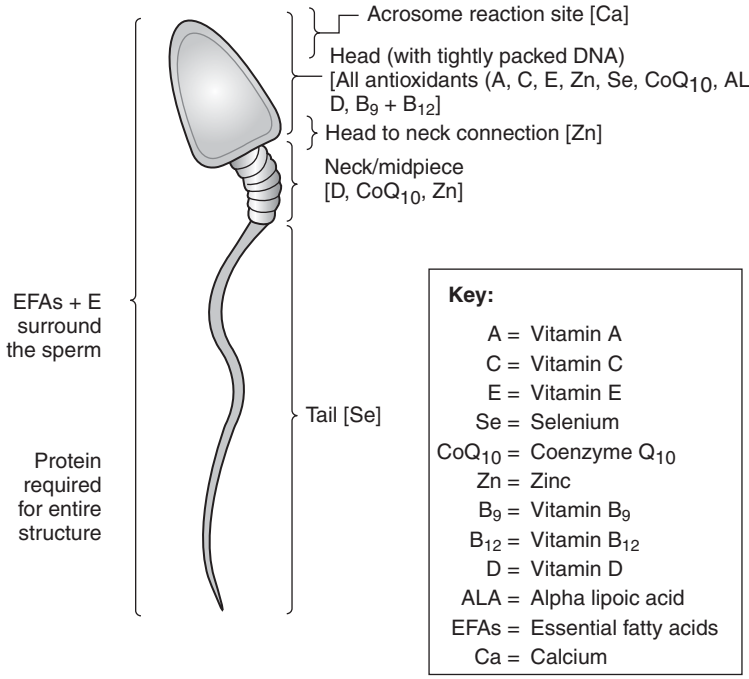


FIGURE 180-1 Sperm morphology and composition.

Because of the effects of fats and oils on agglutination and cell membrane dynamics, certain fats are best avoided in infertile men and consumption of others should be increased. Hydrogenated oils, trans fatty acids, and cotton oils should be avoided. Cottonseed is especially problematic since it may contain toxic residues because of the heavy spraying of cotton and its high levels of gossypol, a substance known to inhibit sperm function. In fact, gossypol is being investigated for possible use in a "male birth control pill." Its potential as an antifertility agent became known after studies demonstrated that men who had used crude cottonseed oil for cooking had low sperm counts followed by total testicular failure.[39] Excessive consumption of long-chain saturated fats from meat should also be avoided; these, combined with inadequate intake of essential fatty acids, can change the fatty acid composition of the sperm membranes, thus reducing fluidity and interfering with sperm motility. The patient must be taught to read food labels carefully and avoid all sources of cottonseed oil and other damaging oils.

To promote proper sperm membrane function, it is important to supplement with the long-chain omega-3 fatty acids from fish oil, because studies have shown that sperm motility strongly correlates with levels of omega-3 fatty acids, in particular docosahexaenoic acid (DHA), in the sperm membrane.[40] One paper noted that excessive omega-6 compared with omega-3 fatty acids in seminal fluid decreased sperm concentration, sperm motility, and sperm morphology among patients with idiopathic oligoasthenoteratozoospermia.[41] It is therefore advisable to encourage omega-3 sources as a preference and to restrict the use of popular omega-6 cooking oils, such as soy, corn, and safflower. Supplemental goals should be to prescribe an optimal dose of 1000 to 2000 mg of EPA+DHA daily, with additional dietary recommendations such as raw nuts and seeds; cold-pressed monounsaturated oils like olive, canola, and macadamia nut oils; avocados; and wild and sustainably farmed high EFA containing fish.

Adequate dietary protein is also an important consideration. The entire sperm is dependent on the protein status of the male. Insufficient protein in the diet undermines the quality of the sperm, reflected primarily in their morphology but undoubtedly also in their inability to move adequately and in the right direction (motility). Similarly to the rest of the body: if protein needs are not met, deterioration of bodily processes and structures can eventuate. It is crucial to thoroughly assess protein levels of all male patients both in laboratory assessments (total protein status) and through dietary calculation. The standard calculation of 0.8 to 1.2 g protein per 2.2 lbs (1 kg) body weight is a positive general rule; 0.8 g protein is best for more sedentary patients, and 1.2 g protein is more appropriate for more active types. For example, an active patient weighing 176 lbs (80 kg) should be prescribed 96 g pure protein per day, ideally from a variety of sources.

Hydration must also be optimized. Sperm are manufactured and spend time within semen. On reviewing the nutritional components of semen, it becomes clear that it is a by-product of the body, as is urine or feces. Therefore, if a male is dehydrated, it is understandable that the resultant coagulation of semen will increase and exposure to toxin and by-products from eliminatory channels will occur. Thus, optimal hydration can dilute semen, reduce sperm exposure, and improve motility considerably. Calculating a male's hydration requirements is best achieved using a 30-mL/2.2-lb (1-kg) rule; that is, for a 176-lb (80-kg) patient, minimal hydration requirements would be 2.4 L per day with additional intake required for dehydration, exercise, and alcohol or caffeine intake.

NUTRITIONAL SUPPLEMENTS

Antioxidants

A recent Cochrane review[42] assessed the impact of antioxidants on male subfertility by reviewing 34 trials and 2876 couples. Of importance, the authors concluded that there is sufficient evidence to prove that antioxidant supplementation in subfertile males improves the outcomes of live births and pregnancy rates for

subfertile couples undergoing ART cycles. In greater detail, important points in this report included the following:

- Antioxidant use was associated with a statistically significant increased pregnancy rate compared with control (pooled OR 4.18, 95%; CI 2.65 to 6.59; P <0.00001).
- No studies reported evidence of harmful side effects of the antioxidant therapy used.
- One man in 20 will be affected by subfertility and 3% to 80% of male-factor subfertility is believed to be due to oxidative stress.[43]
- Subfertile men are confirmed to have lower levels of antioxidants in their semen than fertile men.[43]
- Levels of reactive oxygen species (ROS) are significantly higher in infertile sperm samples compared with others from healthy controls.
- ROS cause fertility problems by
 a. Damaging the sperm membrane, thus affecting sperm motility and the ability of spermatozoa to break down the oocyte membrane (zona pellucida).
 b. Altering sperm DNA: the integrity of sperm DNA is one of the major determinants of normal fertilization and embryo growth in natural and assisted conception.

All antioxidants are concentrated in the head of the sperm to varying degrees. The general recommendation is to encourage the prescription of combination products to ensure that the greatest antioxidant potential is achieved. Antioxidants are responsible for protecting the DNA within the head of the sperm and reducing the workload of the mRNA in the eventual oocyte. By optimizing oxidant status, the survival and longevity of the sperm are also promoted and the sperm is enabled to detect signals from the recently ovulated oocyte. A reduction in antioxidants is likely to present specifically as high DNA damage or poor morphology. However, individual antioxidants such as zinc are responsible for regulating hormone status and thus sperm count; therefore, all must be considered in a holistic infertility treatment protocol.

Free radical or oxidative damage to sperm is thought to be responsible for many cases of male infertility, high levels of free radicals having been found in the semen of approximately 40% of infertile men.[44-46] The following three factors combine to render sperm particularly susceptible to damage by free radicals:

- A high membrane concentration of polyunsaturated fatty acids (PFAs)
- Active generation of free radicals
- A lack of defensive enzymes

All of these factors combine to make the health of the sperm critically dependent on antioxidants. Although most free radicals are produced during normal metabolic processes, the environment contributes greatly to the free radical load. Men exposed to higher levels of free radicals are much more likely to have abnormal sperm and sperm counts.[44-46] Antioxidants are required to protect sperm against oxidative damage (which may alter DNA) as well as to instigate cellular repair of damage caused by environmental factors or aging. In the healthy male, the seminal plasma is naturally rich in antioxidants, since sperm are highly susceptible to the effects of ROS.

Sperm are extremely sensitive to free radicals because they depend so much on the integrity and fluidity of their cell membranes for proper function. Without proper membrane fluidity, enzymes are activated, possibly leading to impaired motility, abnormal structure, loss of viability, and ultimately death of the sperm.

The major determinant of membrane fluidity is the concentration of PFAs, particularly omega-3 fatty acids like docosahexaenoic acid, which are highly susceptible to free radical damage. The sperm have a relative lack of superoxide dismutase and catalase, which can prevent or repair oxidative damage. Adding to this more susceptible state is the fact that sperm generate large quantities of free radicals to help break down barriers to fertilization.

Vitamin C

Vitamin C improves all semen parameters. A marginal deficiency causes oxidative damage to sperm, resulting in reduced sperm motility and viability. Supplementation leads to improvement in both viability and motility, reduced numbers of abnormal sperm, and reduced sperm agglutination.[47,48]

The generation of ROS and associated links with infertility has been established and extensively studied. In particular, the effects of increased ROS in the serum, semen, and testicular tissues have been considered. Alterations in the testicular microenvironment and hemodynamics can increase the production of ROS and/or decrease local antioxidant capacity, resulting in the generation of excessive oxygen species.

Vitamin C (ascorbic acid), a major antioxidant present in extracellular fluid, is present at a high concentration in seminal fluid compared with blood plasma (364 vs. 40 mM) and is present in detectable amounts in sperm,[49] where it prevents sperm agglutination and oxidative damage. In infertile men, vitamin C has been found in reduced quantity in the seminal plasma.[50,51] Males with inadequate seminal vitamin C have also been observed to suffer from sperm DNA damage,[50] suggesting that a defect or inadequate intake of vitamin C may prompt ROS to cause breakage and oxidation of sperm DNA.

When dietary vitamin C was reduced from 250 to 5 mg/day in healthy human subjects, the ascorbic acid content in seminal fluid decreased by 50% and the number of sperm with damage to their DNA rose by 91%.[52] These results indicate that dietary vitamin C plays a critical role in protecting against sperm damage and that low dietary vitamin C levels were likely to lead to infertility.

It is now well documented that cigarette smoking greatly reduces vitamin C levels throughout the body, and it is proved that smokers require at least twice as much vitamin C as nonsmokers. In one study, men who smoked one pack of cigarettes a day received either 0, 200, or 1000 mg of vitamin C. After 1 month, sperm quality improved in proportion to the level of vitamin C supplementation.[53] Nonsmokers appear to benefit from vitamin C as much as do smokers. In one study, 30 infertile but otherwise healthy men received either 200 or 1000 mg of vitamin C or placebo daily.[54] Sperm count, viability, motility, agglutination, abnormalities, and immaturity were measured weekly. After 1 week, the 1000-mg group demonstrated a 140% increase in sperm count, the 200-mg group a 112% increase, and the placebo group no change. After 3 weeks, both vitamin C groups continued to improve, with the 200-mg group catching up to the improvement of the 1000-mg group. One of the key improvements was observed in the number of agglutinated sperm. Sperm become agglutinated when antibodies produced by the immune system bind to them. Antibodies to sperm are often associated with chronic genitourinary tract or prostatic infection. When more than 25% of the sperm are agglutinated, fertility is very unlikely. At the beginning of the study all three groups had more than 25% agglutinated sperm. After 3 weeks, the proportion of agglutinated sperm in the vitamin C groups dropped to 11%. Although this result is significant, the most impressive result of the study was that at the end of 60 days, several men in both of the vitamin C groups had impregnated their wives, compared with none in the placebo group. Therefore, vitamin C supplementation

can be very effective in treating male infertility, particularly if it is due to antibodies against sperm.

Vitamin E

Vitamin E supplementation appears to be especially warranted because this vitamin is the main antioxidant in various cell membranes, including those surrounding sperm. Free radicals, if left alone, lead to the peroxidation of phospholipids in the mitochondria of the sperm, making the sperm immotile. Vitamin E has been shown to play an essential role in inhibiting free radical damage to the unsaturated fatty acids of the sperm membrane[55] and in enhancing the ability of sperm to fertilize an egg in an IVF setting. Additionally, it has been shown to protect DNA within the sperm from damage.[56]

In one study, supplementation with vitamin E was found to decrease malondialdehyde concentration in sperm pellet suspensions and to improve sperm motility. Even more important, however, 11 of 52 (21%) treated infertile men impregnated their spouses, whereas none in the placebo group did so. Following completion of the study, 26 of the placebo patients were switched to vitamin E; soon thereafter, 4 were able to successfully impregnate their spouses.[57] In another study, vitamin E (400 IU) and selenium (225 mcg) significantly improved sperm quality.[58] Supplementation appears to be indicated on the basis of its physiologic effects alone.

Supplementation with vitamin E may also be useful for couples undergoing IVF. Vitamin E (200 mg/day for at least 3 months) was found to improve the in vitro fertilization rate of fertile normospermic males with low fertilization rates after 1 month of treatment, possibly by reducing the lipid peroxidation potential.[59] Beneficial results have also been observed in patients undergoing ICSI, where vitamin E helps to prevent DNA fragmentation, thus improving ICSI outcomes.[60]

Vitamin A, Beta-Carotene, and Lycopene

Vitamin A is an antioxidant required for cellular growth and differentiation, gene expression and cellular differentiation, immunity, regulatory functions, and epithelial tissue integrity. It is necessary for the health of the testes and for sperm production. Low concentrations of vitamin A are associated with abnormal semen parameters in men,[61] and deprivation of vitamin A in animals has been shown to lead to a loss of spermatogenesis due to degeneration of the germ cells, which is restored once vitamin A is reintroduced.[62]

Beta-carotene levels are significantly reduced in immune-infertile men. Intake is associated positively with a higher sperm concentration as well as higher quantities of motile sperm.[63] Lycopene may be even more useful than beta-carotene. Lycopene is found in high concentrations in the testes and seminal plasma, and reduced levels have been demonstrated in men with infertility. In one clinical trial, 30 men with idiopathic nonobstructive oligo/astheno/teratozoospermia were administered 2 mg of lycopene twice a day for 3 months. Twenty patients (66%) showed an improvement in sperm concentration, 16 (53%) had improved motility, and 14 (46%) showed improvement in sperm morphology. In patients showing an improvement, the median changes were 22 million/mL in concentration, 25% in motility, and 10% in morphology.[58]

Selenium

Selenium is a critical antioxidant that is essential for male fertility because of its role in testosterone synthesis, normal sperm maturation, and motility[64]; moreover, clinical trials reveal that selenium has the ability to increase sperm motility and assist in the production of healthy spermatozoa.[65] Selenium is also required structurally, because the sperm's capsular selenoprotein is involved in the stability and motility of the mature sperm and also forms part of the glutathione peroxidase antioxidant system, which is vital for spermatogenesis and protects the sperm against the effects of ROS.[66] In animal studies, depletion of mitochondrial glutathione peroxidase has been found to cause impaired sperm quality and severe structural abnormalities in the midpiece of spermatozoa, leading to infertility.[67] The tail of the sperm relies on adequate selenium status to maintain its "whip-like" action. Without sufficient selenium, sperm are unable to swim in the right direction or may display marked immotility, thus preventing oocyte location and fusion.

The effects of selenium on sperm motility are highlighted in a study involving a subgroup of individuals with poorly motile sperm and subsequent subfertility.[68] Over a 3-month period, the administration of selenium (either on it its own or as a combination of antioxidants, including vitamins A, C, and E) to males led to increased sperm motility when compared with placebo. Five men (11%) achieved paternity in the treatment group, in contrast to none in the placebo group. This small study highlights the efficacy of selenium supplementation in subfertile men and suggests that improved selenium status can, in turn, improve sperm motility and the possibility of successful conception. Although this number may be seen as small, it was highly meaningful to those who were successful in conceiving—and all the more significant in terms of the cost and convenience of supplementation as compared with IVF or ICSI.

More recently selenium (200 mcg/day) in combination with the antioxidant n-acetyl-cysteine (600 mg/day) was found to improve semen parameters in idiopathic oligo-asthenoterato-spermia-plasma males in a double-blind placebo-controlled randomized study undertaken over 6.5 months.[69] Improvements in sperm count, motility, and morphology were all observed; however, once supplementation stopped, the parameters reverted back to their readings at baseline in two spermatogenesis cycles. This study did not include pregnancy rate.

Zinc

Zinc is perhaps the most important trace mineral for male sexual function and is found in high concentrations within the prostate and testes; particularly high amounts are also found in the semen (approximately 2.5 mg of zinc is lost per ejaculate). It is involved in virtually every aspect of male reproduction, including hormone metabolism, spermatogenesis, and sperm motility.[70]

Zinc plays an important role in all human living cells; it is involved in the transcription of RNA, the replication of DNA, and the synthesis of protein, all of which are crucial for reproduction and fertility. Additionally, it protects against free radical damage and ROS, which can impair sperm.[71] Deficiency of zinc in males can lead to gonadal dysfunction[70] and has been observed to be associated with idiopathic male infertility[71] and impotence.

Zinc levels are typically much lower in infertile men with low sperm counts, indicating that a low zinc status may be the contributing factor to infertility.[72,73] It has also been shown that zinc status directly correlates with an increase in sperm count as well as improvements in morphology and motility.[74] In considering sperm structure, zinc has been shown to influence motility and the head-neck connection of the sperm[75]; it is also important in the stabilization of cell membranes and sperm chromatin.[76] Finally, it has been shown to exert an antimicrobial effect on the seminal plasma, which is helpful if sperm antibodies or underlying genitourinary infection is present.[77]

Several studies have evaluated the effect of zinc supplementation on sperm counts and motility.[78-81] The results of all of the studies support the use of zinc supplementation in the treatment of oligospermia, especially in the presence of low testosterone levels. The effectiveness of zinc is best illustrated by a study in 37 men with infertility of greater than 5 years' duration whose sperm counts were less than 25 million/mL.[27] Blood testosterone levels were also measured. The men received a supplement of zinc sulfate (60 mg elemental zinc daily) for 45 to 50 days. In the 22 patients with initially low testosterone levels, the mean sperm count rose significantly from 8 to 20 million/mL. Testosterone levels also increased, and 9 of the 22 wives became pregnant during the study. This result is quite impressive, given the long-term nature of the infertility and the rapidity of the results. In contrast, in the 15 men who had normal testosterone levels before the study, sperm counts increased slightly, but there was no change in testosterone levels and no pregnancies occurred.

Optimal zinc levels must be attained if optimal male sexual vitality is desired. Zinc deficiency is increasing throughout the world and is dependent on the country's soil content and on environmental legislation that prevents harmful farming practices. Additionally, owing to the negative effects of excess copper, it is advisable to check serum zinc and copper status. Where a deficiency state is diagnosed, it is important to ensure that a 1:1 ratio (or better) is achieved.

B Vitamins (Especially Folic Acid and vitamin B_{12})

Folic acid and vitamin B_{12} are concentrated within the head of the sperm and provide vital nutritional potential in sperm generation and survival. Folic acid and B_{12} are required for healthy DNA and RNA synthesis, normal protein synthesis, and the regulation of gene expression.[80] These nutrients are required to ensure that the DNA within the head of the sperm is structured appropriately and that each sperm (and the DNA within it) replicates identically.

Both folic acid and B_{12} facilitate spermatogenesis,[82] which is reliant on DNA synthesis[80] for germ cell growth and the rapid division of cells. Multiple studies have found that low levels of folic acid in seminal plasma are associated with increased sperm DNA damage,[83] whereas B_{12} deficiency is strongly associated with reduced sperm motility and count.[84] Because the human body has a high turnover of B_{12} and requires a continuous supply on a daily basis, supplementation is advisable for all men experiencing infertility regardless of proved deficiency state and especially for men who have sperm counts below 20 million/mL or a motility rate of less than 50%. In one study, 27% of men with sperm counts less than 20 million/mL who were given 1000 mcg/day of B_{12} were able to achieve a total sperm count in excess of 100 million/mL.[81] In another study, 57% of men with low sperm counts who took 6000 mcg/day demonstrated improvements.[85]

It is important to remember that it is advisable to refrain from prescribing one nutrient without the other owing to the possibility of inducing a rebound anemia. Where this occurs, disorders of homocysteine metabolism such as methylenetetrahydrofolate reductase (MTHFR) polymorphisms may present with count or morphologic issues.

Carnitine

Carnitine is derived from the amino acids lysine and/or methionine and plays a vital role in fatty acid metabolism. It works synergistically with coenzyme Q_{10} (CoQ_{10}), highlighting the importance of coprescription for optimal benefit. It is essential in the transport of fatty acids into the mitochondria, and deficiency results in a decrease in fatty acid concentrations in the mitochondria and reduced energy production. It is believed to have protective antioxidant effects and provides energy to the testicles and spermatozoa specifically. Several studies comparing fertile with infertile men found that fertile men had a statistically significant larger amount of carnitine in their seminal sample than the infertile men, and that low levels of L-carnitine in the seminal plasma may be a potent marker for infertility.[86]

Carnitine concentrations are extremely high in the epididymis and sperm, suggesting a role in male reproductive function. The epididymis derives the majority of its energy requirements from fatty acids, as do the sperm, during transport through the epididymis. After ejaculation, the motility of sperm correlates directly with carnitine content; the higher the carnitine content, the more motile the sperm. Conversely, when carnitine levels are low, sperm development, function, and motility are drastically reduced.[44]

Several clinical studies have shown that carnitine supplementation can produce dramatic improvements in sperm counts and sperm motility. In the Italian Study Group on Carnitine and Male Infertility, 100 subjects were given 3000 mg of L-carnitine daily for 4 months.[87] Carnitine was able to increase sperm counts and sperm motility in both a qualitative and a quantitative manner, as follows:

- The number of ejaculated sperm per milliliter increased from 142 billion to 163 billion.
- The percentage of motile sperm increased from 26.9% to 37.7%.
- The percentage of sperm with rapid linear progression increased from 10.8% to 18%.
- The mean sperm velocity increased from 28.4% to 32.5%.

These results are even more impressive if results for only the patients with the poorest sperm motility are examined. This subgroup saw even more significant gains on all parameters. For example, the percentage of motile sperm increased from 19.3% to 40.9%, and the percentage of sperm with rapid linear progression increased from 3.1% to 20.3%. These results have been confirmed in several double-blind studies.[88-92]

Alpha Lipoic Acid

Alpha lipoic acid is a powerful antioxidant indicated for its lipid and water solubility and because it assists in the chelation of heavy metals regardless of their storage site in the body. It is especially useful owing to its ability to regenerate other antioxidants, including vitamins C and E, CoQ_{10}, and glutathione.[93]

Alpha lipoic acid exhibits marked antioxidant activity to sperm in animal studies.[94-96] On review of research, it appears to act as a shield for the sperm, forming a protective barrier around the midpiece (aqueous layer) and within the structure itself (lipid layer). This protection is crucial, because it has been identified as one of the first places at which free radicals attack.[96] It is therefore useful to consider in patients with high DNA fragmentation levels. Additionally, animal studies reveal that alpha lipoic acid improves sperm motility and viability, minimizes DNA damage,[96] and protects against bacterial lipopolysaccharides, which can induce acute inflammation[97]; it and may also assist with energy supply to the sperm.[96]

Coenzyme Q_{10}

CoQ_{10} is concentrated in the head and midpiece (neck) of the sperm. It is considered to be the most crucial and powerful antioxidant in sperm structure because of its role in mitochondrial energy release. It is believed to promote motility, foster sperm

survival, and provide optimal energy to assist the sperm's travel on its journey to the oocyte.

As a fat-soluble antioxidant and free radical scavenger, CoQ_{10} is required for the maintenance of cell membrane integrity and cell functioning. It is also specific for the health of all new cells, especially spermatozoa. CoQ_{10} in the seminal fluid and sperm[98] helps to maintain optimal sperm motility.[99,100] Decreased levels have been found in the seminal plasma and spermatozoa of males with idiopathic and varicocele-associated asthenospermia.[101]

L-Arginine

The amino acid arginine is required for the replication of cells, making it essential in sperm formation. Nitric oxide synthase uses L-arginine to synthesize nitric oxide, which can protect spermatozoa from lipid peroxidase damage. Via its role as a precursor to nitric oxide synthesis, arginine is required for angiogenesis, spermatogenesis, and hormone secretion.[102]

Some studies have shown that L-arginine can improve sperm count and motility.[84,103] Stress, in particular, has been found to decrease the levels of arginine in sperm production pathways. Arginine supplementation is often but not always an effective treatment for male infertility. The critical determinant appears to be the level of oligospermia. If sperm counts are less than 20 million/mL, arginine supplementation is less likely to be of benefit. In order to be effective, the dose of L-arginine must be at least 4 g/day for 3 months. In perhaps the most favorable study, 74% of 178 men with low sperm counts had significant improvements in sperm counts and motility after arginine therapy.[104]

One double-blind randomized placebo-controlled crossover clinical trial examined the effects of Prelox, a combination of 80 mg/day of pycnogenol and 3 g/day of L-arginine aspartate.[105] The results showed an improvement in semen parameters in 50 males with idiopathic infertility over a treatment period of 4 weeks. Also observed were significant increases in ejaculate volume, concentration, and number of spermatozoa as well as the percentage of vital spermatozoa as compared wih placebo. The percentage of spermatozoa with good progressing motility also increased significantly, whereas the percentage of immotile spermatozoa decreased. These results appear to be due to a combination of the antioxidant activity of Pycnogenol and/or the activity of L-arginine in stimulating the activity of endothelial NOS, leading to enhanced motility of spermatozoa. In a small pilot study, Pycnogenol (200 mg daily for 90 days) alone was shown to improve sperm morphology by 38% and the mannose receptor binding assay scores by 19%.[106]

Botanical Medicines

Panax ginseng (Korean ginseng)

Current scientific investigation suggests that *Panax ginseng* (Chinese or Korean ginseng) may be supportive in the treatment of male infertility. Both botanicals have a long history of use as male "tonics." In studies with animals, *Panax* ginseng has been shown to improve the growth of the testes, raise sperm formation and testosterone levels, and increase sexual activity and mating behavior. It is classed as an energy tonic, indicated when there is lowered vitality and therefore impaired physical performance and sexual function. The active constituents (ginsenosides) have been shown to enhance nitric oxide production, which is useful in regulating the capacitating process of spermatozoa and the acrosome reaction, thus improving fertilization sperm motility.[107,108] Additionally, ginsenosodes have been shown to affect different levels of the hypothalamic-pituitary-testicular axis,[109] which can assist in modulating stress-induced infertility or lowered testosterone from insufficient DHEA synthesis. In clinical trials, *Panax* ginseng has been shown to increase testosterone levels as well as, sperm counts and motility in patients with oligospermia, some of whom had varicocele,[109] and to improve erection and libido.[110] For additional information and references, see Chapter 110.

Pygeum africanum (Pygeum)

Pygeum africanum may be effective in improving fertility in cases where diminished prostatic secretion plays a significant role. *Pygeum* has been shown to increase prostatic secretions and improve the composition of the seminal fluid.[111-113] Specifically, *Pygeum* administration to men with decreased prostatic secretion has led to increased levels of total seminal fluid plus increases in alkaline phosphatase and protein content.

Pygeum appears to be most effective in men in whom alkaline phosphatase activity is reduced (i.e., <400 IU/cm^3) and there is no evidence of inflammation or infection (i.e., absence of white blood cells and immunoglobulin A[IgA]). The lack of IgA in the semen is a good indicator of clinical success. In one study, the patients with no IgA in their semen demonstrated an increase in alkaline phosphatase from 265 to 485 IU/cm^3.[113] In contrast, those with IgA showed only a modest increase, from 213 to 281 IU/cm^3.

Pygeum extract has also shown an ability, in a double-blind clinical trial, to improve the capacity of patients with benign prostatic hypertrophy (BPH) or prostatitis to achieve an erection, as determined by nocturnal penile tumescence.[114] BPH and prostatitis are often associated with erectile dysfunction and other sexual disturbances. Presumably by alleviating the underlying condition, *Pygeum* can improve sexual function.

Tribulus terrestris

Tribulus terrestris has been used traditionally in Ayurvedic medicine as a tonic and aphrodisiac and in European folk medicine to increase sexual potency. Protodioscin, one of the steroidal saponins, is considered the chief constituent responsible for the herb's effects on libido and sexual functioning. Of prime importance is correct sourcing of *Tribulus* to ensure its effectiveness. All of the data and clinical outcomes have been based on a leaf extract from Bulgaria, which has been shown to be highest in protodioscin. Therefore, if a *Tribulus* product is made from the root or fruit of the plant or is obtained from anywhere other than eastern Europe, it will probably contain low levels of protodioscin and therefore not be effective.

In animal studies, *Tribulus* has been shown to increase the levels of certain sex hormones including testosterone and also to improve nitric oxide synthesis[115]; however, these same results have not been observed in some human studies.[116] One possible explanation is that there were differences in the extract and plant parts of the *Tribulus* used as well as the fact that many of the studies have comprised healthy males with normal testosterone levels rather than males with testosterone deficiency.

Tribulus appears to enhance male fertility through its ability to increase sperm count, viability, and libido; however, the published material is unclear, reporting studies that were poorly designed and and results that are not sufficiently definitive. A number of papers to support the extract product Tribestan highlight significant efficacy; however, owing to poor study design and lack of reliability, it is difficult to rely on these findings, which include increased ejaculate volume, sperm concentration, and motile sperm[117] and improved conception rates.[118]

Astragalus membranaceous

In experimental studies, *Astragalus membranaceus* has been observed to increase the motility of sperm in semen.[119] Studies show that *Astragalus* increases the motility of sperm in semen, but it also increases the motility of washed sperm, which is of special relevance to those seeking ART treatment.[120] Additionally, it has been shown to increase sperm motility and progression.[121]

Turnera diffusa (Damiana)

The traditional application of damiana was for "its positive aphrodisiac effects, acting energetically on the genito urinary organs of both genders where it was highly indicated for sexual weakness and debility,"[122] and "its ability to act as a stimulant tonic of the sexual apparatus especially if there is enfeeblement of the central nervous system."[123] Modern clinicians continue to prescribe damiana in this context and find it is especially beneficial when there is sexual debility, erectile difficulty, and depression. Human studies are lacking; however, a number of animal studies show promising supportive research. *Turnera diffusa* has been shown to facilitate the sexual behavior of male rats with sexual dysfunction, to reduce ejaculation latency,[124] to produce a restorative effect in sexually exhausted male rats, and to hasten their recovery.[125] It has also been observed to suppress aromatase activity, leading to the hypothesis that it may increase levels of testosterone.[126]

Mucuna pruriens (Velvet Bean)

Velvet bean has been used in Ayurvedic medicine for endurance against stress, general resistance against infection, retardation of the aging process, and eventual improvement of male sexual function; it has been known to alleviate disorders including psychogenic impotence and unexplained infertility.[127] One paper showed that *M. puriens* seed powder produced dramatic improvements in 70% of study participants and helped fight stress-mediated poor semen quality; it has also acted as a restorative and invigorating tonic/aphrodisiac in infertile subjects.[128] The same researchers reporting these positive effects determined that they were achieved through the regulation of steroidogenesis and a resulting improvements in semen quality.[129] Specifically, this herbal treatment significantly improved testosterone, luteinizing hormone (LH), dopamine, adrenaline, and noradrenaline levels in infertile men and reduced levels of follicle stimulating hormone (FSH) and prolactin. Sperm count and motility were also significantly improved in infertile men.

Withania somnifera (Withania)

Withania has shown considerable antistress and adaptogenic effects. To investigate the effects of *Withania* on male fertility, 75 normal healthy fertile men (control subjects) and 75 men undergoing infertility screening participated in a 3-month clinical trial. The men in the *Withania* group received 5 g of the powdered root daily. Before and after the treatment, semen analysis, antioxidant vitamins, and serum sex hormone levels were determined. Results showed that *Withania* inhibited lipid peroxidation and improved sperm count and motility. Treatment also significantly increased serum testosterone and luteinizing hormone (LH) and reduced the levels of follicle stimulating hormone (FSH) and prolactin (PRL), all beneficial effects in infertile men.[130]

THERAPEUTIC APPROACH

Male infertility is a multifactorial condition, making a holistic treatment plan essential. Referral to a urologist or fertility specialist for a complete evaluation is often necessary. It is advisable to encourage a detoxification program at the start of treatment so as to optimize spermatogenesis and the subsequent cohort of spermatozoa. Additionally, nutritional status should be optimized, environmental pollutants identified and eliminated, lifestyle practices modified, and fertility-enhancing botanicals consumed. It is also crucial to avoid all xenobiotics, pollutants, and toxicants owing to their disruptive endocrinologic effects.

General Measures

- Maintain scrotal temperature between 94° F and 96.8° F.
- Avoid exposure to free radicals.
- Identify and eliminate environmental pollutants.
- Stop or reduce all drugs, especially antihypertensives, antineoplastics such as cyclophosphamide, and antiinflammatory drugs such as sulfasalazine.
- Use effective stress-reduction techniques and employ psychological counseling if needed.
- Avoid cigarette smoking and the use of recreational drugs.

Diet

- Avoid dietary sources of free radicals, saturated fats, hydrogenated oils, trans fatty acids, and cottonseed oil.
- Increase consumption of legumes, especially soy (high in phytoestrogens and phytosterols), good dietary sources of antioxidant vitamins, carotenes, flavonoids (dark vegetables and fruits), as well as EFAs and zinc (nuts and seeds).
- Consume 8 to 12 servings of vegetables and 1 to 2 servings of fresh fruits daily.
- Optimize protein intake from both vegetarian and organic animal sources.
- Ensure that hydration requirements are met, using a 30-mL/2.2-lb (1 kg) rule.
- Eliminate caffeine, alcohol, sugar, and artificial substances (preservatives, colorings, additives).
- Ensure sufficient EFA intake several times a week in the form of half a cup of raw nuts or seeds, cold-pressed oils (from organic sources), and sustainably farmed fish.

Nutritional Supplements

- High-potency multivitamin/mineral supplement
- Fish oils: 1000 to 2000 mg EPA+DHA
- Vitamin C: 500 to1000 mg three times a day
- Vitamin E: 200 to 400 IU/day
- Beta-carotene: 15,000 to 30,000 IU/day (preferably as mixed carotenoids)
- Vitamin B_{12} (methylcobalamin): 1000 mcg/day
- Zinc: 30 to 60 mg/day
- Selenium: 200 to 400 mcg/day
- Lycopene: 2 mg/day
- CoQ10: 200 to 400 mg/day
- L-Carnitine: 2000 to 3000 mg/day
- L-Arginine: 2000 to 4000 mg/day

Botanical Medicines

Choose one or more of the following:

Panax ginseng (Korean ginseng)

- High-quality crude ginseng root: 1.5 to 2 g/day
- Standardized extract: Containing a minimum of 10.5 mg/mL ginsenosides with Rg1:Rb1 greater than or equal to 0.5 by HPLC, 1 to 6 mL/day

Pygeum africanum (Pygeum)
- Standardized extract: 100 to 200 mg/day standardized to a 14% content of sterols in divided doses

Tribulus terrestris (Tribulus)
- Standardized extract, equivalent to dried herb (aerial parts of leaf), standardized to contain furostanol saponins as protodioscin 12.22 mg/L g, 9 to 36 g/day
- Fluid extract (2:1): 7 to 21 mL/day

Astragalus membranaceous (Astragalus)

Dosages to be administered one to three times a day are as follows:
- Dried root (or as decoction or as a powder in capsules or tablets): 1 to 2 g
- Tincture (1:5): 2 to 4 mL
- Fluid extract (1:1): 1 to 2 mL solid (dry powdered) extract (standardized to contain 0.5% 4-hydroxy-3-methoxy isoflavone): 100 to 150 mg

Turnera diffusa (Damiana)
- Dried leaves or as tea: 2 to 4 g/day
- Fluid extract (1:2): 3.0 to 6.0 mL/day
- Dry powdered extract (4:1): 500 to 1000 mg/day

Mucuna pruriens (Velvet bean)
- Dosage equivalent to 5 g/day of the powdered dried seed

Withania somnifera (Withania)
- Dosage equivalent to 5 g/day of the powdered root
- Dried powdered extract (root and leaves) 125 to 250 mg/day (standardized to contain 8% withanolide glycoside conjugates and 32% oligosaccharides)
- Fluid extract (2:1): containing a minimum of 4.0 mg/mL of withanosides, 2.5 to 5.0 mL/day

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CHAPTER 181

Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis)

Gerard Mullin, MD

DIAGNOSTIC SUMMARY

Crohn's disease:
- Abdominal pain the most common symptom—can be localized anywhere in the abdomen
- Complicated by intestinal obstruction, abscesses, fistulas, strictures, perianal disease
- Intermittent bouts of diarrhea or constipation, low-grade fever, and weight loss
- Frequently misdiagnosed as irritable bowel syndrome; time to diagnosis from onset is estimated to be approximately 8 years
- Serologies, ileocolonoscopy, and capsule endoscopy are key diagnostic modalities
- Radiographic evidence of abnormality of the terminal ileum is characteristic
- Stools are high in lactoferrin and calprotectin—noninvasive inflammatory markers
- Genetic predisposition, environmental trigger (infection, medications, etc.), chronic full-thickness patchy intestinal inflammation
- Risk of digestive tract cancer higher than in the general population

Ulcerative colitis:
- Bloody diarrhea with cramps in the lower abdomen
- Mild abdominal tenderness, weight loss, fever
- Involves only the colon; distinguishing point from Crohn's disease, which can involve any portion of the alimentary tract
- Inflammation is superficial and continuous
- Diagnosis is confirmed by radiography and sigmoidoscopy
- Risk of colon cancer increased after 10 years of disease and universal distribution throughout colon
- Genetic predisposition, triggers similar to those of Crohn's disease

GENERAL CONSIDERATIONS

Definition

Inflammatory bowel disease (IBD) is a general term for a group of chronic inflammatory disorders of the bowel. IBD is divided into two major categories: Crohn's disease and ulcerative colitis. Clinically, IBD is characterized by recurrent inflammatory involvement of specific intestinal segments, resulting in diverse clinical manifestations.

Crohn's Disease

Crohn's disease is characterized by a granulomatous inflammatory reaction comprising the entire thickness of the bowel wall. In approximately 50% of cases, however, the granulomas are either poorly developed or totally absent. The original description in 1932 by Crohn and colleagues localized the disease to segments of the ileum. However, the same granulomatous process may involve the buccal mucosa, esophagus, stomach, duodenum, jejunum, and colon. Rectal biopsies are routinely recommended during flexible sigmoidoscopy or colonoscopy because granulomas are most commonly found at this site. Crohn's disease of the small intestine is also known as regional enteritis. Involvement of the colon is known as Crohn's disease of the colon or granulomatous colitis; the latter designation is less accurate because granulomatous lesions develop in only some of these patients.

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Ulcerative Colitis

In ulcerative colitis a nonspecific inflammatory response is limited largely to the colonic mucosa and submucosa. Well-developed granulomas do not occur. Crohn's disease and ulcerative colitis do have many features in common, however, and the diseases are discussed together when appropriate. Otherwise they are considered as separate entities.

Common Features of Crohn's Disease and Ulcerative Colitis

- The colon is frequently involved in Crohn's disease and is invariably involved in ulcerative colitis.
- Although rarely, patients with ulcerative colitis who have total colon involvement may experience a so-called backwash ileitis. Thus, both conditions may cause changes in the distal small intestine.
- Patients with Crohn's disease often have close relatives with ulcerative colitis, and vice versa.
- When there is no granulomatous reaction in Crohn's disease of the colon, the two lesions may resemble each other clinically as well as pathologically.
- There are many epidemiologic similarities between the two diseases, including age, race, gender, and geographic distribution.
- The two conditions are associated with similar extraintestinal manifestations.
- There appear to be etiologic parallels between the two conditions.
- Both conditions are associated with a higher frequency of colonic carcinoma.

Etiology

The epidemiologic and etiologic data on ulcerative colitis (UC) and Crohn's disease (CD) are quite similar.[1,2] The incidence and prevalence of the two diseases differ slightly, with most studies showing UC to be more common. The current estimate of the incidence of UC in western Europe and the United States is approximately 6 to 8 cases per 100,000; the estimated prevalence is approximately 70 to 150 cases per 100,000. The estimate for the incidence of CD is 2 cases per 100,000, and that for the prevalence is 20 to 40 cases per 100,000. The incidence of CD is rising in Western cultures.[3,4]

IBD may occur at any age, but it most often occurs between the ages of 15 and 35 years. Females are affected slightly more frequently than males. White people have the disease two to five times more often than African or Asian Americans, and Jews have a threefold to sixfold higher incidence than non-Jews.[1-4]

Theories about the etiology of IBD can be divided into several groups, as follows[1,2]:

- Genetic predisposition
- Infectious agent or agents
- Immunologic abnormality
- Dietary factors
- An assortment of miscellaneous concepts implicating psychosomatic, vascular, traumatic, and other mechanisms

Genetic Predisposition

Although the search for a specific genetic marker for IBD has been futile, several factors suggest a genetic predisposition. As already mentioned, IBD is two to five times more common among white than nonwhite people and four times more common among Jews than non-Jews. In addition, multiple members of the same family have CD or UC in 15% to 40% of cases.[1,2]

Infectious Etiology

Many microorganisms have been hailed as putative causes of IBD; however, in spite of numerous attempts to confirm a bacterial, mycobacterial, fungal, or viral etiology, the idea that a transmissible agent is responsible for IBD is still a hotly debated subject. Viruses—rotavirus, Epstein-Barr virus, cytomegalovirus, measles virus, and an uncharacterized RNA intestinal cytopathic virus—and mycobacteria continue to be favored candidates. Gastrointestinal infections with *Aeromonas* bacteria *(Aeromonas sobria and Aeromonas hydrophila)* and the yeast *Candida albicans* can trigger a flare of disease, and all patients with IBD should be tested for these infections at the start and during the course of their illness.[5-10] Other etiologic candidates are as follows[1,2,11-13]:

- *Pseudomonas*-like organisms
- Enteric anaerobes
- *Chlamydia* spp.
- *Yersinia enterocolitica*

Antibiotic Exposure

Antibiotic exposure is being linked to CD.[1] Before the 1950s, CD was found in select groups with a strong genetic component. Since that time there has been a rapid climb in developed countries, particularly the United States, and in countries that previously had virtually no reported cases. In fact, CD has spread like an epidemic since 1950. Are antibiotics to blame? Penicillin and tetracycline have been available in oral form since 1953. The annual increase in prescriptions of antibiotics parallels the rise in the annual incidence of CD. Comparative statistics have shown that wherever antibiotics have been used early and in large quantities, the incidence of CD is now quite high.

Over the years, researchers have sought to identify CD as an infectious process. The problem may be that the infectious agent is a component of the normal intestinal flora that suddenly produces immunostimulatory toxins or becomes invasive as a direct result of sublethal doses of antibiotics. Administration of sublethal amounts of antibiotics has been shown to induce a capacity for toxin production in intestinal organisms. When microbes are not given a full lethal dose, their usual response is to adapt and become even stronger in virulence and numbers. Other medications that have been implicated as etiopathogenic include nonsteroidal antiinflammatory agents and, most recently, isotretinoin (Accutane).

Immune Mechanisms

An overwhelming amount of evidence points to immunologic derangements in IBD, but whether they are causal or secondary phenomena remains unclear. Theories relating humoral mechanisms, immunologic regulatory defects, and cell-mediated reactions to the etiology of IBD have all been proposed, but the current evidence seems to indicate that these derangements are probably secondary to the disease process.[1,2]

Dietary Factors

Despite the fact that a dietary etiology of CD is barely considered (if mentioned at all) in most standard medical and gastroenterology texts, several lines of evidence strongly support dietary factors as being the most important etiologically.[14-26]

The incidence of CD is increasing in cultures consuming the Western diet, but it is virtually nonexistent in cultures consuming a more primitive diet.[14-19] Food is the major factor in determining the intestinal environment, so the considerable change in dietary habits over the last century could explain the rising incidence of IBD. Several studies that have analyzed the preillness diets of patients with CD have found they habitually eat more refined

sugar, chemically modified fats and fast food, and less raw fruits, vegetables, omega-3–rich foods, and dietary fiber than healthy people.[14-18] In one study, the preillness intake of refined sugar in patients with CD was nearly twice that in controls (122 g/day vs 65 g/day).[18] One researcher found that before the onset of disease, patients with CD had eaten corn flakes more frequently than controls.[21] Although other researchers could not verify this specific finding, corn flakes are high in refined carbohydrates and are derived from a very common allergen (corn). Much of controversy over the role of preillness diet in the etiology of CD is largely due to the fact that the only way to assess this diet is from postdiagnostic interviews. Studies in which the interview has taken place within the first 6 months of diagnosis tend to be more supportive than studies in which the interview was conducted more than 7 months after diagnosis. Increased refined sugar intake and high overall carbohydrate intake precede the development of CD.[27] Along these lines, patients with UC show a higher consumption of refined carbohydrate than control subjects.[28] Increased consumption of chemically modified fats (such as those found in margarine) may be involved in the etiology of UC.[29] Interestingly, high consumption of a fast-food diet is an antecedent of both UC and CD.[30]

Another important dietary factor that is entirely overlooked in the standard texts is the role of food allergy. Support for this hypothesis is offered in clinical studies that have used an elemental diet, total parenteral nutrition, or an exclusion diet with great success in the treatment of IBD.[20-25] The role of food allergy is discussed in greater detail later in the chapter, as is the effect of dietary fiber in the etiology and treatment of IBD (see "Therapeutic Considerations").

A reduced intake of omega-3 oils and an increased intake of omega-6 oils are also being linked with the growing rise of CD in Japan. Because the genetic background of the Japanese is relatively homogeneous, this higher incidence is most likely due to the incorporation of Western foods in the diet. To examine the contribution of diet to the increased incidence of CD in Japan, the incidence and daily intake of a number of dietary components were compared annually between 1966 and 1985. The analysis showed that the greater incidence of CD was strongly correlated with increased dietary intake of total fat, animal fat, omega-6 fatty acids, animal protein, milk protein, and the ratio of omega-6 to omega-3 fatty acids. It was less correlated with intake of total protein, was not correlated with fish protein, and was inversely correlated with vegetable protein. Multivariate analysis showed that higher intake of animal protein was the strongest independent factor, followed by an increased ratio of omega-6 to omega-3 fatty acids.[26] Correction of this increased ratio by reduction of omega-6 oil intake and increase of omega-3 oil intake may lead to significant clinical benefit through an effect on eicosanoid metabolism (discussed later).

Miscellaneous Factors

Psychosomatic factors, primary vascular disease within mural arteries or arterioles, and chronic trauma have received consideration in the etiology of IBD but at present are not considered significant pathogenic mechanisms.[1,2] Mental and emotional stress can promote exacerbation of IBD, so stress management techniques may prove useful for some patients.[31]

THERAPEUTIC CONSIDERATIONS

IBD is the end result of a complex interplay of several factors. This section discusses the key nutritional, microbial, and toxic issues that must be addressed for the successful management of this difficult disease.

Control of Causative Factors

Natural History of Crohn's Disease

Little is known about the natural course of CD, because virtually all patients with the disease undergo standard medical care (drugs and/or surgery) or alternative therapy. The only exceptions are patients in clinical trials who are assigned to the placebo group.[32-34] However, even these patients do not represent the natural course of the disease, because they are seen frequently by physicians and other members of a health care team and are taking medication, even if it is only in the form of a placebo. If proper evaluation of therapies for IBD is to occur, there must be a greater understanding of its natural history. This is particularly important for alternative practitioners, because it is commonly believed that standard medical care often interferes with the normal efforts of the body to restore health. Some aspects of the "natural" course of CD support this idea, especially when coupled with the limited efficacy of current medications and surgery and their known toxicity. However, heroic measures do have their place in many instances and should be used when appropriate.

Researchers in the National Cooperative Crohn's Disease Study (NCCDS) reviewed 77 patients who received placebo therapy in part 1 of the 17-week study.[32,33] They all had active disease, as defined by a CD activity index (CDAI) (see Appendix 3) higher than 150. Of the patients completing the study:

- None died.
- Only 7 (9%) suffered a major worsening of their disease (i.e., either a major fistula developed or the patient required abdominal surgery).
- 25 (32%) suffered a lesser worsening (increase in the CDAI to >450 or presence of fever of 100°F for 2 weeks).
- Treatment was considered to have failed in 25 (32%) because their CDAIs remained higher than 150.
- 20 (26%) achieved clinical remission.

On at least one occasion during the 17 weeks of therapy, 49% of the patients were found to have a CDAI lower than 150.

The patients who showed a favorable response to the placebo continued to be observed with placebo therapy for up to 2 years (part 1, phase 2). Interestingly, although none of these patients' intestinal radiographs showed worsening during phase 1 or phase 2, 18% showed improvement. Of the patients whose disease responded to placebo (20; 26% of the 77), the majority (70%) remained in remission at 1 year, and a fair number (45%) remained in remission at 2 years. These results indicate that many patients undergo spontaneous remission, approximately 20% at 1 year and 12% at 2 years. However, when another factor is considered, the "success" of placebo therapy rises dramatically. Of patients in the placebo group who had no previous history of steroid therapy, 41% achieved remission after 17 weeks. In addition, 23% of this group continued in remission after 2 years, compared with only 4% of the group with a history of steroid use.

The European Cooperative Crohn's Disease Study (ECCDS), although different in some methodologic details, is quite similar to the NCCDS.[32,34] In the ECCDS, 110 patients constituted the placebo group, 68 patients with prior treatment and 42 patients with no prior treatment. The results of the study showed that 55% of the total placebo group achieved remission by 100 days, 34% remained in remission at 300 days, and 21% remained in remission at 700 days. Like the NCCDS, the ECCDS demonstrated that patients with no prior therapy have a greater likelihood of remission.

Although one group of researchers did not advocate placebo therapy, they did carefully point out that once remission was

achieved, 75% of the patients continued in remission at the end of 1 year and up to 63% at 2 years regardless of the maintenance therapy used. These results would suggest that the key is achieving remission, which, once attained, can be maintained by conservative nondrug therapy rather than the "medicines we are currently using with their limited efficacy and known toxicity."[32]

Eicosanoid Metabolism in Inflammatory Bowel Disease

Patients with IBD show greatly increased levels of inflammatory chemicals in the colonic mucosa, serum, and stool samples. Specifically, these patients show an increase in the synthesis of the lipoxygenase products, leukotrienes, and mono-hydroxyeicosatetraenoic acids (mono-HETEs).[35-39] These compounds are produced by neutrophils and are known to amplify the inflammatory process and cause smooth muscle contraction. Release of lipoxygenase products is promoted by activation of the alternative complement pathway. The therapeutic efficacy of sulfasalazine and corticosteroids is due to their effect on eicosanoid metabolism (Figure 181-1). Sulfasalazine is an inhibitor of both cyclooxygenase and neutrophil lipoxygenase, whereas corticosteroids inhibit phospholipase A_2 and thus block the release of arachidonic acid from the membrane phospholipid pool. Sulfasalazine also inhibits the degranulation of mast cells. Several naturally occurring compounds, such as the polyphenols (quercetin, curcumin, resveratrol, etc.), also interact favorably with these enzymes (Figure 181-2).

The formation of these inflammatory compounds can be decreased by reducing or eliminating the consumption of omega-6 rich foods (corn, beef, liver, pork, lamb, and milk/dairy products) and increasing the consumption of omega-3 fatty acids through a higher intake of cold-water fish (salmon, mackerel, herring, and halibut). These fish are good sources of the longer-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Meta-analyses of double-blind studies with fish oil supplements (2.7 to 5.1 g total omega-3 oils) have demonstrated an ability to prevent or delay relapses in both CD and UC.[40,41] The Cochrane Collaboration recently published a systematic review evaluating 214 publications and identified only 15 randomized controlled trials. Only 4 studies were of sufficient quality to be included in the analysis. Enteric-coated omega-3 EFA supplementation reduced the 1-year relapse rate by half, with an absolute risk reduction of 31% and a number needed to treat (NNT) of only 3. A much larger RCT asked whether omega-3 fatty acids could sustain remission once it was achieved. Two randomized double-blind placebo-controlled studies (Epanova Program in Crohn's Study 1 [EPIC-1] and EPIC-2) were conducted between January 2003 and February 2007 at 98 centers in Canada, Europe, Israel, and the United States. Data from 363 and 375 patients with quiescent CD were evaluated in EPIC-1 and EPIC-2, respectively. Patients with a CDAI score of less than 150 were randomly assigned to receive either 4 g/day of omega-3 free fatty acids or placebo for up

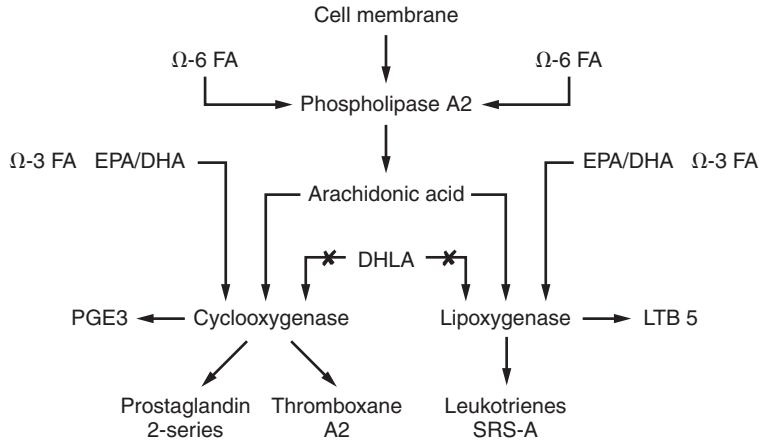


FIGURE 181-1 Omega-3 modulation of arachidonic acid cascade.

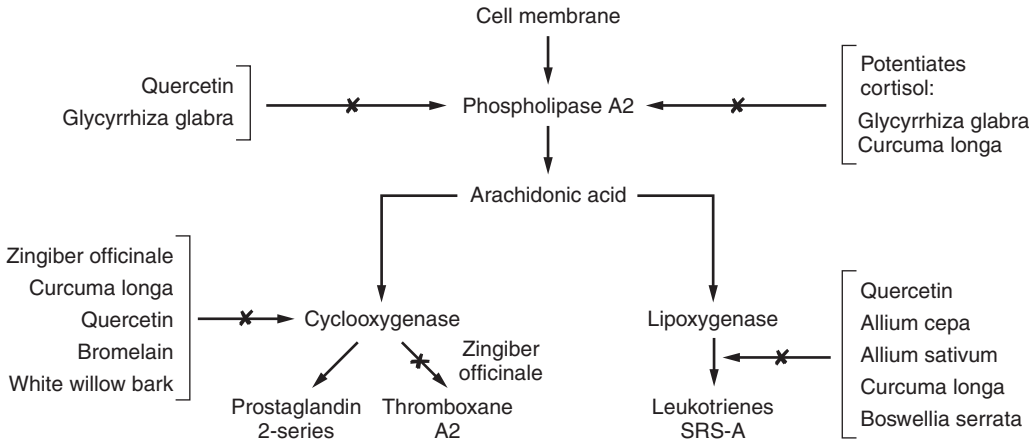


FIGURE 181-2 Botanical modulation of arachidonic acid cascade.

to 58 weeks. No other treatments for CD were permitted. Clinical relapse is defined by a CDAI score of 150 points or greater and an increase of more than 70 points from the baseline value, or initiation of treatment for active CD. In both EPIC-1 and EPIC-2, there were no significant differences in the CD relapse rate for placebo versus fish oils.[42] Flaxseed oil is also of value. Flaxseed oil contains alpha-linolenic acid, an essential omega-3 fatty acid that has antiinflammatory effects and can be converted to eicosapentaenoic acid (EPA) in limited amounts.[43]

Mucin Defects in Ulcerative Colitis

Mucins are an ill-defined class of high-molecular-weight carbohydrate-rich (85% by weight of *N*-acetylgalactosamine, galactose, sialic acids, *N*-acetylglucosamine, and fructose) glycoproteins thought to be largely responsible for the viscous and elastic characteristics of secreted mucus. Alterations in mucin composition and content in the colonic mucosa have been reported in patients with UC.[43-46] The factors responsible for these changes appear to be a dramatic drop in the mucous content of the goblet cells (proportional to the severity of the disease) and a diminution of the major sulfomucin subfraction (designated "species IV," according to diethylaminoethanol-cellulose differentiation). In contrast, these abnormalities are not found in patients with CD. It is significant that, although the mucin content of the goblet cells returns to normal during remission, the sulfomucin deficiency does not. The specific components of the sulfomucin and the cause of its lower concentration have not yet been determined. These mucin abnormalities are also thought to be a major factor in these patients' higher risk of colon cancer.

Many of the herbs used historically in the treatment of UC are demulcents; that is, agents that soothe irritated mucous membranes and promote the secretion of mucus. This effect appears to be very beneficial and supports the use of demulcents in UC.

Intestinal Microflora

The intestinal microflora is extraordinarily complex and contains more than 400 distinct microbial species.[11,12] Accurate simultaneous quantification of all possible species is not possible with current conventional culture techniques. In addition, measurement techniques such as stool cultures do not indicate bacterial metabolic activity, locations of growth within the gastrointestinal tract, or turnover rates. These last two factors may prove to be the more important determinants of the role of the intestinal bacterial flora in IBD than the actual numbers of specific bacterial species. In an effort to describe a nonspecific (qualitative or quantitative) alteration in the intestinal flora, the term *dysbiosis* is often used (see Chapters 10 and 27 for a full discussion of this important topic).[11]

The fecal flora of patients with IBD has been found to contain higher numbers of gram-positive anaerobic coccoid rods and *Bacteroides vulgatus*, a gram-negative rod.[11] Studies have indicated that these alterations in fecal flora are not secondary to the disease, and alterations in the metabolic activity of the various bacteria are thought to be more important than alterations in the number of bacteria per se. In addition, specific bacterial cell components (which vary even within the same species) are thought to be responsible for promoting lymphocyte cytotoxic activity against the colonic epithelial cells.[11,12]

Carrageenan

Interestingly, researchers investigating the intestinal flora of UC often use the carrageenan (a sulfated polymer of galactose and D-anhydrogalactose extracted from red seaweeds, principally *Eucheuma spinosum* and *Chondrus crispus*) model to induce the disease in animals experimentally. In the initial experiments reported by Marcus and Watt[47] in 1969, 1% and 5% carrageenan solutions were provided as the exclusive source of oral fluids for guinea pigs. Over a period of several days, the animals lost weight, demonstrated anemia, and had bloody diarrhea. Gross anatomic studies after sacrifice at 20 and 45 days revealed a loss of haustral folds, mucosal granularity, pseudopolyps, and strictures; microscopic examination showed crypt abscesses, lymphocytic infiltration, capillary congestion of the lamina propria, and gross ulcerations. These results have since been confirmed by numerous investigators and in studies involving other animal species, including primates.[5,48-50]

In its native state the carrageenan polymer has a molecular weight of 100,000 to 800,000 Da, but in the studies it is degraded by mild acidic hydrolysis to yield products with weights in the vicinity of 30,000 Da. Carrageen compounds are used by the food industry as stabilizing and suspending agents, with polymers of different molecular weights being used for a variety of purposes. Typically, carrageenans used in the food industry have a molecular weight greater than 100,000 Da. Carrageenan is widely used in milk and chocolate milk products (e.g., ice cream, cottage cheese, milk chocolate) because of its ability to stabilize milk proteins.

As suggestive as the animal studies are in linking UC with carrageenan and despite the higher consumption of carrageenan in Western diets, at this time there appears to be no correlation between the human consumption of carrageenan and the development of UC. In one study, no lesions of IBD were observed in healthy human subjects fed enormous quantities of degraded carrageenan.[51] However, differences in intestinal bacterial flora are probably responsible for this discrepancy, because germ-free animals do not display carrageenan-induced damage.

On further examination, it was discovered that the bacterium linked to the carrageenan-induced damage in animals is a strain of *B. vulgatus*.[11] As mentioned earlier, this organism is found in much higher concentrations (six times as high) in the fecal cultures of patients with IBD. When all the data are evaluated, they appear to imply that although carrageenan can be metabolized into nondamaging components in most human subjects, those individuals with an overgrowth of *B. vulgatus* may be at risk. Strict avoidance of carrageenan appears warranted at this time for patients with IBD until further research clarifies its safety for them.

Aspirin and Intestinal Permeability

A very interesting study evaluated 30 patients with CD and 37 first-degree relatives of patients with CD for intestinal permeability by means of the lactulose/mannitol ratio. First-degree relatives had a 110% higher intestinal permeability after ingesting acetylsalicylic acid, compared with an increase of 57% in the control subjects. Thirty-five percent were "hyperresponders."[52] A familial permeability defect causing increased permeability would be a significant predisposing factor for CD, because a leaky gut is associated with higher incidence of food allergy and greater absorption of intestinal toxins (see Chapter 20).

Endotoxemia and the Alternative Complement Pathway

Endotoxemia is associated with both CD and UC.[52,53] Endotoxemia-induced activation of the alternative complement pathway could explain some of the extraintestinal (i.e., outside the gastrointestinal tract) manifestations of IBD (discussed later). Whole-gut irrigation significantly reduces the endotoxin pool in the gut and has been shown to have a very beneficial antiendotoxemia effect.[54] Colonic irrigation may offer similar benefit. However, colonic irrigation during an acute inflammatory flare may be contraindicated.

BOX 181-1 Causes of Malnutrition in Inflammatory Bowel Disease

Decreased oral intake
- Disease induced (pain, diarrhea, nausea, anorexia)
- Iatrogenic (restrictive diets without supplementation)

Malabsorption
- Decreased absorptive surface due to disease or resection
- Bile salt deficiency after resection
- Bacterial overgrowth
- Drugs (e.g., corticosteroids, sulfasalazine, cholestyramine)

Increased secretion and nutrient loss
- Protein-losing enteropathy
- Electrolyte, mineral, and trace mineral loss in diarrhea

Increased utilization and increased requirements
- Inflammation, fever, infection
- Increased intestinal cell turnover

Extraintestinal Manifestations

More than 100 disorders, known as extraintestinal lesions (EILs), constitute a diverse group of systemic complications of IBD.[2,55,56] The most common EIL in adults is arthritis, which is found in about 25% of patients. Two types are typically described, the more common being peripheral arthritis affecting the knees, ankles, and wrists. Arthritis is more common in patients with colon involvement. Severity of symptoms is typically proportional to disease activity.[2,55,56]

Less frequently, the arthritis affects primarily the spine. Symptoms are low back pain and stiffness, with eventual limitation of motion. This EIL occurs predominantly in men with HLA-B_{27} and is fairly indistinguishable from typical ankylosing spondylitis. In fact, it may antedate the bowel symptoms by several years. There is probably a consistent underlying factor in both the progression of ankylosing spondylitis and IBD.[2,55,56]

Skin manifestations are also common, being seen in approximately 15% of patients. Typical lesions are erythema nodosum, pyoderma gangrenosum, and aphthous ulcerations. Recurrent aphthous stomatitis occurs in approximately 10% of patients.[2,55,56]

Serious liver disease (i.e., sclerosing cholangitis, chronic active hepatitis, cirrhosis) is also a common EIL, affecting 3% to 7% of the patients with IBD. It probably relates to the increased endotoxin load associated with IBD. If patients are demonstrating liver enzyme abnormalities, hepatoprotection appears indicated, with botanical medicines such as *Silybum marianum* (i.e., silymarin) and curcumin.[57-59]

Other common EILs are as follows[2,55,56]:
- Thrombophlebitis
- Finger clubbing
- Ocular manifestations (episcleritis, iritis, and uveitis)
- Nephrolithiasis
- Cholelithiasis
- In children: failure to grow, thrive, and mature normally

Malnutrition

Many nutritional complications occur during the course of IBD.[60-62] Because these complications can have a significant influence on the morbidity and perhaps also the mortality of these patients, every effort should be made to ensure optimal nutritional status. The major mechanisms that contribute to nutritional depletion in patients with IBD are listed in Box 181-1.

A decreased food intake is the most important mechanism of nutritional deficiency in patients with IBD, and a deficient calorie intake is the most common nutritional deficit in patients requiring hospitalization. Often the patient feels significant pain, diarrhea, nausea, and/or other symptoms after a meal, resulting in a subtle diminution in dietary intake. Protein-calorie malnutrition and associated weight loss are prevalent in 65% to 75% of patients with IBD.[60]

Malabsorption can be anticipated in patients with extensive mucosal involvement of the small intestine and in those who have undergone resection of segments of the small intestine. Particularly common is fat malabsorption, which results in significant loss of calories as well as loss of fat-soluble vitamins and minerals. Involvement of the ileum or surgical resection of that area typically leads to malabsorption of vitamins (in particular vitamin B_{12}) and bile acid. Because of the cathartic effect of bile acids on the colon, the malabsorption may result in a chronic watery diarrhea. Electrolyte and trace mineral deficiencies should be suspected in patients with a history of chronic diarrhea, whereas calcium and magnesium deficiencies may be a result of chronic steatorrhea.

Increased secretion of protein into the intestinal lumen and nutrient loss due to the exudative and inflammatory nature of IBD are common. In particular, there is a significant loss of plasma proteins across the damaged and inflamed mucosa. The loss of protein may exceed the ability of the liver to replace plasma proteins despite a high protein intake. The chronic loss of blood often leads to iron depletion and anemia.

The drugs most commonly used in the allopathic treatment of IBD are corticosteroids and sulfasalazine, both of which increase nutritional needs. Corticosteroids are known to have the following effects:
- Stimulate protein catabolism
- Depress protein synthesis
- Decrease the absorption of calcium and phosphorus
- Increase the urinary excretion of ascorbic acid, calcium, potassium, and zinc
- Increase blood glucose, serum triglyceride, and serum cholesterol levels
- Increase the requirements for vitamin B_6, ascorbic acid, folate, and vitamin D
- Decrease bone formation
- Impair wound healing

Sulfasalazine has been shown to have the following effects[63]:
- Inhibits the absorption and transport of folate
- Decrease serum folate and iron
- Increase the urinary excretion of ascorbic acid

The last consideration in the causes of nutrient deficiency in patients with IBD involves the nutritional consequences of a chronic inflammatory and/or infectious disease. This topic has not been fully investigated; the only conclusion that currently can be drawn is that protein requirements may be raised in patients with acute exacerbations of IBD. An elevated erythrocyte sedimentation rate signifies a rise in both protein breakdown and protein synthesis. Typically, patients with IBD require perhaps as much as 25% more protein than the usual recommended allowance.[60-62]

Prevalence of Nutritional Deficiencies

As shown in Table 181-1, the prevalence of nutritional deficiencies is quite high in hospitalized patients with IBD. Although it is generally agreed that the prevalence of nutritional deficiencies is greater in hospitalized patients (who typically are more severely ill) than in outpatients, a great number of ambulatory patients with CD display one or more nutrient deficiencies as well.[64] In

TABLE 181-1 **Prevalence of Nutritional Deficiencies in Hospitalized Patients with Inflammatory Bowel Disease**

DEFICIENCY	PREVALENCE (%)
Hypoalbuminemia	25-80
Anemia	60-80
Iron deficiency	40
Low serum vitamin B_{12}	48
Low serum folate	54-64
Low serum magnesium	14-33
Low serum potassium	6-20
Low serum retinol	21
Low serum ascorbate	12
Low serum 25-OH-vitamin D	25-65
Low serum zinc	40-50

Data from Aoki K: A study of endotoxemia in ulcerative colitis and Crohn's disease. I. Clinical study. *Acta Med Okayama* 1978;32:147-158.

addition to the deficiencies listed in Table 181-1, low levels of vitamin K, copper, niacin, and vitamin E have been reported.[60]

Diet

The importance of correcting nutritional deficiencies in patients with IBD cannot be overstated. Deficiencies of both macronutrients and micronutrients cause alterations in gastrointestinal function and structure, which may lead to a vicious cycle—the secondary effects of malnutrition on gastrointestinal tract function and structure may further exacerbate malabsorption, further reducing nutrient status. Foremost in nutritional therapy is providing adequate caloric intake. It should be assumed that the majority of patients suffer from micronutrient deficiency, although the deficiency is often subclinical and can be detected only by appropriate laboratory investigation.

In general, patients with IBD should be started on therapeutic vitamin supplements of at least five times the recommended dietary allowances (RDAs). Several minerals may also have to be supplemented at equally high levels. Dietary treatment involves the use of either an elemental diet or an elimination diet (described later).

Elemental Diet

The elemental diet has been shown to be an effective nontoxic alternative to corticosteroids as the primary treatment of acute IBD.[20-23] Such a diet is one that is purported to contain all essential nutrients, with protein being provided only as predigested or free-form amino acids. The improvements noted on an elemental diet, however, are probably not primarily related to nutritional improvement but could be a result of alterations in the intestinal flora (which have been noted to occur in patients consuming an elemental diet). A stronger case could be made for a secondary immune mechanism being bypassed during elemental feeding: the elemental diet is serving as an allergy-elimination diet.

The main drawbacks of the widespread use of elemental diets are their poor palatability and their hyperosmolality, which often result in diarrhea. In addition, hospitalization is often required for satisfactory administration, and relapse is quite common when patients resume normal eating. An elimination diet, rather than an elemental diet, may be a more acceptable alternative in the treatment of acute and particularly of chronic IBD.

Elimination (Oligoantigenic) Diet

Although food allergy has long been considered an important etiologic factor in the pathogenesis of IBD, studies using an elimination diet in the treatment of IBD have been performed only recently (elimination diets are described in Chapter 15).[24-26] These studies demonstrate that an elimination diet is the primary therapy of choice in the treatment of chronic IBD. The most common offending foods were found to be wheat and dairy products.

An alternative approach is to determine the actual allergens with laboratory methods, preferably a method that measures reactions mediated by both immunoglobulins G (IgG) and E (IgE). The allergens are then avoided or a rotary diversified diet is used as appropriate (see Chapter 46).

Minerals

Zinc

Zinc deficiency, a well-known complication of CD, occurs in approximately 45% of patients with the disorder.[65] Low serum zinc concentrations, low hair zinc levels, malabsorption of zinc, altered urinary excretion of zinc, and impaired taste acuity are commonly found in patients with CD.[61,65] The deficiency of zinc is due to low dietary intake, poor absorption, and excess fecal losses.[61-63,65] Zinc deficiency may be the direct cause of the following complications of CD[65-67]:

- Poor healing of fissures and fistulas
- Skin lesions (acrodermatitis)
- Hypogonadism
- Growth retardation
- Retinal dysfunction
- Depressed cell-mediated immunity
- Anorexia
- Chronic diarrhea

Many patients with CD show no response to oral or intravenous zinc supplementation because such patients appear to have a defect in tissue transport of zinc. Intravenous supplementation results in a tremendous rise in urinary zinc excretion but insignificant clinical results. Several clinical trials using oral zinc sulfate have shown the same lack of positive effect.[68]

Administration of zinc in the oral picolinate form may be more advantageous than other forms of zinc, possibly improving both intestinal absorption and tissue transport, although one study displayed no significant difference in zinc absorption between zinc sulfate and zinc picolinate in patients with pancreatic insufficiency.[69] Zinc citrate may also be an appropriate alternative. In any event, every attempt should be made to ensure that adequate tissue stores of zinc are maintained, because disease activity is correlated with zinc deficiency. Parenteral zinc administration may be needed in some cases. Although less than ideal, intravenous administration of zinc is often the only way to attain even marginal zinc levels in patients with CD.[68]

Magnesium

Magnesium deficiency is often seen in patients with IBD.[61,70,71] However, a poor correlation exists between serum magnesium levels—which may be low in only a few patients— and intracellular magnesium levels, which are commonly decreased in patients with IBD.[61] Patients with low intracellular magnesium levels may present with the following problems[61]:

- Weakness
- Anorexia
- Hypotension
- Confusion

- Hyperirritability
- Tetany
- Convulsions
- Electrocardiographic or electroencephalographic abnormalities

These symptoms are generally responsive to parenteral magnesium supplementation.

A daily intravenous dose of 200 to 400 mg of elemental magnesium may be necessary for patients not responding to oral supplementation. Patients with IBD may require this route of supplementation owing to magnesium's somewhat cathartic action and poor absorption in those with a short bowel. Oral supplementation should be with magnesium chelates (i.e., citrate, aspartate) rather than inorganic magnesium salts (i.e., carbonate).

Iron

Iron deficiency anemia is very common in IBD, largely because of chronic blood loss through the gut.[61] Serum ferritin levels are the most useful indices of iron status. A serum ferritin concentration greater than 55 ng/mL indicates adequate iron reserves in bone marrow, whereas a concentration less than 18 ng/mL is highly predictive of iron deficiency (see Chapter 24 for further discussion). The clinician should attempt to increase the patient's iron stores by improving absorption, as with supplemental vitamin C, rather than through direct iron supplementation, which promotes intestinal infection.[72]

Calcium

Patients with IBD are also at risk for the development of calcium deficiency, probably owing to the following factors[61]:

- Loss of absorptive surfaces
- Steatorrhea
- Corticosteroid use
- Vitamin D deficiency

Potassium

Diarrheal diseases are often associated with potassium and other electrolyte deficiencies. Although symptoms of potassium deficiency are quite rare in patients with IBD, levels of this mineral are probably below optimum. In one study, nutritional support to correct potassium deficiency resulted in significantly reduced rates of surgical complications.[73]

Vitamins

Vitamin A

Low serum retinol levels are found in approximately 20% of patients with CD and are correlated with the activity of the disease.[61,67] Vitamin A can profoundly affect the metabolism and differentiation of the intestinal epithelial mucosa because it can increase the number of goblet cells, the production of mucins, and the secretion of mucus; moreover, it can restore normal barrier function. Preliminary case reports indicated that vitamin A may be of therapeutic use in CD.[74,75] However, long-term controlled trials have shown that vitamin A (50,000 IU twice daily) has no therapeutic effect in the majority of patient with CD.[76,77] It should be kept in mind, however, that certain individuals may respond to vitamin A therapy and that zinc supplementation will often normalize disturbances of vitamin A metabolism, because zinc is a necessary component of retinol-binding protein.[67]

Vitamin D

Vitamin D deficiency is quite common in IBD, with laboratory evidence of this in 75% of CD and 35% of UC patients.[61,78] It is probably due to decreased absorption of 25-hydroxyvitamin D. Patients with IBD are at increased risk for the development of metabolic bone diseases such as osteoporosis and osteomalacia. This relates to previously mentioned factors in calcium deficiency. Vitamin D plays an important role in supporting proper immune regulation, much like probiotics; both influence T-regulatory cell function and dampen proinflammatory cytokines produced in animal models of IBD. Clinical studies using vitamin D at supraphysiologic doses are under way.

Vitamin E

Vitamin E deficiency can occur in IBD, as observed in one case report.[79] The patient had a 25-year history of CD and had undergone multiple small bowel resections. Presenting symptoms relating to vitamin E deficiency were as follows:

- Bilateral visual field scotomata
- Generalized motor weakness
- A broad-based gait with marked ataxia
- Brisk reflexes
- A bilateral Babinski response

This patient's serum vitamin E concentration was 0.03 mg/dL (normal is 0.8 to 1.2 mg/dL), and in vitro peroxide hemolysis was 100% (normal is <10%). Supplementation with 270 IU/day of vitamin E eventually brought complete recovery over a period of 2 years.

Vitamin E supplementation is also indicated because of its ability to inhibit the formation of leukotrienes and reduce free radical damage.[80]

Vitamin K

Vitamin K deficiency, resulting in the formation of abnormal prothrombin (deficient in gamma-carboxyglutamic acid), is quite common in patients with IBD.[81,82] It also contributes to the osteoporosis and osteopenia that are so often seen in patients with CD.[83] The best laboratory test to diagnose early vitamin K deficiency prior to lowered serum levels is to measure the incomplete gamma carboxylation of specific serum proteins such as osteocalcin and prothrombin. Low vitamin K status has been linked to bone disease by incomplete carboxylation of osteocalcin and coronary artery disease by unknown mechanisms. The test is called PIVKA II (protein in absence of vitamin K carboxylation) by laboratories such as Quest and Labcorp as well as many designer specialty laboratories.

Folic Acid

Low serum concentrations of folic acid are common in IBD, with reports of occurrence ranging between 25% and 64% of cases.[61,83-85] The drug sulfasalazine exacerbates the condition by interfering with folate-dependent enzymes and with the intestinal folate transport system.[86] A folate deficiency promotes further malabsorption through alteration in structure of the intestinal mucosal cells.[87] These cells have a very rapid turnover (1-4 days) compared with red blood cells (RBCs) (3-4 months); therefore, deficiency affects mucosal cells much earlier than RBCs. Testing CD patients for elevations in serum homocysteine or single nucleotide polymorphisms (SNPs) for enzymes involved in the methylation of folate, such as methyl tetrahydrofolate reductase, may provide valuable diagnostic tools for the early detection of aberrant folate metabolism in CD patients. Patients with UC, on the other hand, require supplemental folate to reduce their higher risk of colon cancer.

Vitamin B_{12}

There is a significant correlation between vitamin B_{12} absorption and the extent of terminal ileal disease and/or resection.[61,88] Overall, abnormal Schilling test results are found in 48% of patients

with CD. When ileal resection exceeds 90 cm, the Schilling test result is abnormal in all patients and does not improve with time. If the length of the resection or the extent of the inflammatory lesion is less than 60 cm, adequate absorption may occur.

Ascorbic Acid

A low vitamin C intake is common in patients with IBD, particularly in those on a low-fiber diet.[61,89] Ascorbic acid levels in serum and leukocytes are significantly lower in patients with CD than in matched controls.[61,89] Vitamin C is thought to be particularly important in the prevention of fistula formation. It has been shown that patients with fistulas have lower ascorbic acid levels than patients without them.[90]

Antioxidant Defenses

Increased oxidative stress and decreased antioxidant defenses in the mucosa are hallmark features of IBD.[91] Patients with IBD have heightened oxidative stress and associated protein and DNA oxidative damage).[91]Likewise, IBD patients have serum and mucosal deficiencies in antioxidant defenses such as selenium-dependent glutathione peroxidase and copper-zinc superoxide dismutase, along with cofactors for these enzyme systems (i.e., zinc, copper) and others (i.e., ascorbate, vitamin E, vitamin A), as previously described in this chapter.[91]

Other Nutrients

Obviously, patients with IBD are at risk for the development of any nutrient deficiency, including nutrients not discussed here. However, there is probably no real need for laboratory investigation to determine micronutrient deficiencies other than for the nutrients discussed here.[61]

Recommendation for a High-Potency Multivitamin/Multimineral Formula

It is absolutely essential that patients with IBD take a high-potency multivitamin/multimineral supplement comprising all the known vitamins and minerals. Table 181-2 lists recommendations for an optimal intake range.

In addition, patients with IBD should consume additional antioxidants (rationale provided above). The two primary antioxidants in the human body are vitamins C and E. Vitamin C is an "aqueous phase" antioxidant, whereas vitamin E is a "lipid phase" antioxidant. Recommended doses in patients with IBD are as follows:

- Vitamin E (mixed tocopherols with approximately 40% gamma-tocopherol): 400 to 800 IU
- Vitamin C (ascorbic acid): 1000 to 3000 mg

TABLE 181-2 **Optimal Range of Nutrients**

NUTRIENT	RANGE FOR ADULTS
Vitamins	
Vitamin A (retinol)	5000 IU*
Vitamin A (from beta-carotene)	5000-25,000 IU
Vitamin D	100-400 IU
Vitamin E (D-alpha tocopherol)	100-200 IU
Vitamin K (phytonadione)	60-300 mcg
Vitamin C (ascorbic acid)	100-1000 mg
Vitamin B_1 (thiamin)	10-100 mg
Vitamin B_2 (riboflavin)	10-50 mg
Niacin	10-100 mg
Niacinamide	10-30 mg
Vitamin B_6 (pyridoxine)	25-100 mg
Biotin	100-300 mcg
Pantothenic acid	5-100 mg
Folic acid	400 mcg
Vitamin B_{12}	400 mcg
Choline	10-100 mg
Inositol	10-100 mg
Minerals	
Boron	1-6 mg
Calcium	250-500 mg
Chromium	200-400 mcg
Copper	1-2 mg
Iodine	50-150 mcg
Iron	15-30 mg†
Magnesium	250-500 mg
Manganese	10-15 mg
Molybdenum	10-25 mcg
Potassium	200-500 mg
Selenium	100-200 mcg
Silica	1-25 mg
Vanadium	50-100 mcg
Zinc	15-45 mg

*Women of childbearing age for whom becoming pregnant is a possibility should not take more than 2500 IU/day of retinol because of the possible risk of birth defects.
†Men and postmenopausal women rarely need supplemental iron.

Botanical Medicines

Curcumin

Turmeric, the major spice in curry, is a natural spice made from the herb *Curcuma longa*, a member of the ginger family. In addition to being a culinary staple, it has been used in Ayurvedic medicine since ancient times. The major chemical constituents of turmeric are curcuminoids, the most prominent of which is curcumin. Recently investigational focus has shifted toward the role of curcumin as an intracellular signaling agent and studies have demonstrated that much like green tea polyphenols, curcumin is an inhibitor of NF-kB and leads to downstream regulation and inhibition of proinflammatory genes and cytokines (Figure 181-2).[93] Administration of curcumin has also been reported to modulate a host of other cytokines and signaling pathways, including iNOS, MMP-9, TNF-a, JNK, p38, AKT, JAK, ERK, and PKC.[94] Four studies involving curcumin administration in murine colitis models showed clinical and histopathologic improvement and, where measured, decreased inflammatory cytokine production.[95-97] These findings were echoed in three further studies involving rodent models of colitis.[98-100]

In 2005, Holt and colleagues reported the preliminary results of a pilot study involving open-label administration of a curcumin preparation to 5 patients with UC and 5 patients with CD. Of these 10 patients, 9 reported improvement at the conclusion of the 2-month study. Of the 5 patients with UC, 4 were able to decrease or eliminate their medications.[101] In a larger randomized double-blind multicenter trial involving 89 patients with quiescent UC, administration of 1 g of curcumin twice daily resulted in both clinical improvement and a statistically significant decrease in the rate of relapse.[102] Given its excellent safety profile, plausible mechanism

for affecting inflammation, and the results above, curcumin is poised to have a prominent role in the future management of IBD.

Boswellia

The Ayurvedic herb *Boswellia serrata* (Indian frankincense) contains boswellic acids, which inhibit leukotriene biosynthesis in neutrophilic granulocytes by noncompetitive inhibition of 5-lipoxygenase.[103] During a small 6-week trial, 350 mg three times a day of *Boswellia* gum resin was as effective as sulfasalazine (1000 mg three times a day) in reducing symptoms or laboratory abnormalities of patients with active UC.[104] The rate of remission was 82% with *Boswellia* and 75% with sulfasalazine.[105] In a randomized, double-blind study from Germany, a proprietary *Boswellia* extract, H15, was found as effective as mesalazine in improving symptoms of active CD.[106]

Quercetin

The plant flavonoid quercetin appears to be particularly indicated in the treatment of IBD. Flavonoids in general are considered natural biological response modifiers.[107,108] Quercetin, as perhaps the most pharmacologically active flavonoid, has remarkable effects on a variety of enzyme systems,[107,108] and many of the enzymes thus affected are important in the secretory, contractile, and motility processes associated with the inflammatory response: the release of histamine and other inflammatory mediators from mast cells, basophils, neutrophils, and macrophages; migration and infiltration of leukocytes; and smooth muscle contraction.

Quercetin's effect on these enzymes and processes is likely due to a common action—antagonizing calmodulin.[109] When bound to calmodulin, calcium activates a great variety of enzymes, including those involved in cyclic nucleotide metabolism, protein phosphorylation, secretory function, muscle contraction, microtubule assembly, glycogen metabolism, and calcium flux. Quercetin is believed to interact directly with calmodulin and calcium channels. This has been shown in many experimental studies and would explain quercetin's effect on such a wide number of enzymes.

Quercetin and many other flavonoids have been shown to be potent inhibitors of mast cell and basophil degranulation.[110-113] A generally accepted hypothesis for this action is that quercetin inhibits receptor-mediated calcium influx, thereby inhibiting the primary signal for degranulation. However, quercetin is also active under conditions in which the calcium channel mechanism is not operative, indicating that other mechanisms are responsible as well.

Quercetin has been shown to inhibit many of the inflammatory processes attributed to activated neutrophils.[114] This is probably due to its membrane-stabilizing action, potent antioxidant effect (which prevents the production of free radicals and inflammatory leukotrienes), and inhibition of the enzyme hyaluronidase (thus preventing the breakdown of the collagen matrix of connective tissue and ground substance). Quercetin's membrane-stabilizing effect could also account for its action in preventing mast cell and basophil degranulation. The effect also inhibits inflammation by decreasing neutrophil lysosomal enzyme secretion.[114] (Neutrophils and monocytes contain lysosomes that, on secretion of their contents, contribute greatly to the inflammatory process.)

Quercetin has been shown to inhibit many steps in eicosanoid metabolism. Probably of most significance in IBD is its inhibition of phospholipase A_2 and lipoxygenase enzymes.[107,108,115] The net result is a significant reduction in the formation of leukotrienes. Excessive leukotriene formation has been linked to asthma, psoriasis, atopic dermatitis, gout, and, possibly, cancer as well as IBD.[116,117] The leukotrienes C_4, D_4, and E_4 (composing the slow-reacting substances of anaphylaxis [SRS-A]) are derived from arachidonic acid and are 1000 times as potent as histamine in promoting inflammation. Leukotrienes promote inflammation by causing vasoconstriction (thereby increasing vascular permeability) and other smooth muscle contraction and by promoting white blood cell (WBC) chemotaxis and aggregation. The reduction of leukotriene formation has significant antiinflammatory effects, particularly in IBD. (For more information on quercetin, see Chapter 92). Despite the overwhelming evidence supporting the role of quercetin in preventing and improving inflammation in IBD, only 3 of 6 animal model–based studies showed a positive effect. Authors have speculated that the methylation of quercetin in the gut is variable in IBD, which could explain the inconsistent results observed thus far. Clinical trials in humans are thus far lacking, so that no conclusions can be drawn.

BOX 181-2 Composition of the Bastyr Formula

- Eight parts *Althea officinalis*
- Four parts *Baptisia tinctora*
- Eight parts *Echinacea angustifolia*
- Eight parts *Geranium maculatum*
- Eight parts *Hydrastis canadensis*
- Eight parts *Phytolacca americana*
- Eight parts *Ulmus fulva*
- Eight parts cabbage powder
- Two parts pancreatin
- One part niacinamide
- Two parts duodenal substance

Aloe Vera

Aloe vera gel has a dose-dependent inhibitory effect on the production of the reactive oxygen metabolites prostaglandin E2 and (at high doses) IL-8 by human colonic epithelial cells grown in tissue culture.[118] When administered via the oral route, aloe vera gel at 100 mL twice a day for 4 weeks produced a clinical response significantly more often than placebo (response ratio 5.6) in patients with UC.[119] Remission occurred in 30% of patients taking aloe vera gel and 7% of those receiving placebo. In this clinical trial, aloe also reduced histologic disease activity, whereas placebo did not. No significant side effects were described in the aforementioned trials on aloe vera for UC, although it should be noted that aloe vera gel is often used as a laxative. Acemannan, an extract of aloe vera, concentrated to a mucopolysaccharide (MPS) concentration of 30% of solid weight, has been demonstrated to reduce symptoms and indices of inflammation in controlled studies of patients with UC.[120]

Bastyr Formula (Modified Robert Formula)

Although no research has been done to document its efficacy, an old naturopathic remedy, Robert formula or its modification (Bastyr formula), has a long history of use in IBD (Box 181-2). It is composed of the following botanical medicines:

- *Althea officinalis* (also known as marshmallow root)—a demulcent with soothing effects on the mucous membranes
- *Baptisia tinctora* (also known as wild indigo)—used for gastrointestinal infections
- *Echinacea angustifolia* (also known as purple coneflower)—antibacterial and used to promote normalization of the immune system (see Chapter 86)
- *Geranium maculatum*—a gastrointestinal hemostatic

- *Hydrastis canadensis* (also known as goldenseal)—inhibits the growth of many enteropathic bacteria (see Chapter 97)
- *Phytolacca americana* (also known as poke root)—used for healing ulcerations of the intestinal mucosa
- *Symphytum offinale* (also known as comfrey)—antiinflammatory and a promoter of tissue growth and wound healing
- *Ulmus fulva* (also known as slippery elm)— a demulcent

The cabbage powder is used because of its documented ability to heal gastrointestinal ulcers (see Chapter 198); pancreatin is used to assist in the digestive process (see Chapter 111); niacinamide is used for its antiinflammatory effects; and duodenal substance is used because it also heals gastrointestinal ulcers.

Other Interventions

Butyrate Enemas in Ulcerative Colitis

Short-Chain Fatty Acids and Colon Function. The short-chain fatty acids (SCFAs)—mainly acetate, propionate, and butyrate—arise in the colon as end products of bacterial carbohydrate fermentation. These SCFAs function as primary energy sources for the luminal colon cells, especially in the distal segments. Decreased levels or decreased utilization of SCFAs leading to impaired cellular energetics has been hypothesized to play a major role in UC. On the basis of this hypothesis, several clinical trials have been conducted with enemas providing SCFAs (usually composed of either butyrate as a sole agent in concentrations ranging from 80 to 100 mmol/L or SCFA combinations composed of acetate 60 mmol/L, propionate 25 mmol/L, and butyrate 40 mmol/L). Excellent preliminary results in pilot studies have led to a well-designed double-blind study.[74,121]

In this study, 47 patients with distal UC randomly received either a combination of SCFAs, butyrate, or a placebo in an enema form retained for 30 minutes twice daily.[74] The primary endpoint of the study was the disease activity index composed of stool frequency, rectal bleeding, mucosal appearance, and physician's rating of disease activity as well as endoscopic examination. After 8 weeks of therapy, there was a drop in activity in all three groups, with the butyrate group showing the lowest disease activity. Endoscopic examination demonstrated less disease in the butyrate and SCFA combination groups. Complete remission occurred in 47% receiving SCFAs, 38% receiving butyrate, and 25% receiving placebo. This study and others indicate that butyrate and SCFA enemas may prove to be useful adjuncts in the treatment of UC. There are a total of four studies demonstrating improved healing of patients with left-sided UC that is refractory to standard medical therapy.

Prebiotics

Prebiotics are nondigestible food ingredients that stimulate the growth or modify the metabolic activity of intestinal bacterial species that have the potential to improve the health of their human host. The criteria associated with the notion that a food ingredient should be classified as a prebiotic are that it remain undigested and unabsorbed as it passes through the upper part of the gastrointestinal tract and that it be a selective substrate for the growth of specific strains of beneficial bacteria (usually lactobacilli or bifidobacteria) rather than for all colonic bacteria. Prebiotic food ingredients include bran, psyllium husk, resistant (high amylose) starch, inulin (a polymer of fructofuranose), lactulose, and various natural or synthetic oligosaccharides, which consist of short-chain complexes of sucrose, galactose, fructose, glucose, maltose or xylose. The best-known effect of prebiotics is to increase fecal water content, relieving constipation. Bacterial fermentation of prebiotics yields short-chain fatty acids like butyrate. Several studies have suggested benefits of various prebiotics for the treatment of patients with UC (Table 181-3). When oat bran at 60 g/day (supplying 20 g of dietary fiber) was given to UC patients, fecal butyrate was increased by 36% and abdominal pain improved.[122] A dietary supplement containing fish oil and two types of indigestible carbohydrate, FOS and xanthan gum, allowed a reduction of glucocorticoid dose as compared with a placebo in patients with steroid-dependent UC.[123] Other prebiotic trials for UC included a Japanese germinated barley foodstuff (GBF) containing hemicellulose-rich fiber; given at a dose of 20 to 30 g/day, it was found to increase stool butyrate concentration,[124] decrease the clinical activity index of patients with active disease,[125] and prolong remission in patients with inactive disease.[126] A mixture of *Bifidobacterium longum* and inulin-derived FOS administered for 1 month as monotherapy to patients with UC produced improvement in sigmoidoscopic appearance, histology, and several biochemical indices of tissue inflammation versus a placebo control.[127]

TABLE 181-3 **Prebiotics in Ulcerative Colitis**

AUTHOR	YEAR	FIBER	OUTCOME
Fernandez-Banares	1999	Plantago ovata seed fiber, 10 g	Equal to mesalamine
Kanauchi	2002-2003	Barley, 30 g	Disease activity ↓
Hallert	2003	Oat bran, 60 g (fiber 20 g)	Abdominal pain ↓ Fecal butyrate ↑
Welters	2002	Inulin, 24 g	Pouch inflammation ↓

Probiotics in Inflammatory Bowel Disease

The term *probiotics* refers to beneficial bacteria and yeasts that can be administered orally to achieve a therapeutic benefit. The results of studies for the use of probiotics in UC have been analyzed in a meta-analysis according to use in active flares and for maintenance of remission of disease (Table 181-4). Overall, patients with UC do not benefit from using probiotics during an active flare of their disease; however, there is a remarkable benefit of probiotics for maintaining remissions. The studies to date have shown inconsistent results with all strains of probiotics for CD overall (Table 181-5). However, supplementation with the beneficial yeast *Saccharomyces boulardii* is a safe and effective treatment for patients with CD, helping to reduce diarrhea, intestinal inflammation, and the risk of relapse.[128,129] Common doses of *S. boulardii* are 250 mg three to four times a day. Likewise supplementation with *Lactobacillus-GG* has proved to be of benefit in patients with CD; the customary dose is 10^{10} colony-forming units (CFUs) in enteric-coated tablets twice a day.[130,131]

THERAPEUTIC MONITORING AND EVALUATION

Fecal Calprotectin

Calprotectin is a protein secreted into the intestinal lumen in direct proportion to inflammation. Measurement of calprotectin in stool samples has been shown to be a sensitive and specific noninvasive assessment for inflammation in patients with IBD, and the test is helpful for distinguishing IBD from other, noninflammatory gastrointestinal conditions, such as irritable bowel syndrome.[133]

TABLE 181-4 **Remission Rate (A) and Relapse Rate (B) of Probiotic Group Versus Control Group**

A. STUDY OR SUBGROUP	Experimental EVENTS	Experimental TOTAL	Control EVENTS	Control TOTAL	WEIGHT	RISK RATIO M-H, RANDOM (95% CI)
Furrie et al., 2005	5	9	3	9	6.7	1.67 (0.56,4.97)
Kato et al., 2004	4	10	3	9	5.8	1.20 (0.36, 3.97)
Matthes et al., 2006	20	46	2	11	5.1	2.39 (0.65, 8.74)
Miele et al., 2009	13	14	4	15	9.8	3.48 (1.49, 8.16)
Rembacken et al., 1999	39	57	44	59	27.3	0.92 (0.73, 1.16)
Sood et al., 2009	33	55	11	29	17.5	1.58 (0.95, 2.64)
Tursi et al., 2004	24	28	37	48	27.8	1.11 (0.98, 1.85)
B. STUDY OR SUBGROUP	**Experimental EVENTS**	**Experimental TOTAL**	**Control EVENTS**	**Control TOTAL**	**WEIGHT**	**RISK RATIO M-H, RANDOM (95% CI)**
Cui et al., 2004	3	15	14	15	9.0	0.21 (0.08, 0.59)
Heinker et al.,	6	24	3	10	7.5	0.83 (0.26, 2.69)
Ishikawa et al., 2003	3	11	9	10	9.4	0.30 (0.11, 0.81)
Kruis et al., 1997	8	50	6	53	9.4	1.41 (0.53, 3.79)
Kruis et al., 2004	40	110	38	112	20.2	1.07 (0.75, 1.53)
Miele et al., 2009	3	14	11	15	8.7	0.29 (0.10, 0.83)
Rembacken et al., 1999	26	39	32	44	21.5	0.92 (0.69, 1.22)
Zocco et al., 2006	20	127	12	60	14.5	0.79 (0.47, 1.01)
Total (95% CI)		390		319	100	
Total events	109		125			

Heterogeneity: $Tau^2 = 0.16$; $x^2 = 18.50$, $df = 7$ ($P = 0.010$); $I^2 = 62\%$.
Test for overall effect: $Z = 1.92$ ($P = 0.05$).
Data from Zhu H-N, Yu J-P, Luo J, et al. Gastric adenomyoma presenting as melena: A case report and literature review. World J Gastroenterol, 2010 April 21; 16(15): 1908-1915.

TABLE 181-5 **Studies to Date for All Strains of Probiotics for Crohn's Disease Overall**

AUTHOR	YEAR	POPULATION	DESIGN	OUTCOME
Plein	1993	Active Crohn's	Conventional medical therapy ± *Saccharomyces boulardii*	Decreased diarrhea
Malchow	1997	Crohn's	*E.coli* Nissle	Decreased relapse
Guslandi	2000	Crohn's	Mesalamine ± *Saccharomyces.boulardii*	Decreased relapse
Campieri	2000	Crohn's	VSL#3 vs. Mesalamine post-operative maintenance of remission	Decreased symptoms
Prantera	2002	Crohn's	Lactobacillus GG vs. placebo	No benefit
10 others		Crohn's	Various	Mixed

Crohn's Disease Activity Index

The CDAI was developed as a monitoring tool in the National Cooperative Crohn's Disease Study (NCCDS).[134] It met the basic requirements necessary for the study—providing uniform clinical parameters that could be assessed and producing a consistent numerical index for recording the results of the study of several centers over a several years.

The CDAI is calculated by adding together eight variables (Table 181-6). It incorporates both subjective and objective information in determining relative disease activity. A form is provided in Appendix 3 that may be photocopied and given to patients to fill out. When the patient returns with the completed form, the calculation of disease activity can be completed. In general, CDAI scores below 150 indicate a better prognosis than higher scores. The CDAI is a very useful way to monitor the progress of therapy.

Monitoring of the Pediatric Patient

Pediatric patients with IBD present a particularly difficult problem in that it is often very difficult for them to achieve normal growth and development. Growth failure occurs in 75% of children with CD and in 25% of children with UC.[63] The pediatric patient with IBD should be evaluated at least twice yearly. Evaluation should include a pertinent history, clinical anthropometry, Tanner staging, and appropriate laboratory testing. Box 181-3 outlines the necessary components of a comprehensive twice-yearly nutritional evaluation in pediatric patients with IBD. An aggressive nutritional program should be instituted, including supplements (it may be necessary to use enteral or parenteral methods in some patients), which is similar to the approach outlined for the adult patient, with the doses adjusted as appropriate.

TABLE 181-6 **Independent Variables and Formula Used to Calculate the Crohn's Disease Activity Index (CDAI)***

X_1	Number of liquid or very soft stools in 1 week
X_2	Sum of seven daily abdominal pain ratings: 0 = none 1 = mild 2 = moderate 3 = severe
X_3	Sum of seven daily ratings of general well-being: 0 = well 1 = slightly below par 2 = poor 3 = very poor 4 = terrible
X_4	Symptoms or findings presumed related to Crohn's disease. Add 1 point for each category corresponding to patient's symptoms: • Arthritis or arthralgia • Iritis or uveitis • Erythema nodosum, pyoderma gangrenosum, aphthous stomatitis • Anal fissure, fistula, or perirectal abscess • Other bowel-related fistula • Episode of fever >100°F during past week
X_5	Taking diphenoxylate HCl/atropine sulfate tablets (Lomotil) or opiates for diarrhea: 0 = no 1 = yes
X_6	Abdominal mass: 0 = none 0.4 = questionable 1 = present
X_7	47 – hematocrit value, males 42 – hematocrit value, females
X_8	100 × (standard weight – body weight) ÷ standard weight

*CDAI = $2 \infty X_1 + 5 \infty X_2 + 7 \infty X_3 + 20 \infty X_4 + 30 \infty X_5 + 10 \infty X_6 + 6 \infty X_7 + X_8$
Data from Ford-Hutchinson AW: Leukotriene involvement in pathological processes. *J Allergy Clin Immunol* 1984;74:437-440.

The CDAI is not as accurate in monitoring the disease in children as it is in adults. To overcome this shortcoming, Lloyd-Still and Green[135] devised a clinical scoring system for IBD in children. It is divided into five major divisions (the maximum score is in parentheses): general activity (10), physical examination and clinical complications (30), nutrition (20), radiography (15), and laboratory (25). An elevated score (i.e., scores in the 80s) represents good status, whereas scores in the 30s and 40s represent severe disease. Table 181-7 outlines the determination of clinical score.

THERAPEUTIC APPROACH

It is important to recognize that in some patients, CD and UC are life-threatening diseases that at times require emergency treatment. A small percentage of patients who have severe colitis may experience severe exacerbations requiring hospitalization. This is more common in patients with UC, who typically present with a fever of 101°F or higher; profuse, constant, loose, bloody stools; anorexia; apathy and prostration; and, although abdominal signs may be normal, physical examination will uncover a distended abdomen, tympany, absence of bowel sounds, and even rebound tenderness.

For the typical patient, IBD is a chronic disease requiring long-term therapy and follow-up. The first step is to identify and remove all factors that may be initiating or aggravating the inflammatory reaction, such as food allergens and carrageenan. The patient is started on a diet that maximizes macronutrients and micronutrients while minimizing aggravating foods and nonfoods.

A broad-based individualized nutritional supplementation plan is necessary for all patients with IBD. Particularly important are the nutrients zinc, magnesium, folic acid, and vitamin A. Nutritional supplements are used as appropriate to correct deficiencies, normalize the inflammatory process, and promote healing of the damaged mucosa. Botanical medicines are used to promote healing and normalize the intestinal flora.

BOX 181-3 **Monitoring of the Pediatric Patient with Inflammatory Bowel Disease**

History
- Appetite, extracurricular activities
- Type and duration of inflammatory bowel disease, frequency of relapses
- Severity and extent of ongoing symptoms
- Medication history

3-Day Diet Diary

Physical Examination
- Height, weight, arm circumference, triceps skinfold measurements
- Loss of subcutaneous fat, muscle wasting, edema, pallor, skin rash, hepatomegaly

Laboratory Tests
- Complete blood count and differential, reticulocyte and platelet counts, sedimentation rate, urinalysis
- Serum total proteins, albumin, globulin, and retinol-binding protein
- Serum electrolytes, calcium, phosphate, ferritin, folate, carotenes, tocopherol, and vitamin B_{12}
- Leukocyte ascorbate, magnesium, and zinc
- Creatinine height index, blood urea nitrogen/creatinine ratio

Diet

All allergens—as well as wheat, corn, dairy products and carrageenan-containing foods—should be eliminated. The diet should be high in complex carbohydrates and low in sugar and refined carbohydrates. Fiber is poorly tolerated in Crohn's disease with luminal narrowing, whereas complex carbohydrates are prebiotic for fostering healthy enteric flora and have been shown to be helpful for ulcerative colitis.[136]

Supplements

- Multivitamin and mineral supplements with trace mineral cofactors for antioxidant systems
- Magnesium: 200 mg/day
- Zinc picolinate or carnosine: 50 mg/day

TABLE 181-7 **Clinical Score in Chronic Inflammatory Bowel Disease**

MEASURE	SCORE	CLINICAL ASSESSMENT
General Activity		
	10	Normal school attendance, <3 bowel movements per day
	5	Lacks endurance, 3-5 bowel movements per day
		Misses <4 weeks of school per year
Physical Examination and Complications		
Abdomen	10	Normal
	5	Mass
	1	Distention, tenderness
Proctoscope	10	Normal, no fissures
	5	Friability, one fissure
	1	Ulcers, bleeding, fistulas, multiple fissures
Arthritis	5	Nil
	3	One joint; arthralgia
	1	Multiple joints
Skin/stomatitis/eyes	5	Normal
	3	Mild stomatitis
	4	Erythema nodosum, pyoderma, severe stomatitis, uveitis
Nutrition		
Height	10	+2 inches/year
	5	Less than optimal %
	1	No growth
X-rays	15	Normal
	10	Ileitis
	5	Total colon or ileocecal involvement
	1	Toxic megacolon or obstruction
Laboratory		
Hematocrit (%)	5	>40
	3	25-35
	1	<25
Erythrocyte sedimentation rate (mm/hour)	5	Normal
	3	20-40
	1	>40
White blood cell count (cells/mL)	5	Normal
	3	<20,000
	1	>20,000
Albumin (g/dL)	10	Normal
	5	0 g/dL
	1	<2.5 g/dL

- Vitamin E: 400 to 800 IU/day mixed tocopherols
- Fish oil: 3000 mg EPA+DHA a day
 Choose one of the following:
 - Quercetin: 400 mg 20 minutes before meals
 - Grape seed extract (>95% procyanidolic oligomers): 150 to 300 mg/day
 - Pine bark extract (>90% procyanidolic oligomers): 150 to 300 mg/day
 - Green tea extract (>90 polyphenol content): 300 to 450 mg/day
- Probiotic (*Lactobacillus* and *Bifidobacter sp.*): minimum of 5 to 10 billion colony-forming units
- Prebiotics (inulin, fructose oligosaccharides, etc.): 5 g/day
- Short chain fatty acid enemas (60 mL of 80-100 mmol/L) nightly for left-sided colitis

Botanical Medicines

- Curcumin from turmeric (*Curcuma longa*): 1000 two to three times a day before meals
- Boswellia extract: equivalent to 400 mg boswellic acids three times a day
- *Aloe vera:* Choose one of the following:
 - *Aloe vera* gel: oral preparations can be consumed at a dose of 100 mL a day
 - *Aloe vera* juice: a variety of different preparations types and concentrations make accurate dose recommendations difficult. They can be consumed orally as a beverage or tonic.
 - Acemannan: 400 to 800 mg/day
- Bastyr formula: 2 to 3 "00" capsules with each meal

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CHAPTER 182

Insomnia

Michael T. Murray, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- Difficulty falling asleep (sleep-onset insomnia)
- Frequent or early awakening (sleep-maintenance insomnia)
- Affects one of every four people in the United States

GENERAL CONSIDERATIONS

Insomnia represents one of the most common complaints seen by physicians. Within the course of a year, up to 30% of the population suffers from insomnia, and roughly 10% of the adult population has chronic insomnia.[1] Many use over-the-counter (OTC) medications to combat the problem, and others seek stronger sedatives. Approximately 12.5% of the adult population uses a prescribed anxiolytic or sedative hypnotic in the course of a year; about 2% of the population takes one on any given day. More than one half of these drugs, especially benzodiazepines, are prescribed by primary care physicians. Nearly 100 million prescriptions are written each year for these drugs.[2]

A thorough history and physical examination are indicated in the patient presenting with insomnia, because it is a symptom that can have many causes (Table 182-1). Psychological factors account for 50% of all insomnias evaluated in sleep laboratories.[1] Insomnia is closely associated with affective disorders (see Chapter 142). Cognitive behavioral therapy is often indicated and can produce effective improvements in sleep quality.[3] A detailed recreational, prescription, and nonprescription drug-use history, along with a dietary and beverage history, are also required to determine whether the patient is consuming any stimulants or other agents known to interfere with sleep. The following agents may be responsible:

- Thyroid preparations
- Oral contraceptives
- Beta blockers
- Marijuana
- Alcohol
- Coffee
- Tea
- Chocolate

Among serious diseases to be considered in the differential diagnosis are narcolepsy and sleep apnea syndromes. Sleep apnea is the most common example of sleep-disordered breathing. First described in 1965, sleep apnea is a breathing disorder characterized by brief interruptions of breathing during sleep. These breathing pauses are almost always accompanied by snoring between apneic episodes, although not everyone who snores has this condition. Sleep apnea can also be characterized by choking sensations. The frequent interruptions of deep, restorative sleep often lead to excessive daytime sleepiness and may be associated with an early-morning headache. Approximately 18 million Americans are thought to suffer from sleep apnea.

Early recognition and treatment of sleep apnea are important because it is associated with marked daytime fatigue, irregular heartbeat, high blood pressure, heart attack, and stroke as well as a loss of memory function and other intellectual capabilities. The patient usually does not know he or she has a problem and may not believe it when told. If a person snores heavily or his or her sleep partner has noted periods of interrupted breathing during sleep, it is important that such a person see a doctor. Sleep apnea should also be considered in anyone with significant daytime

TABLE 182-1 **Causes of Insomnia***

SLEEP-ONSET INSOMNIA	SLEEP-MAINTENANCE INSOMNIA
Anxiety or tension	Depression
Environmental change	Environmental change
Emotional arousal	Sleep apnea
Fear of insomnia	Nocturnal myoclonus
Phobia of sleep	Hypoglycemia
Disruptive environment	Parasomnias
Pain or discomfort	Pain or discomfort
Caffeine	Drugs
Alcohol	Alcohol

*The boundary between the categories is not entirely distinct.

drowsiness or changes in intellectual function. Sleep apnea can be properly diagnosed only through the services of a sleep disorder specialist, usually in a sleep laboratory.

Sleep apnea is most often caused by narrowing of the airway by an excess accumulation of fatty tissue, causing obstructive sleep apnea. With a narrowed airway, the person continues efforts to breathe, but air cannot easily flow into or out of the nose or mouth. This narrowing results in heavy snoring, periods of no breathing, and frequent arousals (causing abrupt changes from deep sleep to light sleep). Ingestion of alcohol and sleeping pills increases the frequency and duration of breathing pauses in people with sleep apnea. In some cases sleep apnea occurs even if no airway obstruction or snoring is present. This form of sleep apnea, central sleep apnea, is caused by a loss of perfect control over breathing by the brain.

In both obstructive and central sleep apneas, obesity is the major risk factor, and weight loss is the most important aspect of long-term management. People with sleep apnea experience periods of anoxia (oxygen deprivation of the brain) with each apneic episode, which ends in arousal and a reinitiation of breathing. Seldom does the sufferer awaken enough to be aware of the problem. However, the combination of frequent periods of oxygen deprivation (20 to several hundred times per night) and the greatly disturbed sleep can greatly diminish the sufferer's quality of life and lead to serious problems.[4]

The most common treatment of sleep apnea is the use of nasal continuous positive airway pressure (CPAP). In this procedure, the patient wears a mask over the nose during sleep and pressure from an air blower forces air through the nasal passages. The air pressure is adjusted so that it is just enough to prevent the throat from collapsing during sleep. The pressure is constant and continuous. Nasal CPAP prevents airway closure while in use, but episodes of apnea return when CPAP is stopped or used improperly. Surgery to reduce soft tissue in the throat or soft palate should be used only as a last resort because it often does not work or can make the problem worse. Laser-assisted uvulopalatoplasty is a highly promoted surgical option. In this procedure lasers are used to surgically remove excessive soft tissue from the back of the throat and the palate. It works well initially in about 90% of sleep apnea sufferers, but within a year many people are the same as or even worse than before because of the scar tissue that invariably forms.[4]

Normal Sleep Patterns

Human sleep is perhaps one of the least understood physiologic processes. Its value to human health and proper functioning is without question. Sleep is absolutely essential to both the body and the mind. Impaired sleep, altered sleep patterns, and sleep deprivation impair mental and physical function.

Normal adult sleep-wake patterns repeat themselves on an approximately 24-hour cycle, of which sleep constitutes one third. Exactly how much sleep is required varies from one person to the next. Sleep tends to decrease with age, but whether this tendency is a normal or abnormal progression is unknown. A 1-year-old baby requires about 14 hours of sleep a day, a 5-year-old about 12 hours, and adults about 7 to 9 hours. Women tend to require more sleep than men. The elderly tend to sleep less at night but doze more during the day than do younger adults.

From observations of eye movement and electroencephalographic (EEG) recordings, sleep is divided into two distinct types: rapid eye movement (REM) sleep and non-REM sleep. During REM sleep, the eyes move rapidly and dreaming takes place. When people are awakened during non-REM sleep, they report that they were thinking about everyday matters but rarely report dreams.

Non-REM sleep is divided into stages 1 through 4 according to level of EEG activity and ease of arousal. As sleep progresses, there is a deepening of sleep and slower brainwave activity until REM sleep ensues, when suddenly the brain becomes much more active. In adults, the first REM sleep cycle is usually triggered 90 minutes after going to sleep and lasts about 5 to 10 minutes. After the flurry of activity, brainwave patterns return to those of non-REM sleep for another 90-minute sleep cycle.

Each night most adults experience five or more sleep cycles. REM sleep periods grow progressively longer as sleep continues; the last sleep cycle may produce a REM sleep period that can last about an hour. Non-REM sleep lasts approximately 50% of this 90-minute sleep cycle in infants and about 80% in adults. As people age, in addition to less REM sleep, they tend to awaken at the transition from non-REM to REM sleep.

The Importance of Adequate Sleep

Adequate sleep is absolutely necessary for long-term health and regeneration. Many physiologic processes occur during sleep, but perhaps the most important are the increased secretion of growth hormone (GH) and the scavenging of free radicals in the brain.

Many of the benefits of sleep are probably mediated through GH. As an anabolic hormone, GH has been called by some the "antiaging" hormone. Several research projects are now studying its rejuvenating effects when it is injected. The reason for the excitement is that GH stimulates tissue regeneration, liver regeneration, muscle building, breakdown of fat stores, normalization of blood sugar, and a host of other beneficial processes in the body. It also helps convert fat to muscle. Small amounts of GH are secreted at various times during the day, but essentially all secretion of GH occurs during sleep.

Sleep functions as an antioxidant for the brain because free radicals are removed during it. Sleep is required to ensure minimal neuronal damage from free radicals accumulated during waking. Most people can tolerate a few days without sleep and fully recover. However, chronic sleep deprivation appears to accelerate aging of the brain, to cause neuronal damage, and to produce nighttime elevations in cortisol.[5]

THERAPEUTIC CONSIDERATIONS

Because insomnia is largely due to psychological and physiologic factors, the clinician should consider and handle these factors

before simply inducing sleep pharmacologically. Counseling and/or stress-reduction techniques (including biofeedback and hypnosis) may be indicated in many cases. The following topics are discussed below as they relate to the promotion of sleep:

- Exercise
- Progressive relaxation
- Nocturnal glucose levels
- Serotonin precursor and cofactor therapy
- 5-Hydroxytryptophan (5-HTP)
- Cofactors for serotonin synthesis
- Melatonin
- Restless legs syndrome and nocturnal myoclonus
- Botanicals with sedative properties

Lifestyle

Exercise

Regular physical exercise is known to improve general well-being as well as to promote improvement in sleep quality.[3] Exercise should be performed in the morning or early evening, not before bedtime, and should be of moderate intensity. Usually 20 minutes of aerobic exercise at a heart rate between 60% and 75% of maximum (approximately 220 minus the patient's age in years) is sufficient.

Progressive Relaxation

Numerous techniques can promote relaxation and prepare the body and mind for sleep. One of the most popular and easy-to-use techniques is progressive relaxation. It is based on a very simple procedure of comparing tension with relaxation. Many people are not aware of the sensation of relaxation. In progressive relaxation, an individual is taught what it feels like to relax by comparing relaxation with muscle tension. Each muscle is first made to contract forcefully for a period of 1 to 2 seconds and then to give way to a feeling of relaxation. Because the procedure goes progressively through all the muscles of the body, a deep state of relaxation eventually results. The procedure begins with contraction of the muscles of the face and neck, with the contraction held for at least 1 or 2 seconds, and then relaxation of the muscles. Next the upper arms and chest are contracted and then relaxed, followed by the lower arms and hands. The process is repeated progressively down the body—abdomen, buttocks, thighs, calves, and feet. This whole practice is repeated two or three times or until sleep is produced.

Nocturnal Glucose Levels

Increased nocturnal blood glucose volatility may be an important cause of sleep-maintenance insomnia, especially when there are rapid drops in blood glucose levels. The brain is highly dependent on glucose as an energy substrate, and a quick drop in blood glucose level promotes awakening via the release of glucose regulatory hormones (i.e., epinephrine, glucagon, cortisol, and GH). Increased nocturnal blood glucose volatility and/or hypoglycemia must be ruled out in maintenance-type insomnia (see Chapter 176).

Serotonin Precursor and Cofactor Therapy

Serotonin is an important initiator of sleep. The synthesis of central nervous system (CNS) serotonin depends on the availability of tryptophan (discussed in more detail in Chapter 98). L-Tryptophan has shown modest effects in the treatment of insomnia[6-8]; it is certainly not a panacea. However, excellent results have been reported even in severe cases. Although not every patient has responded to L-tryptophan in the clinical trials, those who have experienced dramatic relief. It is generally more effective in sleep-onset insomnia and less effective in sleep-maintenance insomnia. The key advantage of L-tryptophan over OTC and prescriptions pills is that, unlike these agents, it does not produce any significant distortions of normal sleep processes whether it is taken only once or for a prolonged period, nor does it cause symptoms upon withdrawal. Doses smaller than 2000 mg are generally ineffective.

Current knowledge of the sleep-inducing effects of L-tryptophan is consistent with the finding that its effectiveness is somewhat limited to sleep-onset insomnia.[6] The sleep-promoting effect is often thought to be due to enhanced serotonin synthesis, but there is evidence to suggest that other mechanisms may also be responsible or contributory, including L-tryptophan–enhanced melatonin synthesis. Administration of L-tryptophan causes a massive elevation of plasma melatonin concentration.[9] Although L-tryptophan reduces sleep latency, it exerts effects in normal subjects that are at odds with the serotonin system, such as reducing REM sleep and increasing non-REM sleep.[10,11] Drugs that prevent the conversion of tryptophan to serotonin enhance these effects. From this information, it is concluded that some of L-tryptophan's effects on sleep do not involve the serotonin or melatonin system. As discussed in Chapter 98, the effects of L-tryptophan can be negated by conversion via the kynurenine pathway. This conversion can be partially inhibited by niacin (30 mg is an appropriate dose), thereby enhancing the effects of L-tryptophan.

It appears that the insomnia-relieving and sleep-promoting actions of L-tryptophan are cumulative in that it often takes a few nights for L-tryptophan to start working, as shown by the results from one of the double-blind studies. In that study, the effects of 3 g of L-tryptophan on sleep performance, arousal threshold, and brain electrical activity during sleep were assessed in 20 males with chronic sleep-onset insomnia.[12] After a sleep laboratory screening night, all subjects received placebo for three consecutive nights; then 10 subjects received L-tryptophan and 10 placebo for six nights. All subjects received placebo on two withdrawal nights. L-Tryptophan had no effect on sleep latency during the first three nights of administration. However, on nights four through six of administration, sleep latency was significantly reduced. Consistent with other studies, this study found that unlike sleeping pills (benzodiazepines especially), L-tryptophan did not alter sleep stages, impair performance, or alter brain electrical activity during sleep. This study indicates that L-tryptophan should be used for a minimum of 1 week to gauge its effectiveness in chronic insomnia. L-Tryptophan does have good sleep-promoting effects with a single administration, as shown by the fact that it is often effective when given to subjects sleeping in a "strange place" who otherwise regularly experience insomnia under such circumstances.

Administration of high-dose L-tryptophan (4 g) during the day can promote sleep. This research information indicates that the consumption of foods high in tryptophan during the day may contribute to daytime sleepiness. Conversely, an evening meal high in tryptophan in relation to competing amino acids may promote sleep.

The important cofactors vitamin B_6, niacin, and magnesium should be administered along with the tryptophan to ensure its conversion to serotonin. Also, because other amino acids compete with tryptophan for transport into the CNS across the blood-brain barrier and insulin increases tryptophan uptake by the CNS, protein consumption should be avoided near administration and a carbohydrate source such as fruit or fruit juice should accompany the tryptophan.

Niacin has been reported to have a sedative effect, probably owing to its peripheral dilating action and shunting of tryptophan metabolism toward serotonin synthesis.

5-Hydroxytryptophan

5-HTP is one step closer to serotonin than L-tryptophan and does not depend on a transport system for entry into the brain. Several clinical studies have shown 5-HTP to produce dramatically better results than L-tryptophan in promoting and maintaining sleep.[13–16]

One of the key benefits of 5-HTP is its ability to increase REM sleep (typically by about 25%) while increasing deep sleep stages 3 and 4 without lengthening total sleep time.[10,11] The sleep stages that are reduced to compensate for the increases are non-REM stages 1 and 2—the least important stages.

The dosage recommendation to take advantage of the sleep-promoting effects of 5-HTP is 100 to 300 mg, 30 to 45 minutes before retiring. The patient should start with the lower dose for at least 3 days before increasing it. For more information, see Chapter 98.

Melatonin

The most popular natural aid for sleep is melatonin. Supplementation with melatonin has been shown in several studies to be very effective in helping induce and maintain sleep in both children and adults and in both people with normal sleep patterns and those with insomnia. However, the sleep-promoting effects of melatonin are most apparent only if melatonin levels are low.[17] In other words, using melatonin is not like taking a sleeping pill or even 5-HTP. It has a sedative effect only when its levels are low. When melatonin is taken by normal subjects just before going to bed or by patients with insomnia who have normal melatonin levels, it produces no sedative effect. This is because just before going to bed, people normally have a rise in melatonin secretion. Melatonin supplementation is effective as a sedative only when the pineal gland's own production of melatonin is very low. Melatonin appears to be most effective in treating insomnia in the elderly, in whom low melatonin levels are common.[18]

In one of the most interesting studies, 26 elderly insomniacs with lower than normal melatonin levels were given 1 to 2 mg of melatonin 2 hours before the desired bedtime for 1 week. Rapid- and slow-release melatonin preparations were used. Both sleep latency and sleep quality were evaluated. Although there was no discernible difference in sleep onset or sleep efficiency (time asleep as a percentage of total time in bed) between the two forms, the slow-release form yielded better effects on sleep maintenance.[19]

A dose of 3 mg at bedtime is more than enough, because doses as low as 0.1 and 0.3 mg have been shown to produce a sedative effect when melatonin levels are low.[20] Although melatonin appears to have no serious side effects at recommended doses, melatonin supplementation could conceivably disrupt the normal circadian rhythm. In one study, a dosage of 8 mg/day for only 4 days resulted in significant alterations in hormone secretions.[21] For more information see Chapter 103.

Restless Legs Syndrome and Nocturnal Myoclonus

Restless legs syndrome and nocturnal myoclonus are significant causes of insomnia. The restless legs syndrome is characterized during waking by an irresistible urge to move the legs. Almost all patients with restless legs syndrome have nocturnal myoclonus,[1] a neuromuscular disorder characterized by repeated contractions of one or more muscle groups, typically of the leg, during sleep. Each jerk usually lasts less than 10 seconds. The patient is normally unaware of the myoclonus and complains only of either frequent nocturnal awakenings or excessive daytime sleepiness, but questioning of the sleep partner often discovers the myoclonus.

If there is a family history of restless legs syndrome (present in about one third of all cases of the syndrome), high-dose folic acid, 35 to 60 mg daily, can be helpful.[22] Doses in this range require a prescription, because the U.S. Food and Drug Administration limits the amount available per capsule to 800 mg. Patients with familial restless legs syndrome appear to have a higher need for folic acid. Restless legs syndrome is also a common finding in patients with malabsorption syndromes.[22]

If there is no family history, serum ferritin levels should be measured to determine iron stores. The association between low iron levels and the restless legs syndrome was documented in clinical studies more than 30 years ago. A later study reproduced these observations, finding serum ferritin levels to be lower in the 18 patients with the restless legs syndrome than in 18 control subjects.[23] Serum iron, vitamin B_{12}, folic acid, and hemoglobin levels did not differ in the two groups. A rating scale with a maximum score of 10 was used to assess the severity of symptoms of the restless legs syndrome. Serum ferritin levels were inversely correlated with the severity of symptoms. Fifteen of the patients with the syndrome were treated with iron (ferrous sulfate) at a dosage of 200 mg three times daily for 2 months. The severity of restless legs syndrome improved by an average of 4 points in 16 patients with an initial ferritin level lower than 18 mg/L, by 3 points in 4 patients with ferritin levels between 18 and 45 mg/L, and by 1 point in 5 patients with ferritin levels between 45 and 100 mg/L. The conclusion of the study is an important contribution to the understanding of the development of restless legs syndrome in elderly patients, and iron supplements were found to produce a significant reduction in symptoms.

In addition to the restless legs syndrome, low serum ferritin levels have been found in psychiatric patients experiencing a condition called akathisia, coming from a Greek word meaning "cannot sit down." Akathisia is a drug-induced state of agitation. The drugs that most commonly produce akathisia are antidepressants, such as fluoxetine (Paxil, Prozac) and sertraline (Zoloft). The level of iron depletion correlates with the severity of akathisia. Anyone suffering from drug-induced akathisia should ask his or her physician to perform a serum ferritin assessment. If serum ferritin levels are below 35 mg/L, the physician should recommend that the patient take 30 mg of iron bound to either succinate or fumarate twice daily between meals. If this recommendation causes abdominal discomfort, the patient should try 30 mg with meals three times daily.

Botanicals with Sedative Properties

Numerous plants have sedative action. Plants commonly prescribed as aids in promoting sleep include the following:

- *Valeriana officinalis*
- *Passiflora incarnata*
- *Humulus lupulus*
- *Scutellaria lateriflora*
- *Matricaria chamomilla*

Of the herbs listed, the one with the most clinical research is *Valeriana officinalis* (see Chapter 133). More than 20 double-blind clinical studies have now substantiated valerian's ability to improve sleep quality and relieve insomnia.[24,25] Additional research is warranted, but these studies show that extracts of valerian root improve sleep quality and sleep latency (the time required to go to sleep). The studies, which were usually performed under

strict laboratory conditions, demonstrated clearly that valerian was as effective in reducing sleep latency as small doses of barbiturates or benzodiazepines. However, although these latter compounds also increase morning sleepiness, valerian usually reduces morning sleepiness.

THERAPEUTIC APPROACH

The treatment should be as conservative as possible and should include some means of dealing with the psychological factors contributing to the insomnia. Metabolically, the foremost component of treatment is the elimination of any factors known to disrupt normal sleep patterns, such as the following:

- Stimulants (e.g., coffee, tea, chocolate, coffee-flavored ice cream)
- Alcohol
- Hypoglycemia
- Stimulant-containing herbs (e.g., ephedra, guarana)
- Marijuana and other recreational drugs
- Numerous OTC medications
- Prescription drugs

If this approach produces no response, more aggressive measures can be taken. Once a normal sleep pattern has been established, the recommended supplements and botanicals should be slowly decreased. If the patient suffers from restless legs syndrome, 5 to 10 mg/day of folic acid should be added to the therapy. Nocturnal myoclonus can be aided with 400 IU/day of natural vitamin E.

Lifestyle

The patient should institute a regular exercise program that elevates heart rate to 60% to 75% of maximum for at least 20 minutes a day.

Supplements

The following supplements should be taken 45 minutes before bedtime:

- Niacin: 100 mg (decrease dose if uncomfortable flushing interferes with sleep induction)
- Vitamin B_6: 50 mg
- Magnesium: 250 mg
- Tryptophan: 3 to 5 g, or 5-HTP, 100 to 300 mg
- Melatonin: 3 mg

Botanical Medicines

The following botanical medicines should also be taken 45 minutes before bedtime:

Valeriana officinalis

- Dried root (or as tea): 2 to 3 g
- Tincture (1:5): 4 to 6 mL (1 to 1½ tsp)
- Fluid extract (1:1): 2 to 4 mL (½ to 1 tsp)
- Dry powdered extract (0.8% valerenic acid): 150 to 300 mg

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CHAPTER 183

Irritable Bowel Syndrome

Gerard Mullin, MD

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

Irritable bowel syndrome (IBS) is a functional disorder of the large intestine with no evidence of accompanying structural defect; it is characterized by some combination of:

- Abdominal pain
- Altered bowel function, constipation, or diarrhea
- Hypersecretion of colonic mucus
- Dyspeptic symptoms (flatulence, nausea, anorexia)
- Varying degrees of anxiety or depression
- In some cases, extraintestinal manifestations such as restless legs syndrome (RLS), migraine headaches, chronic fatigue, irritable bladder syndrome, and dyspareunia

Less acceptable synonyms are *nervous indigestion, spastic colitis, mucous colitis,* and *intestinal neurosis*. The splenic flexure syndrome is a variant of the irritable bowel syndrome in which gas in the bowel leads to pain in the lower chest or the left shoulder. Many patients with IBS also have extraintestinal symptoms, including sexual dysfunction, fibromyalgia, dyspareunia, urinary frequency and urgency, poor sleep, menstrual difficulties, lower back pain, headaches, chronic fatigue, restless legs syndrome (RLS) and insomnia. These conditions tend to increase in number with the severity of IBS. The more extraintestinal symptoms a patient presents with, the more likely he or she is to have a severe case of IBS.[1]

GENERAL CONSIDERATIONS

IBS is the most common gastrointestinal disorder seen in general practice, representing 30% to 50% of all referrals to gastroenterologists.[2,3] Determining incidence or prevalence figures is virtually impossible, because many sufferers never seek medical attention. It has been estimated, however, that approximately 15% of the population has complaints of IBS, with women predominating in a ratio of 2:1 (it is likely that an equal number of men have IBS but that they do not report symptoms as often). The etiology of the greater colonic motility seen in IBS has been attributed to physiologic, psychological, and dietary factors.

Although IBS is often a diagnosis of exclusion, clinical judgment must be used to determine the extent of the diagnostic process required. A detailed history and physical examination have been shown to eliminate much of the vagueness involved in diagnosing IBS.[4] Distention, relief of pain with bowel movements, and the onset of loose or more frequent bowel movements with pain seem to correlate best with the diagnosis of IBS (any three, $P = 0.84$; just one, $P = 0.25$).[2]

In most cases, a comprehensive stool and digestive analysis (see Chapter 27) with special attention to dysbiosis, complete blood count, and measurements of erythrocyte sedimentation rate, free thyroid T_3 hormone level, and celiac testing (antiendomysial antibody test; see Chapter 155) should be performed to establish the diagnosis and exclude other diseases. If diarrhea-predominant IBS symptoms are more pervasive, panendoscopy with duodena, colonic, and terminal ileal biopsies should be obtained to rule out autoimmune conditions such as celiac disease, inflammatory bowel disease, lymphocytic colitis, and collagenous colitis. If food allergy is suspected as a contributor, stool testing for eosinophilic cationic protein should be considered. If no discernible cause can be identified, screening for occult fecal blood and flexible sigmoidoscopy are indicated in patients younger than 50 years and colonoscopy in older patients. Conditions that may mimic IBS are listed in Box 183-1.

BOX 183-1 Conditions That May Mimic Irritable Bowel Syndrome

- Gastrogenic dietary factors such as excessive consumption of tea, coffee, carbonated beverages, and simple sugars
- Infectious enteritis such as amebiasis and giardiasis
- Inflammatory bowel disease
- Lactose intolerance
- Laxative abuse (an easy test to eliminate this possibility is to add a few drops of sodium hydroxide solution to a stool specimen; since most laxatives contain phenolphthalein, the stool will turn red)
- Intestinal candidiasis
- Disturbed bacterial microflora as a result of antibiotic or antacid use
- Malabsorption diseases such as pancreatic insufficiency and celiac disease
- Metabolic disorders such as adrenal insufficiency, diabetes mellitus, and hyperthyroidism
- Mechanical causes such as fecal impaction
- Diverticular disease
- Neoplasm



THERAPEUTIC CONSIDERATIONS

Once other conditions have been ruled out, there appear to be three major treatments to consider in the formulation of a therapeutic regimen for IBS:

- Increasing dietary fiber.
- Eliminating allergic/intolerant foods.
- Controlling psychological components.
- Peppermint oil for spastic colon.

Additional considerations include:

- Acupuncture for pain modulation and motility regulation.
- Melatonin as a stress adaptogen, mood stabilizer, and to promote restful sleep.
- Small intestinal bacterial overgrowth, intestinal dysbiosis and food allergies may be silent triggers of the disease.
- Dietary FODMAPS (Fermentable Oligo-, Di-, and Monosaccharides, And Polyols) appear to play a role in promoting disease activity and should be limited in IBS.

Diet

Dietary Fiber

The treatment of IBS through an increase in dietary fiber has a long though irregular history.[2] Patients with constipation are much more likely to show a response to dietary fiber than are those with diarrhea. One problem that has not been addressed in studies on the therapeutic use of dietary fiber is the role of food allergy. The type of fiber often used in both research and clinical practice is wheat bran.[5] Wheat and other grains are among the most commonly implicated foods in malabsorptive and allergic conditions, and food allergy is a significant etiologic factor in IBS, so the use of wheat bran is usually contraindicated.

Increasing dietary fiber from fruit and vegetable sources rather than cereal sources may offer more benefit to some individuals, although in one uncontrolled clinical study there was no significant difference in improvement when a diet composed of 30 g of fruit and vegetable fiber and 10 g of cereal fiber was compared with a diet consisting of the opposite ratio.[6] Although the two diets resulted in similar significant improvements in abdominal pain, bowel habits, and state of well-being, the presence of large quantities of potentially allergenic cereal fiber in both diets would probably have obscured any differences.

One type of fiber that may be useful and that is without the allergenic component of a wheat-based fiber is partially hydrolyzed guar gum (PHGG). The guar plant, *Cyamopsis tetragonolobus*, has been grown in India and Pakistan since ancient times. PHGG is a natural water-soluble dietary fiber derived from the guar plant.[7] One study of 134 patients found that consumption of 5 g/day of PHGG decreased the frequency of IBS symptoms such as abdominal spasms, flatulence, and abdominal tension.[8] The researchers concluded that PHGG works well in cases of altered intestinal motility and is easy to use because of its nongelling properties, unlike unhydrolyzed gum, which is much higher in viscosity and more difficult to incorporate into the diet. A recent study has shown that the guar gums when combined with the antibiotic rifaximin (Rifaxam) provide an additional benefit to eradicating dysbiosis in small intestinal bacterial overgrowth (SIBO) associated with IBS.[9] Put simply, for most cases of IBS, non-wheat sources of fiber, such as vegetables and fruits, may be the best choicees to help reduce symptoms. For some cases of IBS, especially those with a strong diarrheal component, cooked vegetables in small quantities at first may be most helpful. Because each case is unique, clinical judgment and close patient monitoring are needed. In some cases, fiber may aggravate diarrhea and is therefore contraindicated. For a more detailed explanation of dietary fiber, see Chapter 52.

Food Allergy

The importance of food allergies in the etiology of IBS has been recognized since the early 1900s.[10,11] Later studies have further documented the association between food allergy and the irritable bowel.[12-15] The type of food allergy most significant in IBS is believed to be nonimmunologic, so food intolerance rather than food allergy may be a more appropriate diagnosis. According to double-blind challenge methodologies, the majority of patients with IBS (approximately two thirds) have at least one food intolerance, and some have multiple intolerances.[12] Foods rich in carbohydrates as well as fatty food, coffee, alcohol, and hot spices are most frequently reported to cause symptoms.[1] The most common allergens are dairy products (40% to 44%) and grains (40% to 60%).[14] Because in most cases the reaction appears to be related to prostaglandin synthesis or immunoglobulin G (IgG)–mediaed rather than IgE-mediated reactions, skin tests and the IgE-radioallergosorbent test are poor indicators of food intolerance in these patients. The enzyme-linked immunosorbent assay (ELISA) allergen challenge test or ELISA IgE/IgG_4 may be a better indicator (see Chapter 15), although many sensitivities may still be undetectable by currently available laboratory procedures.[16] Many patients have noted marked clinical improvement with the use of elimination diets.[12-15,17]

Interestingly, many patients with IBS have associated symptoms suggestive of vasomotor instability (such as palpitations, hyperventilation, fatigue, excessive sweating, and headaches), which is consistent with food allergy/intolerance reactions.

Sugar

Meals high in refined sugar can contribute to IBS as well as small intestinal bacterial overgrowth by decreasing intestinal motility.[18] When blood glucose levels rise too rapidly, gastrointestinal tract peristalsis slows down. Because glucose is absorbed primarily in the duodenum and jejunum, the message affects this portion of the gastrointestinal tract most strongly. The result is that the duodenum and jejunum become atonic. A diet high in refined sugar may be the most important reason that IBS is such a common condition in the United States.

Dietary FODMAPs

FODMAPs are short-chain carbohydrates that are osmotically active and fermentable (degradable by intestinal bacteria yielding large amount of gases, like hydrogen or carbon dioxide, thus causing abdominal bloating). FODMAPs include oligosaccharides such as fructans, which are chains of fructose with one glucose molecule on the end. Only minimal amounts of fructans may be absorbed in the human intestine. They may interfere with the absorption of fructose, thus aggravating symptoms in fructose malabsorption. Foods rich in fructans are wheat (white bread, pasta, pastries, cookies), onions, and artichokes; other not commonly problematic foods containing fructans are asparagus, leeks, garlic, chicory roots, and chicory-based coffee substitutes. Fructans with over 10 molecules of fructose in a chain are known as inulins, and those with less than 10 fructoses are referred as fructo-oligosaccharides or oligofructoses. Fructans cause problems mainly in fructose malabsorption. Galactans (like stacchyose and raffinose) are chains of fructose with one galactose molecule on the end. They act much like fructans. The main foods rich in galactans are legumes (soy, beans, chickpeas, lentils), cabbage, and brussels sprouts.

Disaccharides. Lactose (milk sugar). Lactose is found in dairy products, but it may also be found in chocolate and other sweets, beer, pre-prepared soups and sauces, and so on. Lactose is poorly absorbed by individuals with lactose intolerance, SIBO, and small intestinal inflammation (Crohn's disease, celiac disease).

Monosaccharides. Fructose (fruit sugar). Fructose-rich foods include honey, dried fruits (prunes, figs, dates, or raisins), apples, pears, sweet cherries, peaches, agave syrup, watermelon, and papaya. Fructose is often added to commercial foods and drinks as high-fructose corn syrup. Fructose causes symptoms even in healthy people if ingested in excess and especially in those with fructose malabsorption or SIBO.

Polyols. These are also known as sugar alcohols (appearing as artificial sweeteners in commercial foods and drinks). Sorbitol may appear in "sugar-free chewing gum" and "low-calorie foods"; it appears naturally in stone fruits (peaches, apricots, and plums). Xylitol naturally appears in some berries. A pack of chewing gum containing sorbitol or xylitol may cause bloating or diarrhea in a healthy child and especially in persons with fructose malabsorption or SIBO. Other polyols—like mannitol, isomalt, erithrytol, arabitol, erythritol, glycol, glycerol, lactitol, and ribitol—may be problematic in fructose malabsorption and SIBO.

Recent work indicates that FODMAP short-chain carbohydrates that are poorly absorbed in the small intestine are important triggers of functional gut symptoms. Open studies have suggested that three out of four patients with IBS will respond well symptomatically to the restriction of FODMAP intake,[19] as confirmed by a randomized placebo-controlled rechallenge trial.[20] Breath hydrogen testing helps identify which specific sugars behave as FODMAPs in the individual.

Nutritional Supplements

Probiotics

Probiotics are dietary supplements containing live microorganisms that, when ingested, exert a beneficial effect on the host. Among the most commonly used and studied species are *Lactobacillus, Bifidobacterium*, and *Saccharomyces boulardii*. The association between IBS and SIBO is well established.[21] Pimentel et al have demonstrated that successful treatment of SIBO with antibiotics improved IBS symptoms.

The results of randomized controlled clinical trials using probiotics to treat IBS symptoms are shown in Table 183-1. In a study by O'Mahony et al, *Bifidobacterium infantis* 35624 (*B. infantis*) showed improvement in all IBS symptoms except stool frequency and consistency.[22] This coincided with normalization of the proinflammatory cytokine profile (elevated IL-10/IL-12 ratio) in those patients. A confirmatory trial by the same group evaluated optimal therapeutic dosages and found the daily, 10^8-CFU dose of *B. infantis* given for 4 weeks superior to alternative doses of *B. infantis* and placebo in improving abdominal pain and global symptom assessment scores.[23] In the placebo group, there was a decrease in composite IBS scores (6-point scale) by 1.27 versus a 2.12-point decrease in the group receiving a daily dose of 10^8 CFU (P <0.02). This study was well designed, with a practical primary endpoint of abdominal pain or discomfort. Similarly, a study in pediatric IBS patients showed that those treated with *Lactobacillus* GG were more likely to experience treatment success and reduced frequency of pain compared with placebo.[24] Although all of these results are provocative, the placebo response remains quite high in each of the studies.

Kajander et al studied a probiotic mixture containing *Lactobacillus rhamnosus* GG, *L. rhamnosus* LC705, *Bifidobacterium breve* Bb99, *Propionibacterium freudenreichii* species, and *Propionibacterium shermanii* JS in IBS patients over 6 months. There was improvement in total symptom scores (comprising abdominal pain, distention, flatulence, and borborygmi) in the treatment group compared with placebo (7.7 points lower; 95% CI: 13.9 to –1.6).[25] This study differs from previously discussed trials in that the treatment period was much longer and a probiotic mixture was used. Another placebo-controlled

TABLE 183-1 **Randomized Controlled Clinical Trials of Probiotics in the Treatment of IBS**

NUMBER OF PATIENTS	PROBIOTIC(S) MIXTURE	TREATMENT PERIOD	RESULTS
103	*L. rhamnosus* GG, *L. rhamnosus* LC705, *B. breve* Bb99, and *P. freudenreichii* ssp. *shermanii* JS	6 months	42% vs. 6% mean reduction symptom score
48	VSI#3	4 weeks or 8 weeks	Improved flatulence in treatment group vs. placebo
77	*L. salivarius* UCC4331, *B. infantis* 35624	8 weeks	Improved score for abdominal pain and bloating
362	*B. infantis* 35624 (doses 10^6, 10^8, 10^{10})	4 weeks	Improved global symptom score >20% vs. placebo (10^8 dose)
274	*Bifidobacterium animalis, S. Thermophilus, L. Bulgaricus* (yogurt)	6 weeks	Improved health-related quality of life scores and bloating
86	*L. rhamnosus* GG, *L. rhamnosus* Lc705, *P. freudenreichii, B. animalis*	5 months	Improved IBS score

Data from McFarland LV, Dublin S. Meta-analysis of probiotics for the treatment of irritable bowel syndrome, World J Gastroenterol 2008 May 7; 14(17): 2650-2661.

TABLE 183-2 **Peppermint Oil for IBS**

AUTHOR	DESIGN	PATIENTS (ENROLLED/DROPOUT)	TREATMENT PERIOD (WEEKS)	GLOBAL IMPROVEMENT VS. CONTROL
Carling et al.	3-armed, doubled-blind, crossover	40/2	2	17/30 vs. 5/13
Dew et al.	Double-blind, crossover	29/0	2	24/29 vs. 5/29
Lech et al.	Double-blind, 2 parallel groups	47/5	4	13/19 vs. 6/23
Nash et al.	Double blind, crossover	41/8	2	13/33 vs. 17/33
Rees et al.	Double-blind, crossover	18/2	3	13/16 vs. 2/16
Lawson et al.	Double-blind, crossover	25/0	4	No difference
Schneider et al.	Double-blind, crossover	60/13	6	Pain relief: $P = 0.03$, vs. placebo

From Pittler MH, Ernst E. Peppermint oil for irritable bowel syndrome: a critical review and metaanalysis. American Journal of Gastroenterology 93(7): 1131-1135.

trial comparing VSL#3 with placebo in IBS patients with significant bloating found that patients had reduced flatulence during the treatment period.[26] In this study, colonic transit was retarded in the VSL#3 group relative to placebo. More recently, fermented milk containing *Bifidobacterium animalis, Streptococcus thermophilus,* and *Lactobacillus bulgaricus* was compared with placebo in patients with constipation-predominant IBS. The health-related quality-of-life discomfort score and bloating were improved in both groups, although the change was greater in the treatment group.[27] A multispecies probiotic formulation used in a smaller study again showed improvement in composite IBS scores, specifically abdominal distention and pain, compared with placebo.[28]

In summary, probiotics may prove to be key components in the comprehensive approach to treating IBS. Probiotic supplementation appears to be indicated in IBS (see Chapter 116).

L-Tryptophan

The amino acid L-tryptophan or its metabolic derivative, 5-hydroxytryptophan (5-HTP), has been considered for IBS owing to its relationship with serotonin, a neurotransmitter that is produced in both the digestive tract and the brain.[29,30] Because comorbidity of psychiatric conditions such as depression and anxiety is highly correlated with IBS, modulation of the serotonin pathway with the use of L-tryptophan or 5-HTP seems logical and should be further evaluated. Although characterized by a lack of reliable biological markers, the IBS disease state is increasingly viewed as a disorder of the brain-gut axis. In particular, accumulating evidence points to the involvement of both the central and peripheral serotonergic systems in disease symptomatology. Furthermore, altered tryptophan metabolism and indoleamine 2,3-dioxygenase (IDO) activity are hallmarks of many stress-related disorders. The kynurenine pathway of tryptophan degradation may serve to link these findings to the low level immune activation recently described in IBS. IDO, the immunoresponsive enzyme responsible for the degradation of tryptophan along this pathway, is enhanced in IBS patients relative to controls. Clarke et al reported that males with IBS degrade tryptophan owing to higher IDO activity, identifying the kynurenine pathway as a potential source of biomarkers in this debilitating condition and emphasizing the need for supplementation with tryptophan or 5-HTP.[30]

Botanical Medicines

Enteric-Coated Volatile Oils

Peppermint oil, and presumably similar volatile oils, inhibits gastrointestinal smooth muscle action in both laboratory animal preparations and humans. Clinically, peppermint oil has been used to reduce colonic spasms during endoscopy,[31] and an enteric-coated peppermint oil (ECPO) capsule has been used in the treatment of IBS.[32] Enteric coating is believed to be necessary because menthol (the major constituent of peppermint oil) and other plant monoterpenes in peppermint oil are rapidly absorbed.[33] This rapid absorption tends to limit effects to the upper intestine, resulting in relaxation of the cardioesophageal sphincter and common side effects, such as esophageal reflux and heartburn, after administration. A transient hot burning sensation in the rectum during defecation, due to unabsorbed menthol, has been noted by some patients taking the ECPO.

TABLE 183-3 **Effects of Peppermint Oil on the Major Symptoms of Irritable Bowel Syndrome**

PARAMETER	ECPO (%)	PLACEBO (%)
Abdominal pain	79	43
Abdominal distention	83	29
Stool frequency	83	33
Borborygmi	73	31
Flatulence	79	22.5

Most of the studies have used ECPO at a dosage of 0.2 mL twice daily between meals.[33] A meta-analysis of five studies supported the efficacy of peppermint oil in IBS.[34] A well-designed study of ECPO involved 110 patients with symptoms of IBS.[35] The patients took one capsule of either ECPO (0.2 mL) or a placebo three to four times daily 15 to 30 minutes before meals for 1 month. The effects of peppermint oil on IBS are summarized in Table 183-2. The effects on the major symptoms of IBS are listed in Table 183-3. These results are impressive, especially given the safety of ECPO. Only two instances of side effects were reported: one patient experienced heartburn (from chewing the tablet), and one had a transient rash.

ECPO is thought to work by improving the rhythmic contractions of the intestinal tract and relieving intestinal spasm. An additional benefit of these volatile oils is their efficacy against *Candida albicans*.[36] This benefit is of use in IBS, in which an overgrowth of *C. albicans* may be an underlying factor, especially in patients who do not respond to dietary advice and those who consume large amounts of sugar. Administration of nystatin (600,000 IU/day for 10 days) to patients whose IBS did not respond to an elimination diet produced dramatic clinical improvement.[13] Furthermore, in one randomized double-blind controlled trial of 42 children with moderate levels of pain from IBS, peppermint oil was considered a safe and effective treatment.[37]

TABLE 183-4 **Herbal Therapies Studied in IBS**

MADISCH*	BOENSOUSSAN†	LEUNG‡
STW5	TCM-individualized, standard	TCM-standard preprartion
Candytuft	*Codonopsis pilosulae*	*Astragalus membranaceus*
Chamomile	*Agastaches pogostemi*	*Atractylodes macrocephala*
Peppermint	*Coiois lachryma-jobi*	*Paeonia lactiflora*
Caraway	*Ledebouriellae sesloids*	*Buplerum chinense*
Licorice root	*Glycyrrizae urlensis*	*Citrus reticulata*
Lemon balm	*Bupleurum chinense*	*Saposhnikovia divaricata*
Celandine	*Artemesia capellaris*	
Milk thistle	*Atractylodis*	*Murraya paniculata*
Angelica	*Angelica*	*Punica grantum*
	Magnolia officinalis	*Portulaca oleracea*
	Citri reticulatae	*Coptis chinensis*
	Ginger	
	Fraxini cortex	
	Poriae cocos	
	Plantaginis	
	PhellodendriM	
	Saussurea vladimirae	
	Paeonia lactiflora	
	Coptidis	
	Schisandrae	

*Data from Madisch A, Holtmann G, Plein K, et al. Treatment of irritable bowel syndrome with herbal preparations: results of a double-blind, randomized, placebo-controlled, multi-centre trial. Alimentary Pharmacology & Therapeutics, 2004. 19(3):271-279.
†Data from Bensoussan A, Talley NJ, Hing M, et al. Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial. JAMA 1998. 280(18):1585-1589.
‡Data from Leung WK et al. Treatment of diarrhea-predominant irritable bowel syndrome with traditional Chinese herbal medicine: a randomized placebo-controlled trial. Am J Gastroenterol 2006. 101(7):1574-1580.

Herbal Formulas

For centuries, botanicals have been used for medicinal purposes; they are now a commonly used remedy for IBS. The appeal of botanicals likely stems from their accessibility and perceived safety as "natural" products. Various botanical preparations have been studied in IBS, with varied results. Of the 75 randomized trials for combination herbal therapy identified in one systematic review, only three double-blind placebo-controlled trials were considered to be high quality. A comparison of herbal formulations used in these three studies is shown in Table 183-4. In a study of 116 patients, both standard and individualized combination Chinese herbal medicine significantly improved bowel symptoms. The benefit of individualized herbal treatment was maintained at 14 weeks following completion of treatment. Another study in 208 patients demonstrated efficacy with the herbal preparations STW 5 and STW 5-II.[37a] The most recent of the three trials randomized 119 patients to a standard preparation of traditional Chinese medicine extracts containing 11 herbs or placebo. However, the use of this herbal formulation for diarrhea-predominant IBS did not improve symptoms.

Although no research has been done to document its efficacy, an old naturopathic remedy called Robert's formula has a long history of use in this condition (see Chapter 181 for a full description). The Tibetan herbal formula known as Padma Lax also showed efficacy for patients with constipation-predominant IBS in one 3-month double-blind randomized pilot study. A small number of patients did have loose stools with this formula, but this effect was easily remedied by lowering the dose.[38]

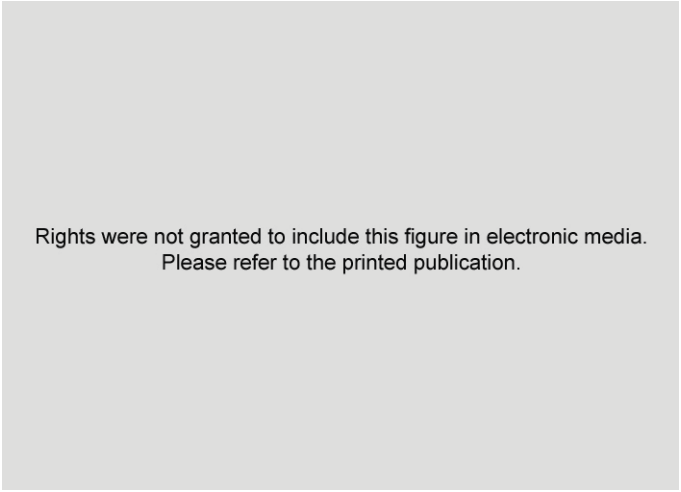


FIGURE 183-1 Current understanding of IBS pathophysiology. Stress, abuse, and emotional feelings influence bowel symptoms via activation of the brain's central circuitry called the emotional motor system (EMS) to produce autonomic and neuroendocrine responses. Bowel symptoms then cause more distress, triggering the release of mediators (cytokines, cortisol, and adrenaline) that act on the EMS, producing a feed-forward cycle of bowel symptoms and emotional distress. From Mayer EA, Naliboff BD, Chang L, Coutinho SV. Stress and irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol. 2001 Apr;280(4):G519-24.

Miscellaneous Considerations

Psychological Factors

Mental/emotional problems—anxiety, fatigue, hostile feelings, depression, and sleep disturbances—are reported by almost all patients with IBS.[39] The severity and frequency of such symptoms tend to correlate with these psychological factors. Anxiety predicts a high degree of food-related symptoms in IBS.[1] Especially significant is sleep quality; poor sleep quality results in a rise in symptom severity.[40]

Several theories link psychological factors with the symptoms of IBS. The "learning model" holds that when exposed to stressful situations, some children learn to develop gastrointestinal symptoms to cope with the stress. Another theory holds that IBS is a manifestation of depression, chronic anxiety, or both. Personality assessments of IBS sufferers have shown them to have higher anxiety levels and a greater feeling of depression.[41] However, these studies were based on postmorbid personality assessments, and it has since been determined, with premorbid personality assessment, that IBS sufferers have normal personality profiles. Therefore, many of the psychological symptoms may be either secondary to the bowel disturbances (particularly malabsorption) or due to a common etiologic factor (e.g., stress, food allergy, or candidiasis) (Figure 183-1).

Greater colonic motility during exposure to stressful situations has been shown to occur in both normal subjects and sufferers from IBS.[42] This finding apparently accounts for the greater abdominal pain and irregular bowel function seen in patients with IBS and normal subjects during periods of emotional stress. Distressed patients with IBS are also known to have decreased immune function, as evidenced by lower percentages of activated T cells and natural killer cells.[43] This finding suggests that patients with long-term IBS have lowered immune function, which may

leave them susceptible to a host of other illnesses. Some researchers believe that IBS sufferers have difficulty adapting to life events, although this belief has not been well demonstrated in clinical studies. Psychotherapy, in the form of relaxation therapy,[44] biofeedback,[45] hypnosis,[45] counseling,[46] or stress-management training[47] has been shown to reduce symptom frequency and severity and to enhance the results of standard medical treatment of IBS. Hypnosis, which the patient may practice at home using simple compact disc recording equipment,[48] has been shown to reduce both fasting colonic motility[49] and rectal sensitivity.[50] In contrast to psychotherapeutic modalities, the use of anxiolytic drugs, a combination of tranquilizers and antispasmodics, or antidepressants has not yielded effective results.

Physical Medicine

An increase in physical exercise also appears helpful for patients with IBS. Many find that daily leisurely walks markedly reduce symptoms, probably owing to the known stress-reducing effects of exercise. A specific massage therapy known as foot reflexology was evaluated in a small study of 34 individuals; no benefit for patients with IBS was found.[51]

THERAPEUTIC APPROACH

Because IBS is a multifactorial disease, the approach to the patient requires consideration and integration of the following factors:

- Dietary fiber
- Determination and elimination of food allergies/intolerances
- Stress reduction
- Exercise

As necessary, peppermint oil and the Robert formula may be used to temporarily ameliorate symptoms. Also, because the diagnosis is typically made by exclusion, a careful diagnostic evaluation is always indicated.

Diet

Fiber-rich foods (see Chapter 52) are to be increased and foods that are allergenic, contain refined sugar, or are highly processed are to be eliminated, along with FODMAPs.

Supplement

- Probiotic supplement that includes *Lactobacilli* and *Bifidobacteria* species: 2 to 12 billion live organisms/day

Botanical Medicine

Enteric-coated volatile oil preparations (e.g., peppermint oil): 0.2 to 0.4 mL twice a day between meals

Physical Therapy

The patient may be advised to take leisurely 20-minute walks a day.

Counseling

The clinician should help the patient develop an effective stress reduction program. Biofeedback may be particularly useful for patients with IBS.

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CHAPTER 184

Kidney Stones (Renal Calculi, Nephrolithiasis)

Geovanni Espinosa, ND, LAc, and Michael T. Murray, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- Usually asymptomatic
- Diagnosed adventitiously or from acute symptoms if urinary tract obstruction
- Excruciating intermittent radiating pain to the groin area originating in the flank or kidney
- Nausea, vomiting, abdominal distention
- Chills, fever, and urinary frequency if infection present

GENERAL CONSIDERATIONS

Stone formation in the urinary tract has been recognized for thousands of years; during the last few decades, however, both the pattern and incidence of the disease have changed markedly. In the past, stone formation occurred almost exclusively in the bladder, but today most stones form in the upper urinary tract. Males have a 3:1 ratio in the formation of kidney stones compared with females except in the sixth decade, where the incidence falls in men but rises in women—a trend toward gender equivalence.[1]

Once a kidney stone does form, there is a 50% chance of recurrence within 5 to 7 years if there is no treatment. Kidney stones are not limited to any cultural, geographic, or racial groups. In the United States, 1 of every 1000 hospital admissions is for kidney stones. The incidence has been steadily growing, paralleling the rise in other diseases associated with the so-called Western diet—ischemic heart disease, cholelithiasis, hypertension, and diabetes.

In the western hemisphere, over 80% of kidney stones are usually composed of calcium salts uric acid (5% to 8%), or struvite (10% to 15%). Molecular research is beginning to link certain mutations in genes responsible for handling renal chloride, which can lead to hypercalciuria. Other identified genetic changes are being linked to excess urinary excretions of oxalate, cystine, and uric acid.[2] The incidence of renal stones varies geographically, reflecting differences in environmental factors, diet, and components of drinking water. Human urine is supersaturated with respect to calcium oxalate, uric acid, and phosphates. These substances normally remain in solution because of pH control and the secretion of inhibitors of crystal growth.

The following primary and secondary metabolic diseases cause kidney stones and must be ruled out early in the clinical process:

- Hyperparathyroidism
- Cystinuria
- Vitamin D excess
- Milk-alkali syndrome
- Destructive bone disease
- Primary oxaluria
- Cushing syndrome
- Sarcoidosis

DIAGNOSTIC CONSIDERATIONS

Stone Formation

Conditions favoring stone formation can be divided into two groups: factors increasing the concentration of stone crystalloids and factors favoring stone formation at normal urinary concentrations. The first group includes reduction in urine

TABLE 184-1 **Causes of Excessive Excretion of Relatively Insoluble Urinary Constituents**

CONSTITUENT	CAUSE OF EXCESS EXCRETION	LABORATORY FINDINGS
Calcium	(>250 mg/day excreted)	
	Absorptive hypercalciuria	Low serum PO_4
		30%-40% of all stone formers
	Renal hypercalciuria (renal tubular acidosis)	High serum parathyroid hormone
		High urinary cyclic AMP
	Primary hyperparathyroidism	High serum calcium
		High $1,25(OH)_2D_3$
	Hyperthyroidism	
	High vitamin D intake	
	Excess intake of milk and alkali	
	Aluminum salt intake	Low serum phospate
		High $1,25(OH)_2D_3$
	Destructive bone disease	
	Sarcoidosis	
	Prolonged immobility	
	Methoxyflurane anesthesia	
Oxalate	Familial oxaluria	Rare
	Ileal disease, resection, or bypass	
	Steatorrhea	
	High oxalate intake	
	Ethylene glycol poisoning	
	Vitamin C excess (extremely unlikely)	Vitamin B_6 deficiency or abnormal oxalate metabolism
Uric acid	(<750 mg/day excreted)	
	Gout	
	Idiopathic hyperuricosuria	
	Excess purine intake	
	Anticancer drugs	Rapid cell destruction
	Myeloproliferative disease	
Cystine	Hereditary cystinuria	

volume (dehydration) and an increased rate of excretion of stone constituents. The second group is related to urinary stasis, pH changes, foreign bodies, and reduction of normal substances that solubilize stone constituents. See Tables 184-1 and 184-2 for an outline of the diagnostic possibilities.

THERAPEUTIC CONSIDERATIONS

Stone Composition

Diagnosing the type of kidney stone is critical to identifying the appropriate therapy. Careful evaluation of the following criteria usually determines the composition of the stone if one is not available for chemical analysis:

- Diet
- Underlying metabolic or disease factors
- Serum and urinary calcium, uric acid, creatinine, and electrolyte levels
- Urinalysis
- Urine culture

Table 184-3 summarizes the findings in the major types of kidney stones.

Dietary Factors

Calcium-containing stones are composed of calcium oxalate, calcium oxalate mixed with calcium phosphate, or very rarely calcium phosphate alone. The high incidence of calcium-containing stones in affluent societies is directly associated with the following dietary patterns:

- Low amounts of fiber[3]
- Intake of highly refined carbohydrates[4,5]
- High alcohol consumption[6]
- Large amounts of animal protein[6,7]
- High intake of fat[8]

TABLE 184-2 **Physical Changes in Urine and the Kidneys**

CONDITION	POSSIBLE CAUSE
Increased concentration	Dehydration
	Stasis
	Obstruction
	Foreign-body concretions
Urinary pH	Low—uric acid, cystine
	High—calcium oxalate and PO_4
Infection	*Proteus*—struvite
Uricosuria	Crystals of uric acid initiate precipitation of calcium oxalate from solution
Nuclei for stone formation	Cells, bacteria, blood clots, etc., initiate precipitation
	Sponge kidney
Deformities of kidney	Horseshoe kidney
	Caliceal obstruction or defect

TABLE 184-3 **Chemical and Physical Characteristics of Urinary Stones**

COMPOSITION	CRYSTAL NAME	FREQUENCY (%)	X-RAY APPEARANCE	URINE CHARACTERISTICS	CRYSTAL CHARACTERISTICS
Calcium oxalate	Whewellite	30-35	Opaque	Nonspecific	Small, hempseed or mulberry-shaped, brown or black
Calcium oxalate + Calcium phosphate		30-35	Opaque	pH>5.5	Small, hempseed or mulberry-shaped, brown or black
Calcium phospate	Apatite	6-8	Opaque	pH >5.5	Staghorn configuration, light in color
Magnesium ammonium phosphate	Struvite Triple phosphate	15-20	Opaque	pH >6.2 Infection	Staghorn configuration, light in color
Uric acid		6-10	Translucent	pH <6.0	Ellipsoid, tan or red-brown
Cystine		2-3	Opaque	pH <7.2	Multiple, faceted, maple syrup color

- High intake of soft drinks[9]
- High intake of fructose

The classification of most stones as either "idiopathic," hypercalciuria" or just "idiopathic" reflects an ignorance of the dietary factors that induce hyperuricemia, hypercalciuria, and stone formation. The cumulative effect of these dietary factors is undoubtedly the reason for the rising incidence of kidney stones.

As a group, vegetarians have a lower risk of stone development. Studies have shown that even among meat eaters, those who ate higher amounts of fresh fruits and vegetables had a lower incidence of stones.[10] Bran supplementation, as well as the simple change from white to whole wheat bread has resulted in lower urinary calcium levels.[3]

Dietary factors may also play a role in acidifying or alkalinizing urine. Depending on the type of stone, this ability to alter urinary pH may help to treat and prevent stones.[11] In one study, 12 healthy men were given a standardized diet plus cranberry, black currant, or plum juice. These subjects then provided 24-hour urine collections for evaluation. The researchers found that cranberry juice decreased the urinary pH and significantly increased the excretion of oxalic acid and the relative supersaturation for uric acid. Black currant juice increased urinary pH, excretion of citric acid, and loss of oxalic acid. Plum juice effected no change.[12] The researchers concluded that black currant juice could support the treatment and prevention of uric acid stones through its alkalizing effect. Conversely, because cranberry juice acidifies urine, it could be useful in the treatment of brushite and struvite stones as well as for urinary tract infections.

Increased fluid intake has been recognized as one of the main approaches to decrease urine supersaturation. An increase in the urine volume results in a decrease in stone prevalence. Numerous randomized controlled trials (RCTs) have found that consumption of more than 2 L/day of water[13] or increased fluid intake to achieve a urine output of more than 2.5 L/day[14] lowered the long-term risk of kidney stone recurrence by approximately 60% versus no treatment.

One trial, conducted in stone-forming men with a baseline soft drink consumption of more than 160 mL/day, reported a reduction in self-reported physician-confirmed episodes of renal colic in those randomized and advised to abstain from soft drink intake versus no intervention for 3 years. Total fluid intake was similar in both groups.[9]



DIET

In one study, high levels of dietary calcium in men younger than age 60 were associated with decreased stone formation, but there was no effect in men older than age 60, nor was a supplemental dietary intake of more than 500 mg of calcium associated with an increased risk of stones.[15]

The specific type of stone was not elucidated in this study and it was assumed that the majority of kidney stones reported by the cohort population consisted predominantly of calcium oxalate, as in the general population. The cause of this age-specific difference is unclear. Dietary calcium may bind to dietary oxalate in the intestine, thereby reducing oxalate absorption and the subsequent concentration of urinary oxalate. Both vitamin D deficiency and a diminished ability to absorb dietary calcium are more prevalent in older people.[15]

Sodium and Salt

Regarding dietary salt content, observational studies suggested a strong relation between sodium consumption and hypercalciuria, but more recent evidence has challenged this idea. High sodium intake is known to reduce renal tubular reabsorption of calcium, thereby increasing the amount of calcium excreted in the urine.[16] Also, a high-sodium diet is known to increase urine pH and has been proposed to reduce urine citrate.[17] Other studies show a positive association between urinary sodium and calcium excretion and suggested that stone formers may be more sensitive to the calciuric effect of sodium.[18]

Nouvenne et al[19] found that when patients with idiopathic calcium stones were treated with sodium restriction (60 mmol/day) and high fluid intake, a reduction of 100 mmol of urinary sodium was accompanied by a reduction of 64 mg/day in urinary calcium, with 30% of patients achieving normal urine calcium.

In contrast, other data, specifically in patients with hypocitraturia (not hypercalciuria), demonstrated that dietary sodium supplementation resulted in increased voided volume and decreased calcium oxalate supersaturation.[20] This must be carefully examined, because these patients were followed for only a short period of time and they were already using pharmacologic interventions for stone disease. Although results continue to be conflicting, reduced dietary sodium is a general recommendation given to most patients with a history of kidney stones.

Fructose

Sports drinks have become increasingly popular within the past decade. The content of citrate in such beverages would be expected to increase urine citrate excretion and urine pH, providing protection against both calcium and uric acid stones. However, the purposely high sodium content of sports drinks, promoted as useful

for "rehydration" in athletes, might be associated with increases in urine calcium excretion. In addition, the ingestion of significant amounts of sucrose and fructose in these drinks could also be associated with increases in calcium excretion.[21] Fructose, a component of corn syrup frequently added to sports drinks and sodas as a sweetener, would also be an undesirable way for most stone formers to increase urine volume, given its recent links to hyperuricemia, metabolic syndrome, and stones.[22,23]

Citrate is an accepted inhibitor of the aggregation and growth of calcium oxalate and calcium phosphate crystals. In the past, dietary interventions to increase citrate have included lemonade and orange juice.[24,25] The results with lemonade are conflicting, with one study showing an increase in urine volume but not in urine citrate.[26] Regular consumption of grapefruit juice should be avoided, however. In one large-scale study, women drinking 8 oz of grapefruit juice daily increased their risk of stones by 44%.

Hyperoxaluria is a metabolic risk factor for stone disease. Dietary oxalate may contribute as much as 80% of the urine oxalate.[27,28] Therefore, a low-oxalate diet may provide benefit for patients with hyperoxaluria. In addition, adequate dietary calcium to minimize intestinal oxalate absorption has been shown to be beneficial. Borghi et al[29] in a randomized trial in men with recurrent calcium oxalate stones, achieved a significant reduction in oxalate excretion and the incidence of recurrent stones for patients on a normal-calcium (1200 mg/day), low-animal-protein, low-salt diet compared with a low-calcium diet (400 mg/day).

Dietary Recommendations for Patients with High Urine Oxalate

Low-Oxalate Diet

A low-oxalate diet is a common prescription for recurrent calcium oxalate kidney stones. The ultimate goal is to reduce the level of oxalic acid being excreted in the urine. It appears that people with recurrent kidney stones have a tendency to absorb higher levels of dietary oxalates compared with normal subjects not prone to kidney stones, who absorb only 3% to 8% of dietary oxalate. A low-oxalate diet is usually defined as less than 50 mg of oxalate per day, so foods in the high- and moderate-oxalate categories have to be curtailed. Box 184-1 is designed to provide an estimate of the oxalate content of food, which is highly variable. The level of oxalate in a particular food in published reports can vary twofold to fifteenfold. Differences in climate, soil quality, state of ripeness, or even which part of the plant is analyzed will also affect the value.

J
K
L

BOX 184-1 **Oxalate Content of Select Foods**

Vegetables
High Oxalate, >10 mg per Serving
Beets—greens or root*
Celery
Collards
Dandelion greens
Eggplant
Escarole
Green beans
Kale
Leeks
Okra†
Parsley
Parsnips
Peppers, green
Potatoes
Pumpkin
Spinach*
Squash, yellow summer
Sweet potatoes
Swiss chard*
Tomato sauce, canned
Turnip greens
Watercress
Moderate Oxalate, <10 mg per Serving
Asparagus
Artichokes
Broccoli
Brussels sprouts
Carrots
Cucumber
Garlic
Lettuce
Mushrooms
Mustard greens
Onions
Peppers, green
Potato chips
Potato salad (¼ cup)
Pumpkin
Radishes
Snow peas
Tomato, fresh‡
Tomato sauce, canned (¼ cup)
Low Oxalate, 2-5 mg per Serving
Acorn squash
Arugula
Ketchup (1 tbsp)
Onions
Pepper, red
Zucchini squash

Fruits
High Oxalate, >10 mg per Serving
Concord grapes
Figs, dried†
Kiwi
Lemon peel
Lime peel
Orange peel
Rhubarb*
Moderate Oxalate, <10 mg per Serving
Apples
Apricots
Berries (¼ cup)
Blackberries
Blueberries
Cherries, red sour
Cranberries, dried
Currants, black
Oranges
Peaches
Pears
Pineapple
Plums
Prunes, Italian
Red raspberries
Tangerines
Low Oxalate, 2-5 mg per Serving
Apples, peeled
Avocado
Cantaloupe
Cherries, bing
Cranberries
Grapes
Lemon juice (1 cup)
Lemons
Lime juice (1 cup)
Raisins

Grains
High Oxalate, >10 mg per Serving
Bread, whole wheat
Buckwheat‡
Oatmeal
Popcorn
Spelt
Stone-ground flour
Wheat bran
Wheat germ
Whole wheat flour
Moderate Oxalate, <10 mg per Serving
Bagel (1 medium)
Barley, cooked

BOX 184-1 **Oxalate Content of Select Foods—cont'd**

Bread, white (2 slices)
Corn
Corn tortilla (1 moderate)
Cornbread
Cornmeal, yellow (1 cup dry)
Cornstarch ($^1/_4$ cup)
Pasta
Rice, brown
Spaghetti
Wheat, white flour
Low Oxalate, 2-5 mg per Serving
Rice, white
Rice, wild
Rye bread

Legumes
High Oxalate, >10 mg per Serving
Garbanzo beans
Lentils
Soy and all soy products
Moderate Oxalate, <10 mg per Serving
Lima beans
Split peas
Low Oxalate, 2-5 mg per Serving
Peas, green

Nuts and Seeds
High Oxalate, >10 mg per Serving
Almonds†
Brazil nuts
Hazelnuts
Peanuts‡
Peanut butter‡
Pecans
Sesame seeds*
Sunflower seeds
Moderate Oxalate, <10 mg per Serving
Cashews
Flaxseed
Walnuts
Low Oxalate, 2-5 mg per Serving
Coconut

Herbs
Moderate Oxalate, <10 mg per Serving
Cinnamon, ground ($1^1/_2$ tsp)
Ginger, powdered (1 tbsp)
Pepper, black (1 tsp per day)
Thyme, dried (1 tsp)
Low Oxalate, 2-5 mg per Serving
Basil, fresh (1 tbsp)
Dill (1 tbsp)
Ginger, raw, sliced (1 tsp)
Malt, powder (1 tbsp)
Mustard, Dijon ($^1/_2$ cup)
Nutmeg (1 tbsp)
Pepper (1 tsp)

Miscellaneous
High Oxalate, >10 mg per Serving
Beer
Chocolate
Cocoa
Soy sauce (1 tbsp)
Tea, black
Tea, green
Moderate Oxalate, <10 mg per Serving
Coffee
Red wine
Sardines
Tea, rosehip
Low Oxalate, 2-5 mg per Serving
Beef
Chicken
Corned beef, canned
Eggs
Fish, haddock, plaice, and flounder
Ham
Hamburger
Lamb
Pork
Turkey
Venison

*Greater than 200 mg per serving.
†Greater than 100 mg per serving.
‡Greater than 50 mg per serving.

Weight and Carbohydrate Metabolism

Weight control and the correction of carbohydrate metabolism are important because excess weight and insulin insensitivity lead to hypercalciuria and are high-risk factors for stone formation.[30,31] After glucose ingestion, there is a rise in urinary calcium, and phosphate reabsorption decreases. This leads to a low plasma phosphate concentration, which stimulates the production of 1,25 dihydroxycholecalciferol and results in the increased intestinal absorption of calcium; concurrently, it also causes hypercalciuria. The ingestion of sucrose and other simple sugars causes an exaggerated rise in the urinary calcium oxalate content in approximately 70% of people with recurrent kidney stones.[32]

Gut Flora

Studies are beginning to find a correlation between the proper balance of intestinal flora and a lower risk of oxalate kidney stones. Oxalate homeostasis depends in part on the intestinal anaerobic bacterium *Oxalobacter formigenes*. It now appears that *O. formigenes* contributes to oxalic acid homeostasis and that its absence may predispose individuals to idiopathic calcium-oxalate kidney stone disease.[33] This bacterium is found primarily in the colon, and its loss through prolonged widespread use of antibiotics is associated with an increased risk of hyperoxaluria and calcium-oxalate stone formation.[34] Studies in animals and human volunteers have indicated that, when administered therapeutically, *O. formigenes* can repopulate the gut and reduce the urinary oxalate concentration after an oxalate load, hence reducing the incidence of calcium-oxalate kidney stone formation.[33] Although more research is needed, it seems possible that supplementing deficient individuals with *O. formigenes* may confer some protection against future kidney stone disease.

Nutrients

Magnesium and Vitamin B_6

A magnesium-deficient diet accelerates the deposition of calcium in renal tubules in rats.[35] Magnesium has been shown to increase the solubility of calcium oxalate and inhibit the precipitation of both calcium phosphate and calcium oxalate.[36-38] A low urinary magnesium/calcium ratio is an independent risk factor for stone formation[39]; supplemental magnesium alone has been shown to be effective in preventing recurrences of kidney stones.

When magnesium is used in conjunction with vitamin B_6, an even greater effect is noted.[40,41] Pyridoxine is known to reduce the endogenous production and urinary excretion of oxalates,[42,43] and patients with recurrent oxalate stones have abnormal activation levels of erythrocyte glutamate pyruvate transaminase, erythrocyte glutamic-oxaloacetic transaminase (EGOT), urinary glutamic-pyruvic acid transaminase, and urinary glutamic-oxaloacetic transaminase, indicating clinical insufficiency of vitamin B_6 and impaired glutamic acid synthesis. These levels return to normal after 3 months of treatment.[43] Induced pyridoxine deficiency in

rats has been shown to produce oxaluria and calcium oxalate lithiasis (which is prevented by magnesium supplementation).[42]

Glutamic Acid

Depressed levels of glutamic acid (from vitamin B_6 deficiency or for other reasons) are significant in the formation of kidney stones because a higher concentration of glutamic acid in the urine induces precipitation of calcium oxalate. Glutamic acid supplementation in rats significantly reduces the incidence of calculi, and it may do so in humans as well.[44] Supplementation with glutamic acid may, however, be superfluous if adequate vitamin B_6 levels are attained.

Calcium

Although most doctors still tell their patients with kidney stones to avoid calcium supplements, this advice is mostly outdated. A strong body of evidence has emerged refuting the general trend to restrict calcium supplementation in patients with kidney stones.

One study has even shown that calcium supplementation reduces oxalate excretion.[45] This study measured urinary oxalate excretion after calcium supplementation and the administration of oxalic acid. Calcium was given in the form of calcium carbonate or calcium citrate malate at a dose of 300 mg elemental calcium daily. Compared with baseline assessment, calcium supplementation significantly reduced oxalate absorption and excretion.

Another study evaluated calcium intake and the dietary profiles in 37 outpatients with kidney stones and 45 control subjects. Dietary calcium, assessed from 4-day dietary records, was significantly lower for patients with urinary calculi.[46] A third study further supporting the benefits of calcium intake is a 5-year randomized trial comparing the effect of two diets in 120 men with recurrent calcium oxalate stones and hypercalciuria.[47] Upon completion, the men consuming the normal calcium diet experienced a 51% reduction in the risk of stone recurrence. During follow-up, urinary calcium levels dropped significantly in both groups, but urinary oxalate was reduced in the normal calcium intake group and increased in the low calcium intake group. Finally, one large prospective epidemiologic investigation also reported that kidney stones were more likely to manifest in individuals with the lowest daily calcium intakes (516 mg) than in those with the highest daily calcium intakes (1326 mg).[48]

These studies clearly demonstrate that calcium supplementation (300 to 1000 mg daily) may prove to be an effective preventive measure against calcium oxalate kidney stones.

One large trial, however, of over 36,000 post menopausal women with no history of kidney stones, showed, compared with placebo, a 17% increase risk of self-reported urinary tract stones in women who consumed 1000 mg of calcium carbonate plus 400 IU of vitamin D daily. For post menopausal women, the implications of calcium carbonate ingestion may differ from those for younger women and men, for unknown reasons. Calcium absorbability comes into question in this population of women, particularly when the elemental form used was carbonate.[49] This study contradicts other data indicating that vitamin D supplementation can be provided to postmenopausal women who are not stone formers and who are vitamin D–insufficient without fear of an increased risk of kidney stones.[50]

Citrate

Low urinary citrate excretion is known to pose a risk for nephrolithiasis.[51] Although urinary calcium rises in patients consuming calcium citrate, some of citrate's effects inhibit the formation of kidney stones. Specifically, citrate has the ability to reduce urinary saturation of calcium oxalate and calcium phosphate and to retard the nucleation and crystal growth of calcium salts. The use of potassium or sodium citrate in the treatment of recurrent urinary saturation of calcium oxalate has been shown to be effective in clinical studies, ending stone formation in nearly 90% of the subjects.[52] For example, in one study, 31 mmol/day of potassium citrate provided to recurrent stone formers who were also hypocitraturic resulted in a drop of stone formation from 0.7 to 0.13 per year.[53]

Another 3-year, double-blind study of 57 people with a history of calcium stones and low urinary citrate levels revealed that those given potassium citrate developed fewer kidney stones than they had previously. In comparison, the group given placebo had no change in their rate of stone formation.[54]

However, rather than potassium or sodium citrate, magnesium citrate appears to offer the greatest benefit.

Magnesium citrate slows the growth rate of brushite crystals, nucleation rate, and supersaturation of urine. In addition, because magnesium competes with calcium in binding oxalates in both the gut and urine, the ratio of magnesium to calcium in the urine is used in estimating stone risk.[55]

Vitamin K

The urinary glycoprotein, a powerful inhibitor of calcium oxalate monohydrate growth, requires posttranscriptional carboxylation of glutamic acid to form gamma-carboxyglutamic acid. Vitamin K is an essential factor for this carboxylation to occur.[56] Impairment of glutamic acid formation or a vitamin K deficiency reduces the formation of this glycoprotein. The presence of vitamin K in green leafy vegetables may contribute to the lower incidence of kidney stones among vegetarians.[57]

Uric Acid Metabolism

The level of dietary purine consumption is linearly related to the rate of urinary uric acid excretion.[58] This relationship is important because hyperuricosuria is a causative factor in recurrent calcium oxalate stones. High levels of supplemental folic acid promote purine-scavenging and xanthine oxidase inhibition, resulting in decreased excretion of uric acid (see Chapter 169). Higher urine pH also helps with uric acid solubility[59]; however, manipulation of urine pH is a complex task because it will be affected not only by diet and hydration status but also by weight and body mass index (BMI). Higher BMIs have been associated with lower urine pH.[60,61] Including a weight reduction goal when appropriate may benefit stone patients with uric acid stones or low urine pH, although long-term benefits are unknown.

Botanical Medicines

There are limited clinical trials with the use of medicinal herbs for kidney stones, and those that exist are poorly designed. We focus briefly on the traditional in vitro and in vivo use of a number of botanicals.

Anthraquinones isolated from the *Rubia, Cassia,* and *Aloe* species bind calcium and significantly reduce the growth rate of urinary crystals when used in oral doses lower than the laxative dose.[62,63] *Rubia tinctura, Rumex, Rheum, Polygonum aviculare, Aloe,*[64] *Senna, Rhamnus alnus,* and *Mitchella repens* are sources of these anthraquinones and may be used to prevent stone formation; during acute attacks, they may help to reduce the size of the stone.

The furanocoumarin-containing herb *Ammi visnaga* has been shown to be unusually effective in relaxing the ureter and allowing

the stone to pass.[65] This action is due to its calcium channel–blocking capabilities, which act primarily on the ureters. Atropine and papaverine have similar but less active smooth muscle–relaxing effects. *Peucedanum, Leptotania, Ruta graveolens,* and *Hydrangea* contain similar furanocoumarins that also promote smooth muscle relaxation, and all of these herbs have historical uses in the treatment of kidney stones.

Eupatorium purpureum (gravel root), as its name implies, has traditionally been used for treating urinary stones ("gravel"). The Eclectics, physicians who employed natural therapies at the end of the nineteenth and beginning of the twentieth centuries, considered it mildly astringent, stimulant, and tonic with a specific action on the urinary tract.[66] It was said to have the power to dissolve concretions.

One of several reasons why kidney stones are painful when they are passed is because they produce spasm in the ureters. Spasmolytic herbs have been clinically effective for controlling ureteral spasm in such cases, whereas diuretic herbs are also used to push sufficiently small stones through the ureters more slowly and tolerably. Currently, the use of these herbs is more dependent on tradition than on scientific data.

Some of the more popular spasmolytic herbs that have been reliably effective in this realm include *Ammi visnaga* (khella) fruit, which is also strong enough to use for angina pectoris and acute asthma; *Lobelia, Piscidia piscipula* (Jamaican dogwood) bark, *gelsemium,* and western pasque flower. *Hyoscyamus niger* (henbane) herb is also useful; it is an even stronger anticholinergic antispasmodic, like belladonna but with an affinity for the genitourinary tract.[67]

In two clinical trials, participants with a history of nephrolithiasis and with radiographic stones present at baseline were randomized to *Orthosiphon grandiflorus* extract 2.5 g in tea twice daily or to sodium potassium citrate 5 to 10 g three times daily for 18 months.[20] Serial ultrasound was used to measure mean annualized reduction in stone diameter at 18 months. The two treatments were equally effective at reducing stone size over a year's time, with far fewer adverse effects in the tea group.[68]

Phyllanthus niruri has been shown to inhibit calcium oxalate crystallization in the test tube. Although reportedly diuretic in rodent and human studies,[69,70] low-dose studies find that it is not significantly diuretic in rats, although it still significantly dissolves stones.[70]

In one clinical trial, 69 subjects were randomized to extract capsules 450 mg of *Phyllanthus* three times daily or to placebo for 3 months.[71] Among those randomized to receive *P. niruri,* there was a reduction of hypercalciuria in those patients who had this problem initially but no significant effect on calculus elimination or calculus size was observed.

Lifestyle

Sleep Position

Even though the etiology of recurrent unilateral kidney stones is unclear, patients with recurrent renal calculi most often present with calculi on the same side. Data from the literature support the notion that sleep posture may contribute to alterations of renal hemodynamics. Researchers studied 110 patients who suffered from kidney stones confined to one side of their bodies. Of these patients, 93 consistently favored sleeping with one side in a dependent position. Further study showed that the side of the stone was identical to the dependent sleep side in 76%, with positive predictive values of right-side-down and left-side-down sleep postures for ipsilateral stone formation at 82% and 70%, respectively.[72]

Stress

One case-control study of 200 patients with symptomatic kidney stones and 200 matched controls demonstrated a statistically significantly higher rate of kidney stone formation in people who had more stressful life events. Such events were defined as those that the subjects perceived as highly stressful by inflicting an intense emotional impact on them, with apprehension and distress, for at least 1 week.[73] It is hypothesized that stressful events may encourage loss of litholytic urinary constituents such as magnesium and citrate.[74] Additionally, the sympathetic "fight or flight" response may increase vasopressin release, thus contributing to a more hypertonic urine.[75]

Miscellaneous

Heavy Metals

Hair mineral analysis may be of value, because many heavy metals (mercury, gold, uranium, and cadmium) are nephrotoxic. Cadmium, in particular, has been shown to greatly increase the incidence of kidney stones. A prospective study of coppersmiths showed a 40% incidence of kidney stones, which correlated with elevations of serum cadmium concentration.[76]

Vitamin C and the Risk of Oxalate Stones

Vitamin C is often cited in the medical literature as a potential factor in the development of calcium oxalate kidney stones. Numerous studies have now demonstrated that in persons not undergoing hemodialysis or suffering from recurrent kidney stones, severe kidney disease, or gout, high-dose vitamin C therapy does not cause kidney stones. Vitamin C ingestion of up to 10 g/day has not had any effect on urinary oxalate levels.[77,78]

On the contrary, several human trials consistently indicate that a large percentage of individuals—regardless of kidney stone history, age, gender, and race—ingesting 1000 to 2000 mg of ascorbic acid for only short periods experience hyperoxaluria to some degree.

A more recent clinical study concurs with previous studies in demonstrating mean increases in total oxalate excretion with ascorbic acid supplementation.[79]

Another recent RCT double-blind crossover trial of 50 healthy adults compared vitamin C with metabolites (Ester-C) to ascorbic acid. Only 41% of subjects on vitamin C with metabolites experienced an increase in 24-hour oxalate, which is 25% fewer compared with ascorbic acid. This implies that if one needs to consume vitamin C, Ester-C maybe most beneficial for stone formers; however, the beneficial effects of Ester-C are still controversial.[80]

Inositol Hexaphosphate

Inositol hexaphosphate (also known as phytic acid or IP6), a naturally occurring compound found in whole grains, cereals, legumes, seeds, and nuts, is known for its antineoplastic activity. One trial showed that the use of 120 mg per day of IP-6 significantly reduced, within in 15 days, the formation of calcium oxalate crystals in the urine of people with a history of kidney stones.[81] One literature review reported several human studies demonstrating effectiveness of phytic acid against four types of kidney stones.[82]



THERAPEUTIC APPROACH

Effective treatment of kidney stones requires accurate differentiation between the various stone types and recognition and control of any underlying metabolic diseases or structural abnormalities of

the urinary tract. Tables 184-1 and 184-2 list diagnosable causes of kidney stones.

Prevention of recurrence is the therapeutic aim in the treatment of kidney stones. Because dietary management is effective, inexpensive, and free of side effects, it is the treatment of choice. The specific treatment is determined by the type of stone and may include the following:

- Reducing urinary calcium
- Reducing purine intake
- Avoiding foods high in oxalate
- Increasing intake of foods with a high magnesium/calcium ratio
- Increasing intake of vitamin K–rich foods

For all types of stones, increasing urine flow to dilute the urine is vital. Enough fluids should be consumed to produce a urine with a specific gravity lower than 1.015 and urinary volume of at least 2000 mL daily.

As far as lifestyle changes are concerned, if stones occur on one side only, it may be helpful to avoid sleeping on that side. Stress-reduction techniques and counseling should be considered for anyone with stones and a history of significant stress.

Acute Obstruction

Surgical removal or lithotripsy may be necessary; the following agents may also be used:

- *Ammi visnaga* extract (12% khellin content): 250 mg three times a day
- *Rubia tinctura, Rumex crispus,* or *Aloe vera* at doses lower than used for laxative effect

Calcium Stones

Diet

- Increase intake of fiber, complex carbohydrates, and green leafy vegetables.
- Decrease intake of simple carbohydrates and purines (meat, fish, poultry, yeast).
- Increase consumption of foods with high magnesium/calcium ratios (barley, bran, corn, buckwheat, rye, soy, oats, brown rice, avocados, bananas, cashews, coconut, peanuts, sesame seeds, lima beans, potatoes).
- If the stones are oxalate, reduce consumption of oxalate-containing foods (black tea, cocoa, spinach, beet leaves, rhubarb, parsley, cranberries, nuts).
- Limit consumption of dairy products.

Supplements

- Vitamin B_6: 25 mg/day
- Vitamin K: 2 mg/day
- Magnesium: 600 mg/day
- Calcium: 300 to 1000 mg/day
- IP6: 120 mg/day

Botanicals

Use any of the following agents in a dose less than that used for laxative effect:

- *R. tinctura*
- *R. crispus*
- *A. vera*

Miscellaneous

Avoid aluminum compounds and alkalis.

Uric Acid Stones

Diet

- Decrease consumption of purines (see list given for calcium stones).
- Ensure adequate fluid intake and a high alkali load with plenty of fruits and vegetables.

Supplements

Folic acid: 5 mg/day

Miscellaneous

Alkalinize urine: citrate, bicarbonate, black currant juice.

Magnesium-Ammonium-Phosphate Stones

Miscellaneous

- Eradicate infection (see Chapter 159).
- Acidify urine with ammonium chloride (100 to 200 mg three times a day).

Cystine Stones

Diet

Avoid methionine-rich foods (soy, wheat, dairy products except whole milk, fish, meat, lima beans, garbanzo beans, mushrooms, and all nuts except coconut, hazelnut, and sunflower seeds).

Miscellaneous

Alkalinize urine: optimal pH is 7.5 to 8.

Bushite and Struvite Stones

Acidify urine with cranberry juice.

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CHAPTER 185

Leukoplakia

Michael Traub, ND, DHANP, FABNO, and Michael T. Murray, ND

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DIAGNOSTIC SUMMARY

- Adherent white patch or plaque appearing anywhere on the oral mucosa
- Asymptomatic until ulceration, fissuring, or malignant transformation occurs
- Diagnosis confirmed by biopsy

GENERAL CONSIDERATIONS

Leukoplakia is a clinical term signifying a white, plaquelike lesion occurring anywhere on the oral mucosa. It is generally a reaction to irritation, such as cigarette smoking or tobacco or betel nut chewing, as well as an early sign of human immunodeficiency virus (HIV) infection. It appears most commonly in men 50 to 70 years of age. In 90% of cases, leukoplakia represents epithelial hyperkeratosis and hyperplasia.[1] In the remaining 10%, there is also epithelial dysplasia; these lesions are considered precancerous.

Oral cancer is among the most common malignant neoplasms, with nearly 50,000 new cases and 12,000 deaths reported in the United States alone each year. Survival rates for patients undergoing chemotherapy, irradiation, and surgical procedures have not significantly changed in the past few decades. Success in preventing death due to oral cancer is achieved through the prevention of oral cancer. Abstinence from tobacco and a higher intake of antioxidant nutrients are the primary preventive measures.

THERAPEUTIC CONSIDERATIONS

Treatment of leukoplakia involves removal of all irritants. Electrodessication, cryosurgery, and proteolytic enzymes have not given predictably favorable results.[2] Photodynamic therapy, vitamin A, beta-carotene, and lycopene have shown clinical resolution rates higher than 50%.[3]

Vitamin A and Beta-Carotene

Historically, vitamin A supplementation and, more recently, beta-carotene supplementation have been clinically effective in the treatment of leukoplakia.[4-9] Stich et al,[8,9] using the micronucleus test to monitor efficacy, were among the first to evaluate vitamin A and beta-carotene for leukoplakia. The micronucleus test is a useful indicator of the neoplastic tendency of epithelial cells because it provides immediate information about genotoxic damage. Micronuclei are formed during chromatid or chromosomal breakage, with the rate of formation tied closely to carcinogenesis in the oral cavity. This rate is a good predictor of cancer, which typically takes years or decades to generate clinically recognizable signs. On the basis of results of the micronucleus test, Stich et al. found that these two dietary factors, particularly beta-carotene, were effective in decreasing the mean proportion of cells with micronuclei on the buccal mucosa in Asian betel nut and tobacco chewers.[8,9] The subjects continued to chew betel nut and tobacco during the study.

The epidemiologic and experimental data documenting the protective effect of carotenoids and retinoids against epithelial cancers are overwhelming. The inverse relationship between serum retinol and carotene levels and cancer incidence holds true for oral carcinomas as well.[10,11]

TABLE 185-1 **Beta-Carotene Trials**

STUDY	DOSAGE	RESPONSE RATE (%)
Stich et al.[8]	180 mg/week	15
Stich et al.[9]	180 mg/week	27
Garewal et al.[19]	30 mg/day	71
Brandt et al.[20]	90 mg/day	60
Toma et al.[21]	90 mg/day	44
Malaker et al.[22]	30 mg/day	50
Garewal et al.[23]	60 mg/day	56
Sankaranarayanan et al.[14]	360 mg/week	33

Dosages used in clinical studies testing vitamin A in the treatment of leukoplakia generally were fairly high (i.e., 150,000 to 900,000 IU/day) but extremely effective.[4-7] Since beta-carotene appears to be as effective as retinol in decreasing the levels of micronuclei and has a much higher therapeutic index, beta-carotene should probably be the treatment of choice for this condition. (Note: Vulvar leukoplakia is also responsive to retinol and could therefore respond to beta-carotene as well.)[12,13] However, the only head-to-head comparison study of the two supplements did find an advantage for retinol (see Table 185-1). In this study, 160 men and women with leukoplakia were randomly assigned to receive oral vitamin A (retinyl acetate 300,000 IU/week for 12 months; n = 50), oral beta-carotene (360 mg/week for 12 months; n = 55), or placebo (n = 55).[14] The complete regression rates were 10% in the placebo arm, 52% with vitamin A, and 33% with beta-carotene. Homogeneous leukoplakias and smaller lesions responded better than nonhomogeneous and larger lesions. No major toxicities were observed even in the group given prolonged vitamin A supplementation.

Lycopene

A randomized controlled trial of the carotenoid lycopene conducted over 5 months found no significant difference in the clinical response of subjects taking 8 mg lycopene twice daily compared with those taking 4 mg twice daily. Both groups had significantly greater responses than those in the control group. Histologic assessment was significantly better in the group taking 8 mg of lycopene.[15]

Other Antioxidants

Antioxidants in addition to beta-carotene may be helpful. For example, studies have shown alpha tocopherol (400 IU twice daily for 24 weeks) to produce a 65% response rate.[16] However, it makes the most sense to use a combination of antioxidant nutrients (including using mixed tocopherols rather than just one of the 8 isomers), given their interactions and limitations as monotherapy. Preliminary results using a combination of vitamin C (1000 mg/day), beta-carotene (30 mg/day), and vitamin E (400 IU/day) are encouraging.[17]

Curcumin

Curcumin has recently shown promise in vitro as a chemopreventive agent for leukoplakia.[18]

THERAPEUTIC APPROACH

Because leukoplakia is due to a combination of excessive carcinogenic irritation in the context of marginal or low levels of vitamin A, the approach is simple: eliminate all sources of irritation and establish optimal vitamin A, beta-carotene, and antioxidant levels. Particularly significant irritation results from the smoking or chewing of tobacco, chewing of betel nut, and exposure to ultraviolet light.

Supplements

- Vitamin A: 5000 IU/day
- Beta-carotene: 30 to 90 mg/day
- Lycopene 8 mg twice daily
- Vitamin C: 1000 to 3000 mg/day
- Vitamin E: 400 IU/day

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CHAPTER 186

Lichen Planus

Sam Russo, ND, LAc

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DIAGNOSTIC SUMMARY

- Lichen planus is an inflammatory, pruritic disease of the skin and mucous membranes described by the "six P's": pruritic, polygonal, planar (flat-topped), purple papules, and plaques. Intense pruritus is commonly the primary complaint, although lesions can present without pruritus.
- Skin lesions are flat-topped, violaceous to purple, polygonal or oval, papules 1 to 10 mm wide with sharply defined edges and shiny. Lesions may be grouped, linear (Koebner phenomenon), annular, or disseminated when generalized. White lines (Wickham striae) may be present. A handheld lens and application of a clear oil over a lesion intensifies the visibility of the striae. In dark-skinned patients, postinflammatory hyperpigmentation commonly occurs. Skin lesions may occur anywhere, with a predilection for the trunk and flexor surfaces, particularly the wrists as well as the lumbar region, eyelids, shins, scalp, glans penis, and mouth.
- Oral lesions appear inflamed, with leukohyperkeratosis, manifesting as reticulated white puncta or papules and lines in a lacelike pattern. Plaques may form and can become hyperkeratotic. Erosions with blisters may occur. Usually both buccal mucosae are affected, although the tongue, lips, and gingivae may be as well. Skin lesions occur in 10% to 60% of cases of oral lichen planus. Biopsy should be performed if there is doubt about the diagnosis or if blisters, plaques, or erosions occur in oral lichen planus.
- Other locations include: (1) the genitalia, as papular, annular, or erosive lesions on the penis, scrotum, labia majora, labia minora, and vagina; (2) the scalp, with atrophic skin and scarring alopecia; and (3) the nails, with destruction of the nail fold and bed and with longitudinal splintering.

Variants

- Hypertrophic: Large thick plaques on the feet and shins; more common in African-American males. Hypertrophic lesions may become hyperkeratotic.
- Follicular: Individual keratotic-follicular papules and plaques that lead to cicatricial alopecia. Graham Little syndrome is the complex of spinous follicular lesions, any lichen planus, and cicatricial alopecia.
- Vesicular: Development of vesicular or bullous lesions within or independent of lesions. In the latter, direct immunofluorescence is consistent with bullous pemphigoid, and patients have bullous pemphigoid immunoglobulin (Ig) G autoantibodies.
- Actinicus: Papular lesions in sun-exposed areas, especially the dorsa of the hands and arms.
- Ulcerative: Therapy-resistant ulcers, particularly on the soles, requiring skin grafting.

GENERAL CONSIDERATIONS

Etiology is often unknown. Drugs, metals, or infection (hepatitis C virus) resulting in the alteration of cell-mediated immunity may play a role. Human leukocyte antigen–associated genetic susceptibility explains a predisposition in some patients. The immune system plays a role, as evidenced by two findings: First, immunoglobulins (primarily IgM; possibly also IgA and IgG) and complement (C3) are found at the

dermal-epidermal junction in 95% of lichen planus lesions. Second, lesions can occur with certain drugs, graft-versus-host disease reactions, dermatomyositis, and as cutaneous manifestations of malignant lymphoma. The primary immune factor involved appears to be cell-mediated processes. In early lesions, activated helper T (T_H) cells target basal cells, which may have antigenic alterations. Suppressor T (T_s) cells predominate in older lesions.

Epidemiologic studies have demonstrated a higher prevalence of hepatitis C virus infection in patients with lichen planus than in the normal population. However, a pathogenic relationship has yet to be established.

Incidence, Onset, and Course

Although not common, lichen planus occurs in 6 per 1000 patients seen by dermatologists, with an annual prevalence of 4.4 per 1000 people in the United States. However, oral lichen planus may be the most common cause of white lesions in the mouth, occurring in 0.5% to 1% of dental patients. Women tend to be affected more than men and the age at onset is 30 to 60 years.

Onset can be acute or insidious with lesions remaining for months to years. The course of oral lichen planus may be chronic, lasting from months to years. Approximately two-thirds of patients experience spontaneous resolution within 1 year. Recurrence is uncommon in both forms, being seen in less than 20% of patients. Patients with mucous membrane involvement usually have a more prolonged course, possibly lasting months to decades, although 50% experience remission within 2 years. The incidence of oral squamous cell carcinoma in individuals with oral lichen planus is 5% higher than in those with lesions in other locations.

The list of possible causative medications is long. The most common are gold, antimalarial agents, penicillamine, thiazide diuretics, beta blockers, nonsteroidal antiinflammatory drugs, quinidine, and angiotensin converting enzyme inhibitors.[1] The interval between administration of the offending agent and the development of lichenoid drug eruptions is usually a few months, ranging from 10 days to several years.[1]

THERAPEUTIC CONSIDERATIONS

Dental Amalgams

Dental amalgams appear to play a role in the etiology of oral lichen planus. In one study, 161 patients with chronic lichenoid reactions (142) or oral lichen planus (19) underwent replacement of mercury amalgam fillings with alternative substances. Five patients served as controls, receiving no restoration. Evaluation 6 to 12 months after restoration showed that 95% of the patients with chronic lichenoid reactions had marked improvement or complete restoration of normal mucosa. The effect was more apparent for those with gold crowns than those with CM (palladium-based) crowns. In the oral lichen planus group, those areas of lesions in contact with amalgam showed an improvement in 63% of patients, but lesions at other sites were not affected.[2] A second study found that if gold crowns are already present, patients should undergo patch testing for gold allergy; removal of the crowns should be considered in those with positive results.[3] The former study downplays the significance of patch testing for mercury, as many patch-negative patients still responded to amalgam removal. However, in cases of positive patch-test reactions to mercury compounds, partial or complete replacement of amalgam fillings will lead to a significant improvement in nearly all patients.[4,5]

Photodynamic Therapy

A retrospective analysis of 50 patients with generalized cutaneous lichen planus treated by broad-band (n = 7) or narrow-band (n = 43) ultraviolet B radiation showed a complete response in 70%; 85% of these respondents were still in remission after a median of 34.7 months.[6] Another report is that of a 64-year-old man with lichen planus of the penis that did not respond to steroids; in this case photodynamic therapy was preceded (4 hours prior to treatment) by application of 5-aminolevulinic acid (20%) ointment. The area was irradiated with a Paterson-Whitehurst lamp (Paterson Institute, Christie Hospital, Manchester, United Kingdom) at a center wavelength of 630 nm and a rectangular pass band of 27 nm. The dose was gradually increased to 50 J/cm^2 at a fluence rate of 55 mW/cm^2 to prevent edema and phimosis. Treatment was repeated after 6 weeks. The lesions resolved completely after another 4 weeks, with no recurrence at 6 months.[7] Photodynamic therapy with medium-dose ultraviolet A-1 has successfully treated ulcerative lichen planus of the feet in another case.[8]

Supplements and Botanical Medicines

Correction of low levels of vitamins B_1 and B_6 resulted in both clinical and subjective improvement in the majority treated, but did not produce complete remission of the lesions.[9]

Vitamin A and Beta-Carotene

Six patients with hypertrophic lichen planus of the palms or soles used topical retinoic acid (0.1% in petroleum jelly base) three times daily for 3 weeks. This frequency caused irritation, so application was switched to two to three times every other day. Regression occurred after 2 to 3 weeks. Duration of treatment was unspecified in the study report. Two cases showed slight recurrences after 3 to 4 months.[10]

A second study compared topical retinoic acid 0.05% (RA) and fluocinolone acetonide 0.1% (FA) applied four times daily. Thirty-three patients with varied stages of oral lichen planus were alternately given RA (15) or FA (18); 56% of patients receiving FA improved, but only 13% of patients receiving RA improved. The extent of change was greater in the FA group as well.[11] Small doses of vitamin A acid locally applied produced improvement or regression in hypertrophic lichen planus of the palms or soles in a small number of patients.[12] Retinaldehyde gel 0.1% showed good clinical efficacy in 17 patients with oral lichen planus, resulting in 6% disappearance and 82% improvement of lesions, confirmed by the downregulation of filaggrin and CK-10 as markers of terminal differentiation.[13] In a trial of 7 patients with lichen planus of either the penis or anal region, application of 0.1% retinoic acid in Orabase overnight and 10 mg (33,330 IU) of oral retinoic acid three to four times daily for 3 days to 3 weeks resulted in improvement or resolution in all cases.[14]

In another study, 18 patients with mucosal dysplasia (10 leukoplakia, 4 lichen planus, 3 erythroplasia, 1 leukokeratosis) were evaluated for serum vitamin A, beta-carotene, and levels of cis-retinoic acid, which were low normal. All patients received beta-carotene 30 mg four times daily. Disease in 1 patient worsened, remained stable in 9, and improved in 8, with eventual complete resolution in 6 of those with improvement. Patients with stable disease were then treated with isotretinoin (Accutane 10 mg three times daily) in

conjunction with beta-carotene; 3 showed improvement. The response to treatment was much higher in smokers (30 packs per year or more) than in nonsmokers.[15]

Synthetic Retinoids

Following topical therapy with 0.1% 13-cis-retinoic acid for 8 weeks, a restoration of physiologic cell morphology was observed in a small group of patients with oral lichen planus.[16] Both 0.05% and 0.18% isotretinoin also appear to be effective in significantly improving atrophic-erosive oral lichen planus.[17]

Glycyrrhizin

Seventeen patients with oral lichen planus and hepatitis C were divided into two groups; 9 received intravenous glycyrrhizin and 8 were given information on dental hygiene. The treatment group received 40 mL of a 0.2% solution of glycyrrhizin daily for four consecutive weeks. Six of the nine treated patients demonstrated clinical improvement. The patients who responded tended to have only mildly raised serum alanine transaminase (ALT) and aspartate transaminase (AST).[18]

Aloe Vera

Thirty-four women with vulval lichen planus, with erosive and ulcerative lesions in 83% and 17%, respectively, were randomized into two groups to receive either topical aloe gel or placebo. Of 17 patients treated with *Aloe vera*, 14 (82%) improved clinically by at least 50% after 8 weeks of treatment, while 1 (5%) of 17 placebo-treated patients had a similar response (P <0.001). Neither group experienced side effects.[19]

Hyaluronic Acid

A total of 124 patients with erosive oral lichen planus participated in a randomized placebo-controlled double-blind trial to evaluate the efficacy of a topical 0.2% hyaluronic acid (HA) preparation for 28 days. Application of topical HA produced a significant reduction (P <0.05) in soreness scores compared with placebo for up to 4 hours postapplication; there was also a significant reduction (P <0.05) in the size of the erosive/ulcerated area after 28 days of treatment compared with baseline. Very frequent applications should be considered in order to obtain a more significant clinical benefit.[20]

Purslane

Twenty patients with oral lichen planus received 235 mg of purslane per day and 17 received placebo for 3 months. Approximately 83% of the purslane patients responded with partial or complete clinical improvement, compared with partial improvement in 17% of the placebo group. According to Visual Analog Scale (VAS) scores, a partial or complete response was observed in all purslane-treated patients, whereas 71% of the controls demonstrated partial responses (P <0.001).[21]



THERAPEUTIC APPROACH

If the lesions are oral and the patient has significant metal-based fillings, heavy metal detoxification and replacement of the metal fillings should be considered.

Topical Treatments

Apply four times a day

- Vitamin A (0.1% solution): May cause inflammation and mildly increase pain temporarily.
- Hyaluronic acid gel
- *Aloe vera* gel
- Glycyrrhizin: topical application

Oral Treatments

- Vitamin A: 33,330 IU three to four times a day for 3 days to 3 weeks while monitoring liver enzymes or beta-carotene 30 mg four times a day
- Purslane: 235 mg dried herb per day

Intravenous Treatment

- Glycyrrhizin: 40 mL of a 0.2% solution a day for 4 consecutive weeks.

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CHAPTER 187

Macular Degeneration

Michael T. Murray, ND

DIAGNOSTIC SUMMARY

- Progressive visual loss due to degeneration of the macula.
- Ophthalmologic examination may show spots of pigment near the macula and blurring of the macular borders.

GENERAL CONSIDERATIONS

The *macula*, the area of the retina where most images focus, is the portion of the eye responsible for fine vision. Degeneration of the macula is the leading cause of severe visual loss in the United States and Europe in persons 55 years and older and is second only to cataracts as a cause of decreased vision in persons older than 65 years. It is estimated that more than 150,000 Americans are legally blind from age-related macular degeneration (ARMD), with 20,000 new cases occurring each year.[1,2]

Types of Macular Degeneration

The two most common types of ARMD are the atrophic (dry) form, by far the more common, and the neovascular (wet) form. In either form, patients may experience blurred vision. The patient may note that straight objects appear distorted or bent; the presence of a dark spot near or around the center of the visual field; and, while reading, that parts of words are missing.

Dry Age-Related Macular Degeneration

Between 80% and 95% of people with ARMD have the dry form of the disease.

The primary lesions are atrophic changes in the retinal pigmented epithelium (RPE), which constitutes the innermost layer of the retina. Apparently, beginning in early life and continuing throughout life, cells of the RPE gradually accumulate sacs of cellular debris (lipofuscin). The lipofuscin bodies are either remnants of incompletely degraded abnormal molecules from damaged RPE cells or derivatives of phagocytized rod and cone membranes. Progressive engorgement of the RPE cells with lipofuscin is associated with the extrusion of tissue components like hyaline, sialomucin, and cerebroside. The hallmark excrescences beneath the RPE apparent on ophthalmoscopic examination are referred to as drusen. The formation of drusen is a result of free radical damage similar to the type of damage that induces cataracts (see Chapter 208). However, decreases in nutrient, blood, and oxygen supply to the retina are the harbinger of the development of drusen and subsequent macular degeneration.

The disease progresses slowly and only central vision is lost; peripheral vision remains intact. It is rare for anyone to become totally blind from dry ARMD. Currently, there is no standard medical treatment for this common form of ARMD, although the use of nutritional supplements designed to address the underlying oxidative damage is becoming the "unofficial" standard of care.

Wet Age-Related Macular Degeneration

Wet ARMD is also known as the neovascular form or advanced ARMD. It affects 5% to 20% of persons with ARMD. Wet ARMD is characterized by the growth of abnormal blood vessels. Because the disease can rapidly progress to a point at which surgery cannot be used, treatment should be performed as soon as possible. A common early symptom of wet ARMD is that straight lines appear wavy.

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Wet ARMD can be treated quite effectively in the early stages with laser photocoagulation therapy. Photodynamic therapy using photosensitive drugs (verteporfin) and a low-powered laser[3] or low-dose radiation therapy are also alternatives.[4] Antiangiogenics or anti–vascular endothelial growth factor (anti-VEGF) agents are also used. These drugs can cause regression of the abnormal blood vessels and improvement of vision when injected directly into the vitreous humor of the eye. The injections have to be repeated on a monthly or bimonthly basis. Examples of these agents include ranibizumab (Lucentis), bevacizumab (Avastin), and pegaptanib (Macugen).[1,2]



THERAPEUTIC CONSIDERATIONS

The primary treatment goal of the dry form and prevention of the wet form of ARMD involves the use of antioxidants and natural substances that correct the underlying pathophysiology—free radical damage and poor oxygenation of the macula. This can be accomplished by reducing the risk factors for ARMD by not smoking, focusing on preventive factors against atherosclerosis, increasing dietary intake of fresh fruits and vegetables, and supplementing with nutritional and botanical antioxidants.

In particular, tobacco smoking greatly increases the risk of ARMD.[5] Someone who smokes a pack of cigarettes a day for any significant length of time increases his or her risk for ARMD by two to three times that of someone who has never smoked.[5,6] This risk does not return to the control rate until after a person has stopped smoking for 15 years.[6]

There is also a strong genetic component to consider. Although a number of genetic markers have been identified, a family history may be the most convenient screening method. The lifetime risk of developing late-stage macular degeneration is 50% for people who have a relative with macular degeneration versus 12% for people who do not—a fourfold higher risk. Although genomic family scans of 364 families have revealed a region of chromosome 10 as possibly containing an association with ARMD,[7] diversity in phenotype and the late onset of disease complicate the feasibility of linkage studies. Interestingly, higher birth weight and lower head circumference/birth weight ratio are associated with significantly higher risk.[8]

Reducing and Preventing Atherosclerosis

Although atherosclerosis is now a well-accepted risk factor for macular degeneration, this association was unconfirmed until 1995.[9] In the confirmation study, 104 subjects with and 1324 subjects without macular degeneration were evaluated for atherosclerosis via ultrasonographic determination of the intimal-medial thickness, assessed for the presence of atherosclerotic plaque in the carotid arteries, and measured for the ankle/arm systolic blood pressure ratio (an indicator of peripheral atherosclerosis). The results indicated that in subjects younger than 85 years, plaques in the carotid bifurcation were associated with a 4.7 times higher prevalence of macular degeneration. Lower extremity atherosclerosis was associated with a 2.5 times greater risk. These results indicated that measures designed to reduce the risk of atherosclerosis are of great significance in the prevention and treatment of macular degeneration (see Chapter 148 for a comprehensive program for prevention and reversal).

Diet

A number of dietary factors are important. Not surprisingly, these mirror those dietary factors that prevent other chronic degenerative diseases, including atherosclerosis. A diet rich in fruits and vegetables is associated with a lower risk for ARMD. Presumably this protection is the result of a greater intake of antioxidant vitamins and minerals.[10-12] However, various "nonessential" food components—such as flavonoids and the non–provitamin A carotenes lutein, zeaxanthin, and lycopene—are proving to be even more significant in protecting against ARMD than traditional nutritional antioxidants (e.g., vitamins C and E, zinc, and selenium). The macula, especially its central portion, the fovea, owes its yellow color to its high concentration of lutein and zeaxanthin. These yellow carotenoids function in preventing oxidative damage to the area of the retina responsible for fine vision and obviously have a central role in protecting against the development of macular degeneration.[13,14]

The carotene lycopene, a component of tomatoes and other red fruits and vegetables, is also protective. In one study, individuals with lycopene content in the lowest quintile were twice as likely to have ARMD.[12]

Moderate wine consumption is also associated with a decreased risk of ARMD.[15] Red wine contains anthocyanins, powerful antioxidants that are probably responsible for the protective effect. It is important to note that beer consumption increased the accumulation of drusen and the risk of exudative macular disease[16] and therefore should be avoided.

Just as in atherosclerosis, the type of dietary fat appears to play a role in ARMD. A cohort study of 261 individuals with early or intermediate stages of ARMD revealed a twofold increased risk of progression with a high intake of animal fats and processed baked goods. In contrast, higher fish and nut intakes were associated with a lower risk of ARMD progression.[17] The intake of long-chain omega-3 fatty acids reduces the incidence of ARMD and was shown to be inversely associated with the 12-year progression to ARMD.[18–20]

Nutritional Supplements

In addition to recommending a diet high in antioxidants, supplementation with nutritional antioxidants (e.g., vitamin C, selenium, beta-carotene, and vitamin E) is certainly important in the treatment and prevention of macular degeneration. Studies conducted by the Age-Related Eye Disease Study (AREDS) research group confirm that a combination of these nutrients will likely produce better results than any single nutrient alone; moreover, other studies have shown that a deficiency of none of these antioxidants alone accounts for the impaired antioxidant status in ARMD.[21] Instead, the lower antioxidant status reflects decreases in a combination of nutrients.[10] The specific daily amounts of antioxidants and zinc used by the study researchers were 500 mg of vitamin C, 400 IU of vitamin E, 15 mg of beta-carotene (often labeled as equivalent to 25,000 IU of vitamin A), 80 mg of zinc as zinc oxide, and 2 mg of copper as cupric oxide.

In addition to the AREDS research, several studies using various commercially available broad-based antioxidant formulas have shown promising results. For example, a 1½-year study demonstrated that the progression of dry ARMD could be halted (but not reversed) with a broad-spectrum 14-component antioxidant capsule (Ocuguard).[22] A retrospective study of a nutritional supplement called ICAPS Plus (which contains beta-carotene, vitamins C and E, zinc, copper, manganese, selenium, and riboflavin) compared 38 patients who used the preparation regularly with 37 patients who used only one bottle and who served as controls. Of the treated patients, 15 showed improvement in their vision by one line or more on a vision acuity chart, compared with only 6 in the control group. In addition,

3 of the 38 in the treatment group lost one line or more of vision, compared with 13 in the control group.[23] In a second prospective blinded clinical trial reported in the same review, vision and contrast sensitivity were evaluated. After 6 months, visual acuity was the same or better in 36 of 61 controls compared with 168 of 192 treated patients.

B vitamins are also important. In a randomized double-blind placebo-controlled trial including 5442 female health care professionals 40 years of age and older, with preexisting cardiovascular disease or three or more cardiovascular disease risk factors, randomly received a combination of folic acid (2.5 mg/day), pyridoxine hydrochloride (50 mg/day), and cyanocobalamin (1 mg/day), or placebo. After an average of 7.3 years of treatment and follow-up, there were 55 cases of ARMD in the combination treatment group and 82 in the placebo group. For visually significant ARMD, there were 26 cases in the combination treatment group and 44 in the placebo group. These results indicate a 34% and 41% reduced relative risk, respectively.[24]

Lutein

In addition to a high-lutein diet, supplementation with additional lutein is of benefit. One 12-month double-blind study, the Lutein Antioxidant Supplementation Trial,[25] sought to determine whether nutritional supplementation with lutein or lutein together with antioxidants, vitamins, and minerals improved visual function and symptoms in atrophic ARMD.[25] Patients receiving lutein (10 mg) alone or in combination with other vitamins and minerals in a broad-spectrum supplementation formula showed improvements in mean eye macular pigment optical density, Snellen-equivalent visual acuity, and contrast sensitivity. Patients who received the placebo, however, showed no significant changes in any of the measured findings.

In a study using a very comprehensive formulation, 27 patients with nonadvanced ARMD and visual acuity at or equal to 0.2 logarithm of the minimum angle of resolution were enrolled and randomly divided into two age-similar groups: 15 patients had oral supplementation of vitamin C (180 mg), vitamin E (30 mg), zinc (22.5 mg), copper (1 mg), lutein (10 mg), zeaxanthin (1 mg), and astaxanthin (4 mg) daily for 12 months, while 12 patients had no dietary supplementation during the same period. Results indicated clearly, based on multifocal electroretinogram response amplitude densities and visual acuity assessments, that early-stage ARMD can respond positively with supplementation with carotenoids and antioxidants.[26]

See Chapter 69 for more information on lutein, zeaxanthin, and astaxanthin.

Zinc

Zinc plays an essential role in the metabolism of the retina, and the elderly are at high risk for zinc deficiency. In addition to the studies with a combination of nutrients, a 2-year prospective randomized double-blind placebo-controlled trial involving 151 subjects with dry ARMD demonstrated that the group taking 200 mg/day of zinc sulfate (approximately 80 mg of elemental zinc) had significantly less visual loss than the placebo group.[27] This initial report was one of the key prompts of the AREDS group to further evaluate whether antioxidant or zinc supplements delay age-related macular degeneration.

In another study using a zinc-monocysteine (ZMC) supplement, 40 subjects with ARMD were randomized to either ZMC 25 mg or placebo twice daily for 6 months. By the end of that time, the ZMC group showed improved visual acuity and contrast sensitivity. Macular light-flash recovery time shortened in the ZMC group at 3 months by 2.1 to 3.6 s and at 6 months by 7.2 s to 7.4 s. No improvement occurred in the placebo group. ZMC was well tolerated, with a gastrointestinal irritation rate of under 2%.[28]

It should be noted that a double-blind study in 112 patients with wet ARMD failed to show any benefit with zinc supplementation.[29]

Flavonoid-Rich Extracts

Flavonoid-rich extracts of bilberry *(Vaccinium myrtillus)*, *Ginkgo biloba*, or grape seed *(Vitis vinifera)* offer significant benefits in the prevention and treatment of ARMD. In addition to possessing excellent antioxidant activity, all three extracts have been shown to exert positive effects on retinal blood flow and function. Clinical studies in humans have demonstrated that all three are also capable of halting the progressive visual loss of dry ARMD and possibly even improving visual function.[30–33] Of the three extracts, bilberry extracts standardized to contain 25% anthocyanidins appear to be the most useful. The anthocyanosides of *V. myrtillus* have a very strong affinity for the retinal pigmented epithelium that constitutes the optical or functional portion of the retina, reinforcing the collagen structures of the retina and preventing free radical damage. Because the retinal pigmented epithelium is the portion of the eye affected in ARMD, *V. myrtillus* anthocyanosides appear to be ideal therapeutic agents for the disorder. However, the *G. biloba* extract with a 24% ginkgo flavoglycoside content is perhaps a better choice if the patient is also showing signs of cerebrovascular insufficiency. Grape seed extract may be the most useful in the patient with significant photophobia or poor night vision.

Exercise

Although exercise may not play a role in reversing or directly preventing ARMD, patients with visual impairment should consider strength and balance training in order to minimize the risk of falling.[18]

THERAPEUTIC APPROACH

As with most diseases, prevention or treatment of ARMD at an early stage is most effective. The treatment of the wet form is clearly laser photocoagulation applied as soon as possible. Because free radical damage and lack of blood and oxygen supply to the macula appear to be the primary causes of macular degeneration, the consumption of antioxidant supplements and promotion of retinal blood flow are the keys to effective treatment.

The use of nutritional supplementation in ARMD has undergone extensive cost/benefit analysis. Compared with no therapy, antioxidant therapy yielded a cost-effectiveness ratio of $21,387 per quality-adjusted life year (i.e, it lowered medical costs by $21,387 per quality-adjusted life year gained) and lowered the percentage of patients with ARMD who ever developed visual impairment in the better-seeing eye from 7.0% to 5.6%.[34]

Diet

Foods to avoid in ARMD are as follows:
- Fried and grilled foods and other sources of free radicals
- Animal fat
- Processed baked goods
- Beer

Foods to add to the diet of a patient with ARMD are as follows:
- Yellow vegetables, green vegetables, tomato products (carotenes)
- Flavonoid-rich berries (blueberries, blackberries, cherries, etc.)

- Fresh fruits and vegetables, nuts, and fish
- Moderate wine consumption (advisable in those without contraindications to alcoholic beverages)

Supplements

- Vitamin C: 500 to 1000 mg/day
- Vitamin E: 200 to 400 IU/day
- Selenium: 200 to 400 mcg/day
- Folic acid: 800 mcg/day
- Pyridoxine hydrochloride: 50 mg/day
- Vitamin B_{12}: 800 mcg/day
- Lutein: 10 to 15 mg/day
- Zeaxanthin: 1 to 2 mg/day
- Astaxanthin: 4 to 6 mg/day

Botanical Medicines

One of the following extracts should be chosen:
- *G. biloba* extract (24% ginkgo heterosides): 120 to 240 mg/day
- *V. myrtillus* (bilberry) extract (25% anthocyanidin content): 120 to 240 mg/day
- Grape seed extract (95% procyanidolic content): 150 to 300 mg/day

Exercise

Balance training and strength exercises, especially for patients who are visually impaired.

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CHAPTER 188

Menopause

Tori Hudson, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- Last spontaneous menstrual period 12 months prior.
- Average age at onset is 51 years.
- Symptoms can but do not necessarily include hot flashes, night sweats, palpitations, headaches, insomnia, mood swings, anxiety, vaginal dryness, urinary incontinence, rheumatism, fatigue, hair thinning, skin dryness, acne, facial hair, low libido, bladder infections, vaginal infections, nausea, mild cognitive changes, and irregular bleeding with perimenopause.

The baseline evaluation of the menopausal woman should consist of the following assessments:

- Detailed personal medical history, including an understanding of the chief complaint, review of other systems, medical history, past and present medications, family history, dietary habits and history, exercise habits and history, social history, occupation
- General physical examination.
- Breast examination.
- Pelvic examination.
- Laboratory tests to consider: complete blood count, blood chemistry panel, lipid panel with subfractions, thyroid function panel, FSH, homocysteine, C-reactive protein, estrogen metabolites.
- Screening mammography.
- Bone density testing.
- Cervical cytology (Pap smear or liquid-based technologies).
- Electrocardiogram.
- Colonoscopy.

Some of these tests are routinely performed either initially or on a yearly basis. Indications and frequency for other tests are determined by individual health history, disease risks, current health problems, and family history.

INTRODUCTION

Menopause denotes the cessation of menstruation in a woman, which usually occurs when she reaches the age of 51 years. Twelve months without a spontaneous period is the commonly accepted rule for diagnosing menopause. The time prior to menopause is referred to as *perimenopausal,* whereas the time after menopause is referred to as *postmenopausal*. During the perimenopausal period, women ovulate irregularly, infrequently, or not at all; therefore, they begin to experience changes in the menstrual cycle with or without other symptoms.

With the prolongation of life expectancy, the menopausal and postmenopausal periods are becoming more significant in a woman's life. In fact, today's average woman can expect to live at least one third of her life in the postmenopausal stage.

By the year 2015, nearly 50% of the women in the United States will be menopausal. Between 1990 and 2020, the menopausal population in the country will double. This dramatic rise in the number of menopausal women is changing the way health care providers work with women and changing medicine itself. At no other time in history have so many individuals been dealing with the same set of health issues. Now more than ever, clinicians have options for the management of menopause.

Current conventional medical treatment of menopause primarily involves short-term (1 to 4 years) hormonal therapy (HT) for the primary indication of moderate to severe vasomotor symptoms, using estrogen with or without a progestogen. The obvious question is "Is hormone replacement therapy necessary?" The goal of this chapter is to answer this question and offer an approach to perimenopause and menopause that provides many different options.

GENERAL CONSIDERATIONS

The goals of an integrative medicine approach to menopause are to provide relief from common menopausal symptoms and to prevent and/or treat osteoporosis, cardiovascular disease, and other diseases of aging while minimizing the risks of breast cancer, coronary heart disease (CHD), venous thromboembolism, strokes, and gallbladder disease. The evaluation process reveals a woman's perimenopausal/menopausal symptoms, other acute and chronic health problems, health habits, mental/emotional stressors, and risks for future diseases.

One of the most complicated and difficult health care decisions that menopausal women face today is whether to use HT. Women look to their health care providers for definitive answers to these questions. Practitioners are faced with an even greater challenge: evaluating the benefits and risks of conventional hormone therapy (cHT) and natural hormone therapy (nHT) for an individual patient.

In the year 2000, some 46 million prescriptions for conjugated estrogen (Premarin) were written in the United States. An additional 22.3 million prescriptions were written for the same preparation with medroxyprogesterone (PremPro). Almost one in three women given a prescription for cHT never has it filled. Of those who do start cHT, the majority discontinue its use shortly after starting therapy. Reasons given for discontinuing the drug include uterine bleeding; side effects including mood changes, breast tenderness, bloating, and weight gain; a fear of breast cancer; and not understanding or believing in the need for its long-term use. Lack of compliance can also be attributed to inadequate education of many health care practitioners regarding the needs of menopausal women, both gynecologic and nongynecologic. Many practitioners also have a limited understanding of the many therapeutic options for menopausal symptoms and of the more global issues of menopause. In addition, holistic menopause practitioners who use both cHT and nHT hold that compliance improves with the use of nHT and that many side effects disappear or improve when patients switch from cHT to nHT.

Sadly, many menopausal women have a limited understanding of the long-term health risks associated with this change in hormone status, and very few women believe that they are well informed about the benefits and risks of cHT or nHT. Each woman wants to know whether HT is right for her—how she may benefit, how long she will have to take the drug to receive those benefits, and what the short-term side effects as well as the potential long-term negative effects are.

Scientific evidence regarding the use of postmenopausal HT comes in many shapes: observational studies, large-scale randomized trials, small clinical trials, biological plausibility, in vitro studies, and animal studies. Other factors involved in the hormone conundrum are theoretical questions, areas of scientific uncertainty, popular consumer opinions and fears, and history. Definitive evidence for the benefits and risks of HT has been clarified by the two Heart and Estrogen/Progestin Replacement Studies (HERS I and HERS II) and the Women's Health Initiative (WHI). Another large-scale trial conducted in 14 countries, the Women's International Study of Long Duration Oestrogen after Menopause (WISDOM), was discontinued in November 2004 for scientific and practical reasons. Because WISDOM was to be completed after the publication of WHI results, "there were no safety concerns for the 5700 women enrolled in the study. However, the trial was not expected to provide substantial evidence that would have an impact on clinical practice decisions in the next 10 years."[1]

The North American Menopause Society has a very comprehensive position statement, last updated in 2010.[2] In summary, this document says that although there are many benefits (with regard to vasomotor symptoms, urogenital atrophy, urinary health, osteoporosis, and reduction in the onset of type 2 diabetes mellitus), there are also slight statistical risks (of breast cancer, stroke, venous thromboembolism, and ovarian cancer). A still unfolding picture focuses on cardiovascular disease, cognitive decline, and dementia.

The bottom line is that women and their health care practitioners are faced with trying to make the best decisions possible on the basis of what we do know, what we do not know, and what we are still uncertain about.

Benefits

Symptoms

The decline of endogenous estrogen leads to multiple tissue and organ changes and problems. In addition to the reproductive and urinary tracts, estrogen-sensitive tissues are skin, bone, vascular lining, teeth and gums, eyes, the brain, and the central nervous system.

Some 50% to 80% of women in the United States report menopause-related hot flashes, night sweats, vaginal dryness, insomnia, mood swings, and depression. During the first 5 to 10 years of menopause, vulvovaginal symptoms begin to appear. Later, as the other mucous membranes of the urogenital tract become affected, rates of incontinence and infection rise.

There is strong evidence and data from randomized clinical trials that estrogen therapy is very effective in controlling vasomotor and genitourinary symptoms. Vaginal estrogen is as efficacious as oral or transdermal estrogen for genitourinary symptoms and may be an advantageous method because of the local delivery and effect.

Sex steroids also affect sleep, libido, cognitive function, motor coordination, and pain sensitivity. Data are mixed regarding the role of menopause in depression and mood swings; however, depression and mood disorders appear to be more common or at least exacerbated in perimenopause or early menopause compared with the reproductive period, and HT benefits many women.

The North American Menopause Society and its advisory panel published a post-WHI report and recommendations on postmenopausal HT. One of its basic recommendations is that the treatment of menopausal symptoms (especially vasomotor and urogenital) remains the primary indication for HT or estrogen replacement therapy (ERT).

Osteoporosis

Estrogen is known to inhibit the age-related bone loss that occurs in most menopausal women. Observational studies have indicated that the use of estrogen reduces the risk of vertebral fracture by approximately 50% and the risk of hip fracture by 25% to 30%.[3] Estrogen has been considered the therapeutic agent of choice for both the prevention and treatment of postmenopausal osteoporosis in women for many years—until the WHI results. It has been

the most studied agent for prevention and has been shown to decrease bone resorption, prevent osteoporosis, and reduce fractures. Nevertheless, the U.S. Food and Drug Administration (FDA) has removed estrogen from the list of agents approved as effective in treating women who already have osteoporosis. This decision has nothing to do with any new discovery of a decrease in effectiveness for this indication; rather, it arose as an issue of fairness in new standards that have been applied to approving other drugs for osteoporosis treatment, such as the bisphosphonates (risedronate and alendronate). These agents have involved prospective fracture reduction studies on women with low bone mass and/or fracture. The data on estrogen treatment for existing osteoporosis are largely observational and retrospective in nature. These studies do demonstrate the efficacy of estrogen in treating patients with osteoporosis, but randomized clinical trials will be required before the FDA reinstates its indication.[4]

That being said, the WHI was a large clinical trial in which 16,608 postmenopausal women 50 to 79 years of age were studied at 40 U.S. clinical centers.[5] The regimen used, was continuous combined estrogen-progestogen therapy (CCEPT) (e.g., PremPro). Women in the CCEPT group experienced lower rates of hip fracture (10 per 10,000 person-years vs 15 per 10,000 person-years in the placebo group, a 34% lower relative risk) and vertebral fracture (9 events per 10,000 women annually vs 15 events per 10,000 women annually for placebo, also a 34% lower relative risk). Statistically significant fracture reductions were also seen in other osteoporotic fractures (23%) and total fractures (24%).

The different estrogen agents approved for the prevention of osteoporosis and their antiresorptive effects are as follows:

- Oral micronized estradiol, 1.0 mg/day
- Conjugated equine estrogens (CEE), 0.625 mg/day
- Ethinyl estradiol, 5 mcg/day
- Transdermal estradiol, 50 mcg/day
- Esterified estrogen, 0.3 mg/day

It is important to keep in mind that some women derive benefits from these doses, some will need higher doses, and others will have adequate bone protection with lower doses. Dual-energy x-ray absorptiometry (DEXA) scans provide the most reliable objective information on the status of bone mineral density.

Colorectal Cancer

Accumulated observational studies now suggest that the use of ERT reduces the risk for colorectal cancer as well as the risk of dying from colon cancer.[6] Although not all study findings are consistent, some studies have shown that the risk of developing fatal colon cancer was reduced by 33%[7]; others show as little as an 8% reduction in risk.[8]

Risks

Endometrial Cancer

Unopposed estrogen administration is associated with an increase in the risk of endometrial cancer by a factor of 8 to 10. This results in an excess of 46 cases per 10,000 women for women who use unopposed estrogen for at least 10 years.[9] The risk decreases after discontinuation of the ERT, but it is still elevated after more than 10 years. Adding a proved dose and delivery method of a progestogen (progestins or progesterone), which opposes the effects of estrogen on the endometrium, reduces the risk to a minimum and is essential to preventing endometrial hyperplasia and endometrial cancer.

A boon to the use of natural hormones, particularly oral micronized progesterone (OMP), came in the form of the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial and its study of the effects of HT on endometrial histology in postmenopausal women.[10] This trial confirmed that daily CEE, 0.625 mg, enhanced the development of endometrial hyperplasia, and that combining CEE with cyclic or continuous medroxyprogesterone acetate (MPA) protected the endometrium from hyperplastic changes. What was new was that the trial also concluded that cyclic OMP (200 mg daily for 12 days per month) also protected the endometrium from the hyperplastic changes associated with estrogen-only therapy. Thus, the PEPI was the first clinical trial proving that OMP was as appropriate as MPA for use in the protection of the endometrium. Compounded OMP was already available, but the product Prometrium came on to the market as a result of that study.

Venous Thromboembolism

Venous thromboembolism (VTE) is an almost expected complication of the postmenopausal use of exogenous hormones. Observational studies have demonstrated that in postmenopausal women who use ERT, the risk of VTE is increased by a factor of 2 to 3.5. These observations are consistent with the data found in HERS I (discussed later). The investigators reported that the risk of thromboembolic events was increased by a factor of 2.7 in the women receiving the estrogen-progestin therapy.[7] HERS II showed that the relative risk (RR) of VTE increased 108% (RR 2.08) and the absolute risk was 0.59% in the HT group compared with 0.29% in the placebo group (59 events vs. 28 events annually per 10,000 women, respectively).[11]

The WHI reported similar results. The relative risk was 2.11 in the HT group, a 111% increased risk. The absolute risk was 34 events in the HT group compared with 16 events in the placebo group per 10,000 women.[7] Owing to the uncommon presence of idiopathic venous thromboembolism in women above 50 years of age, the absolute risk associated with postmenopausal HT is pretty small. For women who are already at risk for thromboembolism or who are older, the absolute risks of HT will be higher.

Coronary Heart Disease

For the past 30 years, practitioners have been advising menopausal women that HT reduces the risk of CHD. More than 40 observational studies in these past three decades have suggested that this risk is 35% to 50% lower among women who take estrogen than in women who do not.[12,13] These observational data have been reinforced by additional research demonstrating some of the impact of estrogen on individual factors known to be associated with CHD, thereby also establishing a biologically plausible mechanism for the association of HT and reduced CHD. Randomized trials have shown that estrogen therapy reduces plasma levels of low-density-lipoprotein cholesterol (LDL-C) by 10% to 14% and raises plasma levels of high-density-lipoprotein cholesterol (HDL-C) by 7% to 8%.[7,14] Estrogen has also been shown to reduce Lp(a) lipoprotein, inhibit oxidation of LDL-C, improve the endothelial vascular function, reduce fibrinogen, and reduce thickening in the arterial walls.

However, estrogen may have detrimental effects on cardiovascular risk markers, as by raising triglyceride levels, increasing clotting, and raising levels of C-reactive protein. These detrimental effects of estrogen may override the beneficial effects of estrogen on cardiovascular function and may explain the surprising results of randomized, placebo-controlled trials indicating that HT did not reduce the overall rate of CHD. In HERS II and the WHI, it actually increased the rate of CHD. These new data from randomized trials, compared with the 30 years of observational data and

the biologically plausible mechanisms, have rendered recommendations to postmenopausal women about HT more complex and challenging. Both patients and practitioners have questions with no clear-cut answers, and concerns about the benefits and risks of HT are more difficult to sort out.

Heart disease is the leading cause of morbidity and mortality in women, and an understanding of the current state of the evidence and the potential for the cardioprotective effects of HT, as well as the cardiovascular negative effects of HT, is of vital importance to women's health. In this discussion, however, one must not forget the potential cardioprotective effects of nutrition, exercise, stress management, and select nutrients such as niacin, magnesium, and fish oils.

The basic problem with HT and CHD is that the later randomized trials of estrogen among women with preexisting CHD have not confirmed the 40 observational studies of the last 30 years. The first large-scale randomized double-blind placebo-controlled trial of HT (a combination of CEEs [Premarin] and CEEs with medroxyprogesterone acetate [Provera]) for the secondary prevention of CHD was the Heart and Estrogen/Progestin Replacement Study (HERS I).[7] In a total of 2763 women with established CHD studied at 20 clinical centers throughout the United States, the death rates from coronary causes and nonfatal myocardial infarctions in the hormone group and the placebo group were similar. Perhaps more worrisome was the 50% increase in the risk of CHD events (thromboembolism) during the first year in the women receiving HT. The HERS I data prompted a barrage of questions, as follows:

- Are the HERS data simply wrong?
- Does one clinical trial outweigh the vast array of observational studies?
- Is the pattern of early risk real, and if so, what caused it?
- Is the early risk related to some other factor present in a subgroup of women but not others?
- Were the results related to the hormone regimen used?
- Would the results be different with a natural estradiol and/or a natural progesterone?
- Did the MPA counteract the potential beneficial effects of estrogen?
- Do these HERS I results for secondary prevention have implications for questioning HT's role in primary prevention?

A brief attempt at some answers was made after HERS I: The early risk for increased CHD events in the hormone-treated group has been a pattern seen in subsequent studies—the Puget Sound Group Health Cooperative of Seattle,[15] the Nurses' Health Study,[16] and the early data from WHI.[17] An early risk for blood clots in the legs and lungs, heart attack, and stroke appears to be a real phenomenon in postmenopausal women who begin HT. Two hypotheses to explain this finding are that estrogen has a prothrombotic effect and a proinflammatory effect on the vascular endothelium.

There indeed may be some subgroup of women with a predisposition for the prothrombotic and/or proinflammatory effects of estrogen—for example, women with hyperinsulinemia, hypertension, elevated homocysteine levels, increased C-reactive protein and Lp(a) lipoprotein levels, obesity, and/or elevated LDL-C. Interestingly, in the HERS I trial, differences were observed between hormone-treated women who also took lipid-lowering therapy (statins) and hormone-treated women who did not. The rate of CHD events after 1 year was much lower in the HT-plus-statin group than in those who did not use statins. The same was true for risk of venous thromboembolic events.

Another controlled trial attempted to address the question of whether estrogen inhibits atherosclerosis. In the placebo-controlled Estrogen Replacement and Atherosclerosis (ERA) trial, neither estrogen alone nor estrogen plus the progestin[18] affected the progression of coronary atherosclerosis. Plasma levels of LDL-C were reduced by 9.4% in the unopposed estrogen group and by 16.5% in the estrogen-plus-MPA group. Both groups had significant increases in HDL-C (18.8% and 14.2%, respectively) compared with the placebo group. The two estrogen groups had rises in triglyceride levels (6.1% and 10.1%, respectively), but these changes were not significantly different from the levels in the placebo group. The ERA trial provided the first anatomic endpoint (angiographically determined effects on coronary arteries) in women who had known CAD. The ERA trial supported the overall null effect found by the HERS I trial and also showed that the MPA did not cancel out the beneficial effects of estrogen, as was suspected in the HERS I trial. These data and other study results indicate that HT does not have a significant impact on the progression of atherosclerosis in women with established heart disease.

Preliminary data from the Papworth Hormone-Replacement Therapy Atherosclerosis Study (PHASE), a small clinical trial in 225 postmenopausal women with angiographically proved CAD, showed no cardiovascular benefits of HT and also possibly a slight increase in the rates of cardiovascular events during the first 2 years of HT.[19] This trial evaluated transdermal natural estradiol alone or with norethindrone, a different progestin.

An interim analysis of the WHI data also suggested that there had been a slight increase in the number of heart attacks, strokes, and thromboembolic events during the first 1 or 2 years in postmenopausal women undergoing HT.[20]

One clinical trial looked at estrogen use in postmenopausal women without clinical coronary disease. The Estrogen in the Prevention of Atherosclerosis Trial (EPAT) was designed to determine whether unopposed natural estradiol reduces the progression of subclinical atherosclerosis.[21] Postmenopausal women with high cholesterol levels but no preexisting cardiovascular disease, diabetes, or smoking history received either oral micronized natural estradiol or placebo and also lipid-lowering medication if serum LDL-C exceeded 160 mg/dL. The women were monitored for 2 years. The investigators evaluated the rate of change in carotid artery intimal-medial thickness. Women in the placebo group had an expected progression in the thickening of the carotid arteries over the 2 years. The women taking estradiol had a small amount of regression of the thickness of the carotid arteries. In women not receiving lipid-lowering therapy, the placebo group had a greater progression and the estradiol group had no progression of intimal-medial thickness—a dramatic difference. Curiously, in the women who received lipid-lowering drugs, there was no difference in the rate of progression between the women receiving estrogen and those receiving placebo.

On the basis of data from these randomized clinical trials conducted before HERS II and WHI, HT did not appear to reduce the risk of cardiovascular events in postmenopausal women who already had CHD. Then along came the world-shifting news in July 2002, when the results of HERS II and the WHI were published less than a week apart.

HERS II investigated the effects of 0.625 mg of CEE plus 2.5 mg of MPA on the prevention of CHD in older U.S. women (average age 71 years) with preexisting CHD.[11] This study, a continuation of HERS I, was intended to determine whether a trend toward prevention of heart disease would appear if the study were continued longer. Once again, though, the results were not positive for women with heart disease. In HERS II there were no significant decreases in rates of primary CHD events (or strokes or clots) among women assigned to the HT treatment group who

had already had CHD before starting the HT regimen (RR, 1% decreased risk and absolute risk of 3.66% for HT vs. 3.68% for placebo). The investigators concluded that "postmenopausal hormone replacement therapy should not be used to reduce the risk of CHD events in women who already have CHD."[11]

A few days later, results of the landmark WHI study were published.[5] The WHI investigated the effect of the most common HT regimen in the United States (0.625 mg Premarin plus 2.5 mg Provera, or PremPro) on the incidence of heart disease, breast and colorectal cancers, and fractures in postmenopausal women. The cardiovascular research was intended to investigate the effect of this HT regimen on the prevention of CHD in healthy postmenopausal U.S. women (aged 50 to 79 years) who do not have CHD. After a mean of 5.2 years of follow-up, the trial was stopped earlier than planned for the women using combined HT (mostly owing to harm from breast cancer incidence). In the WHI, there was a significantly higher risk of CHD annually per 10,000 women: a 29% increase in the relative risk and 37 more events in the HT group compared with 30 events in the placebo group. These findings, showing that estrogen plus progestin does not confer benefit in preventing CHD among women with a uterus, concurs with the HERS findings among women with clinical CHD as well as those of the ERA trial and others. The WHI results extend the findings of the earlier trials to include a wider range of women.

Stroke

In the WHI, there was no excess risk of stroke in the estrogen-plus-progestin group in the first year, but such a risk did appear in the second year, and it persisted.[22] The mechanism does not seem to be related to an increase in blood pressure. The WHI findings were consistent but more dramatic than those of the HERS, which reported a nonsignificant 23% increase in the treatment group.[11] WHI results were also more extreme than those of the Women's Estrogen for Stroke Trial (WEST) of estradiol (without progestin) in women with a history of a prior stroke. Overall, the WEST trial found no effect of estrogen on recurrent strokes but some rise in rates in the first 6 months.[23] Some might criticize the WHI statistics because they include older women. However, there was no indication that excess strokes were more likely to occur in older women, in women with prior stroke, through differences in race/ethnicity, or in women with high blood pressure. It is apparent that estrogen plus a progestin increases the risk of stroke in women who have been judged to be healthy. The estrogen-only arm of the WHI showed a slight increase in stroke for women in the youngest age group at study entry.[24] The ERT arm was quite different from the HT arm.

One of the most recent studies on estrogen leads us to the most provocative question: Do different kinds of estrogens have different effects? In this study, the risk of VTE was compared among those who used esterified estrogen, conjugated equine estrogen, and no estrogen at all.[25] The findings concluded that CEE but not esterified estrogen was associated with venous thrombotic risk.

Gallstones

The risk of gallstones or cholecystectomy appears to be raised by a factor of 2 to 3 in postmenopausal women who are taking ERT. This finding has been reported by several large observational studies. In HERS I, the women taking estrogen plus progestin were at a 38% higher risk of gallbladder disease than women who were taking placebo.[7] HERS II found similar results, reporting a higher incidence of biliary tract surgery, with a 48% increased relative risk for those in the HT group and an absolute risk of 191 versus 129 events annually per 10,000 women.[26]

Areas of Uncertainty

Breast Cancer. Fears about breast cancer and higher risk of breast cancer from HT dominate many women's decision-making process about menopause management. Clinicians must be educated about this topic and must be prepared to summarize the results of relevant research in order to counsel each woman about the benefits and risks in her particular situation.

It is true that there are unanswered questions about the long-term safety of HT, especially regarding the risk of breast cancer. What is often forgotten is that the clinical trials data on ERT span the last 100 years. No other pharmacologic agent has been as thoroughly studied as estrogen. A half-century of research preceded the early 1940s, when HT became commercially available. Even though patient fears are high and alternative practitioners are particularly suspicious and skeptical about its safety, no data clearly and consistently demonstrate a higher risk of breast cancer associated with HT. Nevertheless, many patients and practitioners continue to be certain that taking HT will cause breast cancer.

Close to 60 observational studies of the association between HT and breast cancer have been published during the past 25 years, and no definitive answer exists because of inconsistency in the results of those studies. One analysis (prior to the WHI) of the evidence in those studies found that more than half of them reported either no difference in risk or a decrease in risk of breast cancer with ERT/HT use.[27] The remainder of the studies reported only slight rises in breast cancer risk. Another group of researchers attempted to reanalyze more than 90% of the published data on breast cancer and HT use.[28] They reported that postmenopausal women who had ever used HT had a small but statistically significant increase in risk for breast cancer compared with women who had never used HT. In women who were currently using HT or had recently used it, the relative risk rose by a factor of 1.02 to 1.04 for each year of use. After HT had been discontinued for 5 years, no significant excess risk remained. Also, breast cancers diagnosed in women who had used HT tended to be less advanced and were more localized.

Later reports from observational studies are also inconsistent. The report from the National Cancer Institute's Breast Cancer Detection Demonstration Project was published in January 2000.[29] These findings showed that the risk associated with recent HT use (both current use and use within the previous 4 years) was twice that associated with ERT. However, the relative risk for recent use of ERT was not statistically significant, and the difference between risks with ERT and HT was not tested for statistical significance. Right after that report was published, another group of investigators published and reported higher risk estimates for sequential HT regimens for 5 years or more of use than for continuous combined HT, although the difference was not statistically significant.[30] In contrast to previous reports, this study found no difference in risk between current and past users.

At the end of 2000, the Nurses' Health Study published its estimates of breast cancer risk associated with HT in postmenopausal women.[31] The results were expressed as percentage increases in the cumulative risk of breast cancer and were frightening to many: The use of estrogen alone for 10 years was found to lead to a 23% increase by age 70 years, and the use of estrogen plus progestin for 10 years to a 67% increase by age 70 years. It is important for clinicians to realize (1) that the result is not an actual mathematical conclusion but the conclusion of the model—the consequences of a small difference in risk at the beginning that then is magnified as the math is carried out into the future—and (2) that risk estimates represent a projection, not an actual measurement.

One of the most disturbing reviews was published in 1998. Colditz[32] summarized the evidence that endogenous estrogen and ERT not only increase the risk but are causally related to breast cancer. In his review of hormones and breast cancer, he included reports on cell proliferation and endogenous hormone levels as well as epidemiologic studies of the relationship between the use of postmenopausal hormones and the risk of breast cancer. He found evidence of a causal relationship between female hormones and breast cancer based on consistency, dose-response pattern, biological plausibility, temporality, strength of association, and coherence. He stated that the magnitude of the increase in breast cancer risk per year of hormone use is comparable with that associated with delaying menopause by a year. The fact that women who menstruate longer have a higher risk of breast cancer also provides support for a biological mechanism for the relationship between the use of exogenous hormones and increased risk. Colditz concluded that existing evidence supports a causal relationship between use of estrogens and progestins, levels of endogenous estrogens, and breast cancer incidence in postmenopausal women.

The WHI was the first randomized controlled trial confirming that conjugated equine estrogens combined with progestins do increase the incidence of breast cancer and the first to quantify the increase. The 26% higher risk of breast cancer occurred after about 4 years and translated to 8 more cases annually per 10,000 women.[5] This is consistent with other epidemiologic data. The study was discontinued primarily because of the breast cancer incidence, which crossed the monitoring boundary for safety.

At the other end of the pendulum, investigations that have found no increased risk of breast cancer with HT or ERT use receive much less attention. The Iowa Women's Health Study is prospectively following a cohort of women who were selected in 1985.[33] After 6 years of monitoring, a statistically significant increase in the risk of breast cancer could not be detected in women who either had ever used or were currently using HT. Another report through 8 years of follow-up examined whether postmenopausal HT raised the risks for breast cancer and death from cancer in women with a family history of breast cancer.[34] There was no significant increase in the rate of breast cancer even in women who had a family history of breast cancer and had been using HT longer than 5 years. These results are consistent with those of other reports that there is no additional risk in using HT/ERT for women who have a first-degree relative with breast cancer. My main criticism of these kinds of reports is that use of the words *no significant increase* is disturbing in that even a single additional case of breast cancer is significant. With a current incidence of one in nine, one more woman with breast cancer is one too many.

The latest analysis from the Iowa Women's Health Study, an 11-year follow-up, showed an association between women who had ever used postmenopausal HT and the risk of breast cancers that were more localized and had a better prognosis.[35] The researchers did not find an increased risk of invasive ductal or lobular carcinoma in women who had used HT either less than or more than 5 years. A slight increase in risk was observed in current users and users for less than 5 years; current users with more than 5 years of use had no increase in risk. These results are the opposite of those seen in the Nurses' Health Study, that women who use HT for more than 5 years have a higher risk.[36] Two other studies, the Carolina Breast Cancer Study[37] and analyses from the National Health and Nutrition Examination Survey (NHANES),[38] found no increase in risk with postmenopausal hormones. These later studies perpetuate the inconsistency in research on this issue that has been seen in the last 25 years. This pattern provides some logic to the point of view that if there is an increased risk of breast cancer associated with ERT/HT, the risk must be small, because by now, after so many years, we would have seen more consistency in the data, and the size of the risk estimates would be large rather than slight.

It is to be hoped that, in consultations with patients, clinicians can offer a balanced view, reassuring them that no studies find an increased risk of breast cancer with short-term use of HT and that the conflicting, inconsistent results of more than 60 studies shows that if there is an increased risk with long-term use, it is a small one. We can evaluate the benefits and risks for each patient and make our recommendations on a short-term basis, which can help each individual to make decisions that are not necessarily permanent. Research in this area of medicine is prolific, and if we keep up to date on the latest findings, we can inform our patients so that they can make informed, timely choices about their health care.

Cognitive Function. Observational studies have suggested that there is a relationship between endogenous estrogen exposure and cognition.[39] A number of other observational reports have demonstrated that HT use may prevent or delay the onset or progression of Alzheimer's disease, but additional observational results have been conflicting.[40] A meta-analysis and systematic review was conducted in March of 2001 in which 29 studies were rated.[41] In women who were symptomatic from menopause, postmenopausal use of estrogen improved verbal memory, vigilance, reasoning, and motor speed. There were no consistent effects on visual recall, working memory, complex attention, mental tracking, mental status, or verbal functions. Estrogen did not appear to enhance asymptomatic women's performance consistently on formal cognitive testing. The meta-analysis did suggest that HT was associated with a lower risk of dementia, but the reviewers acknowledged that the studies analyzed had important methodology problems and information was inadequate to allow proper assessment of the effects of various estrogen preparations or doses, progestin use, and duration of use.

Studies in animals and the laboratory suggest plausible mechanisms for the potential of estrogen and the prevention and/or treatment of Alzheimer's disease. Estrogen increases dendritic spine growth, axonal elongation, synapse formation, and neuronal survival. It also influences several neurotransmitters including acetylcholine, modulates nerve growth factor, increases apolipoprotein E, enhances blood flow, serves as an antioxidant, and enhances the uptake and metabolism of glucose. All of these effects could possibly inhibit the neurotoxicity of beta-amyloid and the damaging effects of free radicals, moderate the inflammatory events involved in plaque formation in the brain, enhance cerebral blood flow, and facilitate neuronal repair after brain injury.

Results of randomized trials of ERT and Alzheimer's disease and the potential of estrogen for the treatment of this disorder have not been impressive in terms of benefits. In one study, estrogen replacement for 1 year did not slow disease progression or improve global, cognitive, or functional outcomes in women with mild to moderate Alzheimer's disease.[42] In another, participants at 10 of the 20 HERS centers were enrolled in the cognitive function substudy. The mean age of participants at the time of cognitive function testings was 71 ± 6 years. Among these older women with CAD, 4 years of treatment with conjugated equine estrogens plus progestins did not result in better cognitive function as measured on six different standardized tests.[43]

In the latest prospective study of dementia, prior use of HT was associated with reduced risk of Alzheimer's disease, but duration

of use very specifically affected the benefit; there was no apparent benefit from current use of HT unless the use exceeded 10 years.[44]

Ovarian Cancer. Evidence concerning a possible positive association between HT use and ovarian cancer risk is less consistent and of lesser significance than that for endometrial and breast cancers. Most of the data show a weak positive association. A large prospective cohort (observational) U.S. study of 211,581 postmenopausal women treated for longer than 10 years with conventional HT was associated with an increased risk of ovarian cancer.[45] No distinction was made regarding type or regimen of HT or whether a progestogen was added to the ERT. Participants had no history of cancer, hysterectomy, or ovarian surgery. The study, monitoring women from 1982 to 1996, showed that women who were using HT at study entry had higher death rates from ovarian cancer than women who had never used HT. Risk was slightly but not significantly higher among former estrogen users. Women who used HT at baseline and for 10 years or more had a relative risk of 2.20, and former users with at least 10 years of use had a relative risk of 1.59. The annual age-adjusted cancer death rates from ovarian cancer per 100,000 women were 64.4 for baseline HT users with 10 or more years of use, 38.3 for former users with 10 or more years of use, and 26.4 for women who had never used HT.

In this observational study, as in the Nurses' Health Study, the lack of information is almost more disturbing than the actual information. We have no data as to the type, dose, or combination of estrogen and progestogen used by the participants. As a result, many assumptions were made that influenced data analysis and the effect on relative risk. We know that the way in which hormones have been prescribed has changed from 1982 through 1996 and since then. In the early 1980s, most women were prescribed unopposed daily estrogen. During the 1980s, sequential estrogen plus progestogen therapy was introduced to eliminate the increased risk of endometrial cancer. Most women began to take 7 to 10 days of progestogen per month along with their estrogen. In the 1990s, common prescribing habits involved continuous and combined estrogen/progestogen regimens and lower doses of both hormones. Whether sequential or cyclic, progestogen is generally prescribed for at least 12 days per month. The number of different estrogens and progestogens has also significantly expanded and changed since the early 1980s and even in the last few years.

The investigators also reported on relative risk. Given the low incidence of ovarian cancer, even if there is a significant increase in relative risk, it may not have much of an impact on absolute risk. Although this study shows a doubling of the relative risk, the incidence of ovarian cancer mortality in postmenopausal women is extremely low, at 1.6%. It is also interesting to remember that 7 years or more of oral contraceptive use in reproductive-age women actually lowers the incidence of ovarian cancer.

A large, prospective study reported a significant twofold higher risk of ovarian cancer among long-term users of HT and ERT.[46] A total of 44,241 postmenopausal women were selected from the Breast Cancer Detection Demonstration Project (BCDDP); 329 women who experienced ovarian cancer were identified. Women who used estrogen-only replacement therapy, especially for more than 10 years, were at significantly higher risk of ovarian cancer, with a relative risk of 1.8; women who used estrogen only for 20 or more years had a relative risk of 3.2. The good news was that women who used short-term combination replacement therapy were not at increased risk.

Focus on Estrogen Only

The WHI originally had three components: HT, a low-fat dietary modification, and supplementation with calcium and vitamin D. In addition, many of the women who did not qualify for the active treatments of the WHI became part of an observational group that was studied. Both arms of the placebo-controlled HT component (estrogen plus progestin [HT] and estrogen only [ERT]) were terminated before the planned ending date. The ERT arm of the WHI was halted on March 1, 2004, after 6.8 years of follow-up and less than a year before the planned closing date.[24] The ERT arm was quite different from the HT arm in that the risks in the ERT arm did not exceed the benefits. The study showed a slightly increased risk of stroke, a decreased risk of hip fracture, a lack of increase in the risk of breast cancer and a possible reduction in breast cancer risk, and no effect on the incidence of CHD.

The key clinically relevant issues from the WHI ERT study are as follows:

- CHD was reduced by almost half in the youngest age group (the most common age group of women who initiate ERT).
- The risk of stroke increased only slightly for women in the youngest study-entrance age group.
- The risk of VTE was increased in all three age groups, but the degree of risk increased with age at study entry.
- The risk of invasive breast cancer was reduced in all three age groups.
- The risk of colorectal cancer was decreased in the two younger groups, especially in women aged 50 to 59; it was increased in women aged 70 and older.
- The overall reduction in risk of fracture was most evident in younger women.
- ERT was associated with a lower death rate in the group that was youngest at study entrance.

The middle age group had about the same death rate in both the ERT and placebo groups, and there was a slightly higher death rate in the oldest age group.

What the WHI ERT study basically showed is that ERT, using CEE, is safe for most menopausal women who do not have a uterus. ERT reduced the risk of CHD in those women who started ERT near the age of menopause, it decreased the risk of fractures, it did not increase the risk of breast cancer, the risk of colorectal cancer was increased in women who started therapy at age 70 or older, and ERT was associated with a slight increase in the risk of stroke and VTE but there was no increase in death rates.

It would appear that use of ERT alone by women without a uterus is safer than using estrogen plus a progestin.

Natural Hormones

It is important to understand that most of the research on hormone regimens is on CEEs and MPA. However, that is not exclusively the case, and certainly some of the cardiovascular research has equally implicated 17-beta-estradiol (bioidentical estradiol). Nonetheless, in the most damaging data to date, from HERS I and II and the WHI, the hormones used were the equine estrogens and progestin. So, what we definitely know to be negative effects are associated with those regimens, and we do not in fact know whether the data can be applied to other regimens. It would be naive to dismiss the data and not to admit the possibility that the results would be the same. When hormones are determined to be appropriate or even necessary, however, it would at the very least seem logical to use the hormones we know not to be those with adverse effects.

Natural compounded estrogens and natural compounded progesterone, as well as natural testosterone and dehydroepiandrosterone (DHEA), such as those used by compounding natural pharmacies and the natural progesterone creams sold over the counter, are distinct and different in several critical ways from

CEEs, conjugated plant estrogens, synthetic estrogens, and synthetic progestins. Natural hormones are made from either beta-sitosterol extracted from the soybean or from diosgenin extracted from Mexican wild yam root. Those compounds are then made into the desired hormone and are biochemically identical to the hormone the body produces. By definition, a natural hormone is plant-derived and bioidentical. The natural compounded estrogens are either estriol, estrone, or estradiol. Estriol is particularly unique because it has approximately one-fourth the potency of estradiol and estrone. Natural compounded estrogens are generally used in lower doses owing to the combined effect of the weaker estriol along with the estradiol and/or estrone. These natural estrogens are thought to be metabolized significantly differently by the body, have shorter half-lives, can be used in customized dosing regimens and potencies to fit each individual woman and clinical situation, and can be adjusted to be stronger or weaker in small units to taper someone off or onto hormones.

CEEs, those that were used in the WHI study, are quite different. In the 1970s it was believed that Premarin consisted only of 10 estrogens: 17-β-estradiol, 17-β-dihydroequilin, 17-β-dihydroequilenin, 17-α-dihydroequilin, 17-α-estradiol, estrone, equilin, 17-α-dihydroequilenin, Δ-8-9-dehydroestrone sulfate, and equilenin. Since then, advancements in technology have shown that the original 10 estrogens make up less than 40% of the hormonal content of Premarin. Through the use of modern analytic techniques, more than 200 individual components have been identified, including androgens and progestins.[47] The composition of Premarin is complex, and different estrogens have various effects in different tissues. Herein may lie an explanation for problems with conjugated equine estrogens versus natural bioidentical estradiol, estrone, and estriol.

The steroid hormones, including the sex steroids produced by the ovaries, represent a subclass of lipids that share a four-ring steroid structure. The native compound from which all the sex steroids are derived is cholestane, the parent of cholesterol. When nutritional states of the individual and cell are normal, the principal precursor of steroid production is cholesterol in the plasma. The cholesterol enters the cells through a lipoprotein receptor system. The activity of the enzymes within the cells of that tissue determine the particular classes of steroids produced. Steroids, either endogenous or exogenous, enter the cells via passive diffusion. The tissues responsive to steroids have very specific intracellular receptors, each with a high affinity for its particular steroid. The primary action of the steroids is the binding of a steroid hormone to a receptor and the interactions of this receptor-hormone complex with the components of the cell. When the steroid binds, the steroid-receptor complex becomes activated and binds with very specific regions within the steroid-responsive regions of the genes. Most of the effects of steroids on responsive cells are mediated through the activation of very specific genes. The hypothesis is that a nonbioidentical hormone may act like a constant and indiscriminant environmental toxin to the genetic material within the cell because, even though it can bind to the receptor-hormone complex, it is a foreign substance.

Consider CEEs, which consist of more than 200 substances mostly foreign to a human. These substances, once ingested, are a part of that complex and therefore are activating those genes within the cell. Thus, there is a profound distinction between a hormone that is bioidentical to human hormones and one that is not. Beside the effect on the genes themselves, bioidentical hormones and nonbioidentical hormones may very well leave different metabolic footprints on the rest of the body, with different metabolic consequences. They may be directly cytotoxic to estrogen-sensitive tissues, alter binding of other hormones to those receptors, or change the liver's metabolism of carcinogens. It is because of this distinction and the potential difference in metabolic consequences—as well as the shorter half-life of natural hormones—that naturopathic physicians prefer bioidentical natural hormones almost exclusively for the treatment of symptomatic menopause when hormones are required.

The distinctions between synthetic progestins and progesterone are even clearer. Natural progesterone has been studied and shown to have less adverse effects on the cardiovascular system than synthetic progestins such as MPA. Specifically, natural progesterone lowers HDL-C significantly less than MPA, is less atherogenic, and does not cause coronary artery spasm, whereas MPA does.

Natural estradiol may not be without concerns about its effects on the cardiovascular system and breast. However, it is typically used in a half-strength dose (0.5 mg total daily) because it is combined with the significantly weaker estriol. Estriol has been shown to have some ability to act as an antiestrogen in the breast and no significant effect on the cardiovascular system.

Further consideration of a natural hormone approach and a more holistic approach to menopause would lead one to use the hormones in combination with other strategies known to reduce the risk of breast cancer and heart disease. For examples, soy, flax seeds, cabbage family foods, and supplements can promote the metabolism of estrogens to their anticarcinogenic breakdown products. Diets designed to help prevent breast cancer and heart disease can also be emphasized, along with nutritional and botanical supplements to be considered, such as vitamins E and C, the carotenes, soy, coenzyme Q_{10}, green tea, and garlic.

Women who are using CEE and MPA should consider other natural estrogen and natural progesterone regimens or nonhormonal menopause management. Women who are using natural estrogens and natural progesterone, should consider a reevaluation of the hormone regimen to establish the lowest dose for achieving the benefits and minimizing the risks. Regular, at least annual, consideration should be given to duration of use on an individual basis. Women who do not have a uterus and are being treated with any hormone regimen should take estrogen alone. Neither synthetic MPA nor natural progesterone is needed.

Additional herbal and nutritional supplements may be considered as well. Studies on black cohosh, red clover, soy, maca, bioflavonoids, and kava have all shown proved scientific efficacy in the treatment of menopausal symptoms. The majority of women require only these nonhormonal supplements for symptom relief and never need any kind of HT. Other women may be able to lower their dose of cHT or natural hormones by using them in combination with the herbal and nutritional supplements.

Guidelines on the use of the different forms of HT are given following the discussion of nonhormonal approaches.

The Major Symptoms of Menopause

Common complaints of perimenopause and menopause are as follows:

- Irregular bleeding (in perimenopause)
- Hot flashes (or night sweats)
- Vulvovaginal thinning, dryness, dyspareunia, burning (known as atrophic changes)
- Bladder frequency/urgency/leakage
- Mood changes
- Cognitive changes
- Body aches
- Sleep disturbances

Other symptoms can include fatigue, sexual dysfunction, hair thinning, the appearance of facial hair, headaches, voice impairment, dry skin, and joint pains.

TREATMENT OVERVIEW

The goal of a holistic and integrative approach to menopause is to recognize that there are many options for symptom management, disease prevention, and disease treatment. One might categorize these in the following way:

1. Diet, exercise, and stress management
2. Nutritional supplementation
3. Botanical medicines
4. Compounded bioidentical HT (cbHT)
5. Bioidentical HT (bHT) (FDA-approved prescription items)
6. Nonbioidentical HT (HT) (FDA-approved prescription items)
7. Condition-specific nonestrogen pharmaceuticals (for either symptom relief or disease prevention/treatment)

There are three fundamental goals in treatment: relief of symptoms, prevention of disease, and treatment of disease. Each woman is assessed individually to determine the scope and severity of her symptoms and is evaluated subjectively and objectively as to her risks of osteoporosis, heart disease, breast cancer, Alzheimer's disease, type 2 diabetes, and colorectal cancer as well as other chronic health problems.

Diet, exercise, lifestyle, and/or nutritional supplements and botanical therapies will be effective for the management of menopausal symptoms in the majority of women. When these are not adequate, HT or other medications can be recommended.

Diet, Exercise, and Stress Management

Nutrition

Nutrition plays a fundamental role in integrative medicine. Although dietary advice should be individualized, common themes include a diet rich in whole "natural" and unprocessed foods, with an emphasis on vegetables, whole grains, beans, seeds, nuts, fruits, lean low-fat proteins, and healthy fats; to be minimized are saturated fats and fried foods, simple carbohydrates, alcohol, sugar, and salt. Some foods, such as soy and flax, have been studied for their beneficial effects on menopause-related symptoms.

Soy. Soy foods may be useful in menopause primarily for their potential benefits in moderating hot flashes, slowing bone loss, improving the lipid profile and blood pressure, and lowering the risk for CAD. There are conflicting studies on soy for hot flashes, some showing effect and others not, making it difficult to draw any definitive conclusion. Two systematic reviews of isoflavones (from soy and red clover [*Trifolium pratense*]) and menopausal symptoms and the consensus opinion from the North American Menopause Society offer a good summary of the research.[48-50] The first systematic review evaluated the literature of randomized controlled clinical trials on soy and perimenopausal symptoms.[48] Only 4 out of 10 trials showed benefit. In the second systematic review, 25 trials of soy and red clover isoflavones involving approximately 2300 women met the study criteria results were mainly positive, but not consistent.[49]

A consensus opinion of the North American Menopause Society[48-50] reports many diverse areas of the impact of soy. The evidence for isoflavones and hot flashes showed mixed results but appear to be modestly effective in relieving menopausal symptoms; supplements that provide higher amounts of genistein or an increase in S-equol may be more beneficial. In addition, they conclude that soy food consumption is associated with a lower risk of breast and endometrial cancer in observational studies. They also report their opinion that the efficacy of soy on bone health has yet to be adequately proved. Cardiovascular benefits are still evolving but the effect of soy does appear to lessen the arterial stiffness, yet the evidence is mixed on the lipid values in postmenopausal women. Preliminary evidence of the cognitive benefit from soy isoflavones seems to point in the direction that younger postmenopausal women derive more benefit within the first few years of menopause rather than older postmenopausal women. Another study has shed some light on why the research on soy isoflavones and vasomotor symptoms is so contradictory. This randomized double-blind placebo-controlled clinical trial comprising 96 menopausal women was conducted over 6 months.[51]

A total of 66 women were given 135 mg of soy isoflavones while 30 women were given placebo. After 1 week, the women in the treatment group were tested and further divided into 2 subgroups, equol-producing (EP) and non–equol-producing (non-EP), according to peak levels of equol in their urine. Women in both of these subgroups were then given 3 g of soy germ extract powder twice a day, totaling 135 mg of isoflavones daily, for 6 months. Menopausal symptoms were evaluated using a modified Kupperman Index measuring 17 items (hot flashes, excessive sweating, coldness of the extremities, shortness of breath, numbness of the extremities, paresthesias of extremities, insomnia, easy awakening, excitability, nervousness, melancholia, vertigo, weakness, arthralgia or myalgia, headaches, palpitations, and formication. Symptoms were scored as none, mild, moderate, or severe. Compared with the placebo group, symptoms of hot flashes and excessive sweating were significantly reduced after 3 months, and weakness, palpitations, limb paresthesias, and total symptoms significantly decreased after 6 months, ($P < 0.05$), but only in the EP group. At 3 months, total scores had decreased by 66% in the EP group, 54% in the non-EP group, and 59% in the placebo group. At 6 months, symptom scores had decreased by 84% in the EP group, 58% in the non-EP group, and 66% in the placebo group. Studies that may have had a higher percentage of women who were equol producers have been previously suspected to be the determining factor in the effectiveness of soy isoflavones, but the current study seems to be the first to demonstrate more clearly that a woman's ability to produce equol determines her response to soy isoflavone supplementation. Daidzein and genistein are the two most significant phytoestrogens in soy. Daidzein is converted to equol, a metabolite of daidzein, by bacterial flora in the gut. For clinicians, part of the task in treating menopausal women with soy may be to test for equol production prior to treatment and/or improve their gut flora so that they can more easily transform soy isoflavones to equol.

In reviewing traditional Asian diets, the average adult daily intake of soy isoflavones is somewhere between 50 and 150 mg per day. The isoflavone content of soy foods varies with the form (Table 188-1).

Flaxseed. Another significant dietary source of phytoestrogens is flaxseed *(Linum usitatissimum)*. Flaxseed contains the lignans matairesinol and secoisolariciresinol, which are known to have estrogenic activity, as well as other lignans that are modified by intestinal bacteria to form estrogenic compounds. Lignans are absorbed in the circulation and have both estrogenic and antiestrogenic activity.[52]

Only a small amount of research has been done in the area of flaxseed and hot flashes. One small but encouraging study, in 2007, showed that women who consumed 2 tbsp of flaxseed twice

TABLE 188-1 **Isoflavone Content of Soy Foods**

SOY FOOD	AMOUNT	ISOFLAVONES (MG)
Textured soy protein granules	¼ cup	62
Roasted soy nuts	¼ cup	60
Tofu, low-fat and regular	½ cup	35
Tempeh	½ cup	35
Soy beverage powders	1-2 scoops	25-90 (varies with product)
Regular soy milk	1 cup	30
Low fat soy milk	1 cup	20
Roasted soy butter	2 tbsp	17
Cooked soybeans	½ cup	150
Soy isoflavone pills	Varies with the manufacturer; read label	Varies with the manufacturer; read label
Fermented soy isoflavone pills		Will contain lower amount of isoflavones but may be better absorbed

daily halved their number of hot flashes within 6 weeks and reduced the intensity of their hot flashes by 57%.[53]

Exercise

The benefits of exercise for peri- and postmenopausal women are numerous (Box 188-1). Women can achieve substantial reductions in cardiovascular disease[54] and breast cancer risk,[55] increases in bone density,[56] and reductions in body fat and body mass index while also experiencing an improved sense of well-being.[57]

However, whether exercise can reduce hot flashes during menopause is not clear. Moderate exercise may be beneficial for hot flashes; more vigorous exercise may actually exacerbate them.

Stress Management

Perimenopause/menopause can be a stressful time in a woman's life. Surprisingly, studies of women in midlife suggest that depression, as defined by the current Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), is no more common during menopause than at any other time of life.[58,59] Most studies indicate that the perimenopausal transition is associated with depressive symptoms and that women experience mood changes but fail to meet the DSM-IV criteria for the diagnosis of depression.[60–62]

A woman's ability to manage stress can be enhanced with self-care tools that may include meditation, yoga, breathing exercises, being out in nature, and getting regular exercise.

Dietary Supplements

There are a number of nutritional supplements that may be beneficial for hot flashes and night sweats. Most women should probably take a good multivitamin—one that provides 70% to 100% of the recommended daily allowances of vitamins and minerals. In addition, there are numerous supplements for other individual symptoms commonly experienced during menopause such as insomnia, depression, and anxiety. These supplements include melatonin, L-tryptophan, and 5-HTP for insomnia; vitamins B_6 and B_{12}, folic acid, and L-tyrosine for depression; GABA and L-theanine for anxiety.

BOX 188-1 **Health Benefits of Regular Exercise in Menopause**

- Relief from hot flashes
- Decreased bone loss
- Improved heart function
- Improved circulation
- Reduced blood pressure
- Decreased blood cholesterol levels
- Improved ability to deal with stress
- Improved oxygen and nutrient utilization in all tissues
- Increased self-esteem, mood, and frame of mind
- Increased endurance and energy level

Hesperidin, Vitamin C, and Procyanidolic Oligomers

Combined with vitamin C, hesperidin and other citrus flavonoids may be effective in relieving hot flashes. In one clinical study, 94 women suffering from hot flashes were given a formula containing 900 mg of hesperidin, 300 mg of hesperidin methyl chalcone (another citrus flavonoid), and 1200 mg of vitamin C daily.[64] At the end of 1 month, symptoms of hot flashes were relieved in 53% of the patients and reduced in 34%. Improvements in nocturnal leg cramps, nosebleeds, and easy bruising were also noted. The only side effect was a slightly offensive body odor with a tendency for the perspiration to discolor the clothing.

Perhaps more useful than hesperidin are preparations containing procyanidolic oligomers (PCOs); see Chapter 117. In a double-blind study, a group of perimenopausal Taiwanese women 45 to 55 years of age were given either placebo or 100 mg of PCOs (as Pycnogenol) twice daily for 6 months.[65] Of the total, 155 women received the Pycnogenol and 75 women the placebo. The 36-item Women's Health Questionnaire was used to evaluate the climacteric symptoms at baseline and at 1, 3, and 6 months. Blood pressure decreased similarly in both groups. HDL-C increased and LDL-C decreased significantly from baseline with Pycnogenol, but no significant differences were seen in HDL-C between the two groups. However, LDL-C was more significantly reduced in the Pycnogenol group. Perimenopausal symptoms of depression, vasomotor symptoms, memory, anxiety, sexual function, and sleep all improved significantly (P <0.001) in both severity and frequency with Pycnogenol as soon as 1 month after starting the treatment. Most symptoms also improved with placebo, but not significantly.

Gamma-Oryzanol

Gamma-oryzanol (ferulic acid) is a growth-promoting substance found in grains and isolated from rice bran oil. In the treatment of hot flashes, its primary action is to enhance pituitary function and promote endorphin release by the hypothalamus. Gamma-oryzanol was first shown to be effective in the treatment of menopausal symptoms, including hot flashes, in the early 1960s.[66] Subsequent studies have further documented its effectiveness.[67]

In one of the earlier studies, 8 menopausal women and 13 women whose ovaries had been surgically removed were given 300 mg/day of gamma-oryzanol. At the end of the 38-day trial, more than 67% of the women had a 50% or greater reduction in menopausal symptoms.[66] In a later study, the benefit of a 300-mg/day dose of gamma-oryzanol was even more effective in that 85% of the subjects reported improvement in their menopausal symptoms.[67]

Gamma-oryzanol is an extremely safe natural substance. No significant side effects have been produced in experimental and clinical studies. In addition to being helpful in improving the symptoms of menopause, gamma-oryzanol has also been shown to be quite effective in lowering blood cholesterol and triglyceride levels.[68]

Fish Oils

A study on fish oil supplementation and hot flashes has afforded clinicians with another option in treating hot flashes and night sweats. Women in this study were between 40 and 55 years of age and had moderate to severe psychological distress, defined as a score of 72 or greater on the Psychological General Well-being Schedule. Only women with hot flashes were included in the current analysis.[69] A total of 120 women were randomly assigned to an ethyl-eicosapentaenoic acid (E-EPA) plus omega-3 fatty acid supplementation or placebo for 8 weeks. The E-EPA supplementation was a 500-mg capsule taken three times daily, with each capsule containing 350 mg of EPA and 50 mg of DHA. The baseline level of hot flashes was an average of 2.8 per day. After 8 weeks, the frequency of hot flashes decreased by a mean of 1.58 per day in the E-EPA group and by only 0.50 per day in the placebo group. There was a significant reduction of 55% in frequency of hot flashes in the E-EPA group compared with only a 25% decrease in the placebo group. There was also a greater responder rate in the E-EPA group of 58.5%, versus 34.4% in the placebo group. However, there were no differences in the severity of hot flashes or in quality-of-life scores between the two groups.

In another fish oil–hot flash study, 20 perimenopausal or postmenopausal women received 8 weeks of fish oil (840 mg EPA and 375 mg DHA). Hot flashes were monitored using diaries and the hot flash related daily interference scale. The response rate was 70% (a MADRS score decrease of 50% or more; the remission rate was 45%). Responders had significantly lower pretreatment DHA levels than nonresponders did with a pre-treatment score of 4.3 and post-treatment score of 1.8 for daytime hot flashes and a pretreatment score of 4.6 and posttreatment score of 0.7 for night time hot flashes.[70]

Vitamin E

In the late 1940s, several clinical studies found vitamin E to be effective compared with a placebo in relieving hot flashes and menopausal vaginal complaints.[71,72] Unfortunately there have been no further clinical investigations. In one study, vitamin E supplementation was shown to improve not only the symptoms but also the blood supply to the vaginal wall when taken for at least 4 weeks.[71] A follow-up study published in 1949 demonstrated that vitamin E (400 IU/day) was effective in about 50% of postmenopausal women with atrophic vaginitis.[72]

Vitamin E oil, creams, ointments, or suppositories can be used topically to provide symptomatic relief of atrophic vaginitis. Vitamin E may be effective in relieving the dryness and irritation of atrophic vaginitis as well as other forms of vaginitis.[64]

Botanical Medicines

Many plants have been shown to exert a tonic effect on the female glandular system. As a class, these botanicals are often referred to as "uterine tonics." Much of their effect is thought to result from phytoestrogens in the plants as well as the plants' ability to improve blood flow to the female organs. Some of the botanicals used in menopausal women work to nourish and tone the female glandular and organ system rather than exerting a druglike effect. This nonspecific mode of action makes many botanicals useful in a broad range of female conditions. Other plants are used for specific symptoms, such as valerian for insomnia or chaste tree for dysfunctional uterine bleeding. Their mechanisms of action do have pharmaceutical effects, whether it be a sedative effect in the case of valerian or increasing luteinizing hormone and an indirect progesterone-like effect in the case of chaste tree. Mechanisms of action of other botanicals have so far eluded us.

TABLE 188-2 **Sources of Phytoestrogens**

PHYTOESTROGEN	SOURCES
Lignans	Vegetables, fruits, nuts, cereals, spices, seeds—especially flaxseeds
Isoflavones	Spinach, fruits, clovers, peas, beans—especially soy
Flavones	Beans, green vegetables, fruits, nuts
Chalcones	Licorice root
Diterpenoids	Coffee
Triterpenoids	Licorice root, hops
Coumarins	Cabbage, peas, spinach, licorice, clover
Acyclics	Hops

Phytoestrogens are found in many medicinal herbs with a historical use in conditions that are now treated by estrogens. Phytoestrogen-containing herbs offer significant advantages over the use of estrogens in the treatment of menopausal symptoms. Although both synthetic and natural estrogens may pose significant health risks, phytoestrogens have not been associated with these side effects. In fact, epidemiologic data and experimental studies in animals have demonstrated that phytoestrogens are extremely effective in inhibiting mammary tumors, not only because they occupy estrogen receptors but also through other unrelated anticancer mechanisms.[73,74]

Plants manufacture thousands of chemical compounds that are vital to the health and function of the plant. Those chemical compounds, generally known as micronutrients, are consumed in the diet by humans whenever the plants are eaten. One of these classes of chemical compounds manufactured by plants comprises the phytoestrogens. More than 300 plants contain phytoestrogen compounds. They compose a large part of our diet and are found in medicinal plants as well. There are several subclassifications of phytoestrogens; the partial list in Table 188-2 may be helpful.

Phytoestrogens in medicinal herbs are capable of exerting estrogenic effects, although their activity is at most only 2% as strong as that of estrogen.[75] Isoflavones have a structure similar to that of endogenous steroidal sex hormones. They have the ability to bind to estrogen receptors on human cells; in women, they have a preference for binding to the beta form of the estrogen receptor. As a result, they preferentially express estrogenic effects in the central nervous system, blood vessels, bone, and skin without causing stimulation of the breast or uterus.[76]

In light of often confusing and contradictory research on menopausal HT, with slight risks as well as benefits, even more women are looking for safe and effective botanical alternatives for symptom relief. Botanical alternatives for menopausal symptoms are increasingly popular despite limited research to demonstrate efficacy. Many women are determined to use nonhormonal therapies, bioidentical hormones, or lower-dose hormones in combination with botanicals in order to create a risk/benefit ratio they feel comfortable with.

Black Cohosh (Cimicifuga racemosa)

In the last 30 years, black cohosh has emerged as the most studied of the herbal alternatives to hormone replacement therapy for menopause symptoms (see Chapter 77 for a complete description). Despite some studies demonstrating no benefit of black cohosh, the collective findings in black cohosh studies and long-term clinical anecdotal evidence on black cohosh indicate that it is most effective for menopause symptoms of daytime or nighttime hot flashes, mood swings, sleep disorders, and body aches.[77]

In one of the largest studies, 629 women with menopausal complaints were seen by 131 general practitioners.[78] In this study, as early as 4 weeks after beginning the therapy, a clear improvement in the menopausal ailments was seen in approximately 80% of the women. After 6 weeks, complete disappearance of symptoms occurred in approximately 50%.

Some recent studies have used black cohosh in combination with other botanical extracts. For example, in a trial of black cohosh combined with St. John's wort, healthy perimenopausal women with typical climacteric symptoms and not on HT for at least the previous 3 months were given a 264-mg tablet containing 0.364 mL of extract from black cohosh, equivalent to 1 mg terpene glycosides, and 84 mg of St. John's wort extract with 0.25 mg hypericin.[79] Forty-two women in the treatment group and 35 women in the placebo group completed the study. Mean Kupperman Index scores at 4 and 12 weeks were significantly lower in the treatment group ($P \leq 0.002$). At the end of the study, the average decrease in the Kupperman Index was 20 points in the treatment group and only 8.2 points in the placebo group ($P < 0.001$). Vaginal dryness and low libido were two symptoms that did not improve, but the average hot flash score was significantly lower in the black cohosh/St. John's wort group.

In 2007, a clinical trial of a combination of black cohosh, red clover, soy, chaste tree, valerian and vitamin E resulted in a significant lowering of the mean score value of the Kupperman Index after 4 and 6 months, yet it was found equal to placebo after 2 months.[80] This multicenter randomized double-blind placebo-controlled trial included 125 symptomatic postmenopausal women 45 to 65 years of age. The supplement tested contained 72 mg of total isoflavones with 60 mg of soy isoflavones and 12 mg of red cover isoflavones in combination with the following: 40 mg of black cohosh extract, 30 mg of chaste-tree extract, 250 mg of valerian extract, and 121 mg of vitamin E. After 2 months, the reduction in mean score value of the Kupperman Index was the same in the placebo and treatment groups. At months 4 and 6, the Kupperman Index was significantly lower in the treatment group (4 months: 13.6 score for placebo and 11.1 for treatment; 6 months: 12.2 for placebo and 9.6 for treatment) Secondarily, lipids were evaluated. No difference was seen on total cholesterol or HDL-C, but there was a nonsignificant decrease ($P = 0.0608$) in LDL-C and a statistically significant reduction in triglycerides ($P = 0.0151$) in the herbal treatment group. The study investigators and patient's clinical global impression on the treatment group were superior compared with placebo. Both herbal and placebo groups tolerated the treatment well, while a few individual had mild and temporary side effects.

Also in 2007, black cohosh was studied for its effects on lipids, fibrinogen, glucose, and insulin. A total of 351 perimenopausal or postmenopausal women aged 45 to 55 were randomized to a 3-month double-blind trial of either (1) black cohosh extract at 160 mg/day; (2) a multibotanical formula containing black cohosh, alfalfa, chaste-tree berry, dong quai, false unicorn, licorice root, oats, pomegranate, Siberian ginseng, and boron; (3) a multibotanical formula administered with boron and a soy diet with dietary counseling; (4) 0.625 mg of conjugated equine estrogen with or without 2.5 mg of medroxyprogesterone acetate (women with a uterus received both medications while women without a uterus received the estrogen only); or (5) a placebo.[81] Whereas the primary objective of the study was to determine the effects on hot flashes, the secondary measures included the effects on lipids, fibrinogen, glucose, and insulin. Study participants were women who were experiencing hot flashes, mostly white and with college degrees. The average total and LDL-C levels were borderline high (219 and 146 mg/dL); HDL-C was medium at 53 mg/dL, triglycerides were normal at 107 mg/dL. At the 3-month mark, there were no statistically significant treatment effects on total cholesterol, LDL-C, HDL-C, triglycerides, fibrinogen, glucose or insulin among women who had any of the three herbal regimens (all three of which contained black cohosh). The evidence from this randomized controlled trial of perimenopausal and postmenopausal women does not support any short-term benefit or adverse effects of black cohosh on lipids, fibrinogen, glucose, or insulin when used alone, in combination with other botanicals, or in conjunction with soy consumption. This is reassuring in that black cohosh does not appear to affect any thrombotic biomarkers, as does oral estrogen therapy (OET), nor does it increase triglycerides, as seen with OET.

Hops (Humulus lupulus)

Hops have shown positive effects for mood issues, such as anxiety and restlessness, and for sleep disruptions in menopausal women. In one randomized double-blind placebo-controlled study, 67 menopausal women were given either a placebo or a 120-mg or 300-mg of standardized hop extract (providing 100 mcg and 250 mcg of 8-prenylnaringenin, respectively) for 12 weeks.[82] At 6 weeks, the 120-mg dose was significantly superior to placebo, but not at 12 weeks. Even so, there was a more rapid decrease in menopausal symptoms scored for both doses of hop extract, especially the hot flash score. The higher dose was not any better than the lower one.

A second double-blind study in 36 menopausal women indicated significant reductions in the Kupperman Index and the visual analog scale (VAS) for the hops group and a marginal reduction in symptoms for the menopause rating scale (MRS) after 16 weeks.[83]

Maca (Maca peruvianum)

Research on perimenopausal and menopausal women using a proprietary maca product (Maca-GO) found that, unlike hormone replacement therapy (HT) and phytoestrogenic botanicals, maca can increase the body's production of estrogen—versus simply adding estrogen replacement to the body—and lower levels of cortisol and adrenocorticotropic hormone.[84] What makes this especially interesting is that, from other research conducted on the composition of various powdered preparations of maca root, it appears that the herb does not contain plant estrogen or hormones.[85–88] It has been suggested that maca's therapeutic actions rely on plant sterols stimulating the hypothalamus, pituitary, adrenal, and ovarian glands and therefore also affecting the thyroid and pineal glands. Thus, it has effects in improving sleep, mood, fertility, energy, and hot flashes. As such, maca tends to treat menopausal symptoms as a whole rather than only one specific symptom of menopause (such as hot flashes).

In one double-blind randomized 4-month study of early postmenopausal 20 women, patients were given either placebo or two 500-mg capsules of Maca-GO twice daily for a total of 2 g/day.[84] Menopausal symptoms were assessed according to Greene's Score

and Kupperman Index. After 2 months, this maca product stimulated estradiol production and suppressed follicle-stimulating hormone, T3, aderenocorticotropic hormone, and cortisol. It also had a small effect on increasing bone density and alleviated numerous menopausal symptoms including hot flashes, insomnia, depression, nervousness, and diminished concentration.[6]

A small randomized double-blind placebo-controlled crossover trial comprising 14 postmenopausal women was completed using 3.5 g of powdered maca *(Lepidium meyenii)* for 6 weeks and matching placebo for 6 weeks.[89] Measurements of estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and sex hormone–binding globulin (SHBG) were taken at baseline, and then at weeks 6 and 12. The Greene Climacteric Scale was used to assess the severity of menopause symptoms. Serum concentrations of estradiol, FSH, LH, and SHBG were similar in both groups. The Greene Climacteric Scale revealed a significant reduction in psychological symptoms including anxiety, depression, and sexual dysfunction after maca consumption compared with baseline and placebo. These findings were independent of androgenic or alpha-estrogenic activity present in the maca using assays to measure hormone-dependent activity.

Red Clover (Trifolium praetense)

Red clover, a member of the legume family, has been used worldwide as a source of hay for cattle, horses, and sheep and used by humans in the past as a source of protein in the leaves and young sprouts. Historically it has also been recognized as a medicinal plant for humans and, more recently, as a menopausal herb. The principal substances of red clover are the flavonoid glycosides, coumestans, volatile oils, L-dopa, caffeic acid conjugates, polysaccharides, and some miscellaneous resins, fatty acids, hydrocarbons, alcohols, chlorophylls, minerals, and vitamins.

At least six clinical trials have been conducted on the effect of red clover isoflavones on vasomotor symptoms; three showed benefit and and three did not. The first two published studies on red clover and vasomotor symptoms showed no statistically significant difference between the red clover standardized extract and placebo during a 3-month period, although both groups did improve.[90,91] It was suggested that the negative results of these studies were due to inadequate controls and that women in the control group were in fact obtaining meaningful amounts of phytoestrogens in their diets. Two other studies using 40 mg of standardized red clover extract produced a 75% reduction in hot flashes after 16 weeks in 30 women. The difference between placebo and red clover isoflavones was statistically significant (P <0.001).[92] A similar study evaluating 40 mg of red clover standardized isoflavones for 2 months in 23 postmenopausal women found that the red clover users had a 54% reduction in hot flashes versus 30% in the placebo group.[93] Two more recent studies continue the contradictions. In 2002, the use of 80 mg of isoflavones daily resulted in a significant reduction in hot flashes as compared with baseline.[94] Another study, called the ICE study, compared two different doses of red clover isoflavones—82 mg and 57 mg per day—with placebo for 12 weeks. The reductions in the mean daily hot flash count at 12 weeks were similar for both treated groups as well as the placebo group.[95]

Other intriguing effects of red clover reported by these studies are as follows: no endometrial thickening and an increase in HDL-C as well as and no abnormalities in liver function parameters, complete blood count, or estradiol determination. Last, a published study showed that red clover isoflavones may reduce the risk of coronary vascular disease by increasing arterial elasticity by 23%.[96,97]

Siberian Rhubarb (Rheum rhaponticum)

A special extract, ERr 731, from the roots of rhapontic rhubarb has been in wide use in Germany since 1993, specifically for the treatment of menopausal symptoms. This medicinal species of rhubarb is not the same species as the garden rhubarb used for food. Other rhubarb species included *R. officinale, R palmatum, R polygonatum*; these have been traditionally used as laxatives owing to their content of anthraquinone glycosides such as emodin and aloe-emodin. The *R. rhaponticum* used in clinical studies and in the extract form of Err 731 does not contain any emodin or aloe-emodin and thus has no laxative effects.

A standardized extract, ERr 731, from the roots of *Rheum rhaponticum*, also known as Siberian rhubarb, was studied in a 12-week randomized double-blind placebo-controlled clinical trial in 109 perimenopausal women with climacteric complaints. One tablet (250 mg) containing 4 mg of dry extract was used in the treatment group (n = 54) while the control group (n = 55) received placebo. The primary outcome was the change in the Menopause Rating Scale II (MRS II). After 12 weeks, the MRS II total score and each MRS II symptom significantly decreased in the rhubarb extract group compared with the placebo group (P <0.0001). The overall menopause quality-of-life score was also significantly better in the treatment group compared with placebo. No adverse events were observed.[98]

Another randomized double-blind placebo-controlled clinical trial of the standardized extract of *Rheum rhaponticum* was conducted in 109 perimenopausal women with menopausal symptoms, including anxiety. One tablet containing either 250 mg of ERr 731, (containing 4 mg of *Rheum rhaponticum* dry extract) or placebo, was given for 12 weeks. After only 4 weeks of treatment, the Hamilton Anxiety Scale total score and anxiety score for ERr 731 group decreased significantly. This was maintained after the 4 weeks and was even more significant after 12 weeks of treatment. Anxiety decreased from moderate or severe to slight in 33 of 39 ERr 731 women. Quality-of-life issues also increased in the ERr 731 group far more significantly than in the placebo group, by 22.4 points versus 7.6 points.[99]

In an observational study, 363 menopausal women with menopausal symptoms were given one 4-mg tablet of ERr 731 for 6 months. The MRS was used to evaluate symptoms, and a change in the MRS was the primary outcome. After 6 months of treatment, 252 women completed the study. At that point, there was a significant decrease in the total MRS score from an average of 14.7 points at baseline to 6.9 points (P <0.0001)—a decrease of 7.8 points. The most pronounced improvement occurred within the first 3 months of treatment in those women who were the most symptomatic at baseline, with a score equal to or greater than 18 points. The most significant improvement was for symptoms of hot flashes, irritability, sleep problems, depressive mood, and physical/mental exhaustion.[100]

St. John's Wort (Hypericum perforatum)

Research on St. John's wort extract has focused mainly on mild to moderate depression (see Chapter 99) and several studies have also considered menopausal symptoms. In the most recent trial, a total of 100 women with an average age of 50 participated in a randomized double-blind placebo-controlled clinical trial comparing St. John's wort with placebo in women with perimenopausal/menopausal hot flashes.[101] Fifty women received 20 drops three times daily of St. John's wort extract (Hypiran) containing hypericin 0.2 mg/mL and 50 women received a placebo of distilled water. The study duration was 2 months. Clinical examinations and interviews were performed at baseline, 4 weeks, and 8 weeks.

Treatment effectiveness was measured by the Blagg-Kupperman Index. Evaluation of frequency, duration and severity of hot flashes was the main objective of the study. Forty-five women in the treatment group and 43 in the control group completed the study.

In women taking St. John's wort, the frequency of hot flashes began to decline during the first and second months, but more improvement was shown during the second month. There was no statistical change in hot flash frequency during the first month of placebo but some improvement during the second month. Women who used St. John's wort showed more improvement in frequency than did those on placebo. The decline in duration of hot flashes was statistically significant at week 8, and the decline was much more evident in the St. John's wort arm. The severity of hot flashes was relieved by St. John's wort during the 2 months of treatment and was more significant in the second month. Women in the placebo group did not show any significant decrease in the severity of hot flashes during the first month. They did have some improvement during the second month, but not as much as those in the St. John's wort group.

Another double-blind randomized clinical trial studied the effect of St. John's wort extract compared with placebo on symptoms and quality of life of 47 symptomatic perimenopausal women aged 40 to 65 with three or more hot flashes per day.[102] Women were randomly assigned to receive a St. John's wort extract (900 mg three times daily) or placebo. After 12 weeks of treatment, a nonsignificant difference in favor of the St. John's wort group was observed on the daily hot flash frequency and the hot flash severity scores. After 3 months of treatment, women in the St. John's wort group reported significantly better quality-of-life scores and significantly fewer sleep problems compared with those on placebo.

A drug monitoring study conducted in women with menopausal symptoms using 900 mg of St. John's wort for 12 weeks found that about three quarters of the women experienced improvement in both the self-rating scale and the physician rating; they also improved significantly in psychological and psychosomatic symptoms as well as a feeling of sexual well-being.[103]

Several double-blind studies have used a combination of St. John's wort and black cohosh extract. These studies have been described previously.

Although it appears to be common for practitioners to use chaste tree *(Vitex agnus castus)* in perimenopause and menopausal women for symptom relief, there have been no mono-ingredient studies on this plant for these symptoms. Vitex has been shown to be helpful when combined with black cohosh. The most recent menopause related study using Vitex was in combination with St. Johns wort. In this double-blind, randomized, placebo-controlled 16 week trial of late perimenopausal or postmenopausal women who reported hot flushes and other menopause symptoms, the herbal combination showed no significant difference from that of placebo.[135]

Kava (Piper methysticum)

Kava has most often been associated with analgesic, sedative, anxiolytic, muscle relaxant, and anticonvulsant effects. It is not typically thought of as an herb for menopause; however, anxiety, irritability, tension, nervousness, and sleep disruption are common perimenopausal and menopausal symptoms for which kava can offer some help. Several controlled trials have investigated the value of kava for menopausal symptoms.[104–106] The main results noted were a significant reduction in anxiety and depression. For more information on the pharmacology of kava, see Chapter 114.

Ginseng (Panax ginseng)

Panax ginseng, also known as Korean or Chinese ginseng, contains at least 13 different triterpenoid saponins, collectively known as ginsenosides. Whether it involves reducing mental or physical fatigue,[107–110] enhancing the ability to cope with various physical and mental stressors by supporting the adrenal glands,[111] or treating the atrophic vaginal changes due to lack of estrogen,[112] ginseng is a valuable tool for many menopausal women. In one trial, a standardized extract of *P. ginseng* was studied in 384 postmenopausal women.[113]

Depression and well-being showed a statistically significant improvement with ginseng. In another randomized controlled trial, 1 month of *P. ginseng* increased energy and decreased insomnia and depression.[114] These results indicate that *P. ginseng* can significantly improve the general sense of well-being of women going through menopause.

Kudzu (Pueraria mirifica)

Pueraria mirifica was examined for its effect on vaginal symptoms, vaginal health index, vaginal pH, and vaginal cytology in postmenopausal women.[115] In this randomized double-blind placebo-controlled study, 51 women were given either 20, 30, or 50 mg of *Pueraria mirifica* or placebo daily for 24 weeks. After 12 weeks of treatment, significant improvements in vaginal symptoms were seen, and they were maintained over the study period. The mean vaginal dryness symptoms decreased at all the herbal doses, but the results were not significantly different from those seen in the placebo group. The frequency of dyspareunia decreased from 56.9% to 39.2% in the study group, whereas it did not change in the placebo group. The changes in the vaginal health index (scoring vaginal appearance with regard to moisture, fluid volume, elasticity, epithelial integrity, and pH on a scale of 1, poorest, to 5, best) were significantly improved in the herbal group, as noted in weeks 12 and 24. Before treatment, the mean vaginal pH was 8.41 in the treated group; after 12 and 24 weeks, the mean pH was 5.52 and 5.83 respectively. After 12 weeks of treatment, most measures of vaginal health in the treated group were significantly higher than in the placebo group.

After 12 and 24 weeks of treatment, the maturation value and maturation index were also significantly higher in the study group than in the placebo group. In essence, *Pueraria mirifica* improved the parabasal:intermediate:superficial cells, which is what occurs when vaginal estrogen is used. There were no statistically significant changes in endometrial thickness and no significant difference in adverse effects between the treatment and placebo groups.

Dong Quai (Angelica sinensis)

By far the most popular use of *Angelica* species has been the use of *A. sinensis* in the treatment of menopausal complaints. Although a double-blind placebo-controlled study showed no significant benefit, the preparation used (a dried aqueous extract) was clearly lacking some of the important volatile compounds, although it was standardized for ferulic acid content.[116] In addition, the traditional use of *Angelica* has been in combination with other plants. A study conducted in China showed that a combination of *A. sinensis, Paeonia lactiflora, Ligusticum monnieri, Atractylodes chinensis, Sclerotium poriae,* and *Alisma orientalis* was effective in roughly 70% of women experiencing menopausal symptoms.[117] Although not double-blind, this study shows promise for using *Angelica* in the management of menopausal symptoms in combination with other compounds. Also, in a double-blind study, the combination of 100 mg *Angelica*, 60 mg soy isoflavones, and 50 mg of black cohosh extract significantly reduced menstrual migraines.[118]

Interestingly, in an in vitro study with human bone, the aqueous extract of *A. sinensis* was found to directly stimulate proliferation, alkaline phosphatase activity, protein secretion, and type I collagen synthesis in a dose-dependent manner.[119] These results indicate the *A. sinensis* may have an effect on preventing age-related bone loss.

Valerian

A double-blind study on the impact of valerian for sleep quality in postmenopausal women who were experiencing insomnia concluded that valerian may be helpful. The postmenopausal women studied were generally healthy women 50 to 60 years of age who were menopausal for at least 1 year, who were not using a hormone therapy, and were experiencing insomnia as evaluated by the Pittsburgh Sleep Quality Index (PSQI). One group of women was given capsules containing 530 mg of concentrated valerian extract twice per day and the other group was given a placebo twice per day, for 4 weeks. A statistically significant change was reported in the quality of the sleep in the valerian group when compared to the placebo group. The average score on the sleep scale before valerian was 9.8 and after valerian it was 6.02. The placebo group had an initial average sleep scale score of 11.1 and after placebo 9.4. Overall, 30% of the women taking valerian and 4% taking placebo reported an improvement in their sleep quality. [136]

Hormone Therapy

Recommending estrogen/progestogen HT, regardless of their source or their makeup, requires weighing the benefits and risks of short- and long-term treatment. These benefits and risks continually change for any individual woman as she ages, as her menopause-related symptom picture and her general health change. Risk factors are related to baseline diseases and the risks they incur, age, age at menopause, cause of menopause (surgical, physiologic, medication-induced), as well as the prior use of HT, including route of administration and response or medical problems that emerged during HT treatment.

It is easy for practitioners to be confused by the last 60 years of research on HT, but understanding these benefits and risks of HT is critical to sound clinical decision making and the education of patients. Any HT, whether bioidentical or nonbioidentical, should be used in the lowest dose for the shortest duration and in the safest way possible. Each type of estrogen and progestogen, route of administration, timing of initiation, and duration of use will have distinct benefits and adverse effects.

The North American Menopause Society (NAMS) has strongly recommended that new uniform and consistent terminology be adopted in describing HT in menopause management. The NAMS menopausal HT terminology is as follows[2]:

- EPT: combined estrogen-progestogen therapy (form of estrogen and progestogen is not specific)
- ET: estrogen therapy (the form of estrogen is not specific)
- HT: hormone therapy (encompassing ET and EPT; the form of estrogen and progestogen is not specific)
- Local therapy: vaginal ET administration that does not result in clinically significant systemic absorption (the form of estrogen is not specific)
- Progestogen: encompassing both progesterone and progestin
- Systemic therapy: HT administration that results in absorption in the blood high enough to provide clinically significant effects
- Timing of HT initiation: length of time after menopause occurs when HT is initiated

Additional terms that can be helpful in making distinctions between hormone regimens (not NAMS terminology):

- cHT: conventional HT (FDA-approved prescription items)
- cET: conventional estrogen therapy (FDA-approved prescription items)
- bHT: bioidentical HT (FDA-approved prescription items)
- bET: bioidentical estrogen therapy (FDA-approved prescription items)
- cbHT: compounded bioidentical HT (from a compounding pharmacy)
- cbET: compounded bioidentical estrogen therapy (from a compounding pharmacy)

Bioidentical or Natural Hormones

One of the greatest areas of confusion in menopausal management today is the subject of bioidentical or natural hormones. Bioidentical estrogens require a prescription and are available from regular pharmacies or as nonpatented forms prepared by compounding pharmacies. Advantages of conventional pharmaceutical HT include years of scientific study and the assurance of standardization. Insurance coverage generally pays for pharmaceutical hormone prescriptions but does not always pay for compounded hormones. Pharmaceutical preparations are limited in dose forms and combinations; they also contain additives, binders, adhesives, and/or preservatives. Occasionally these substances can cause side effects including skin reactions, headaches, and digestive problems.

The use of compounded forms of hormones has three distinct inarguable advantages in that there is a greater array of dosing, hormone combinations, and delivery options. Customized doses of a particular hormone are available that pharmaceutical companies do not make. Compounded hormones also are available in capsules, sublingual lozenges or pellets, creams, gels, vaginal creams/gels or tablets, nasal sprays, injections, and subcutaneous implanted pellets. In addition, any combination of estradiol, estriol, estrone, progesterone, testosterone, and DHEA can be formulated in a compounded hormone prescription to best meet the individual needs of the patient.

Bioidentical Estrogens

Some would argue that the advantage of conventional pharmaceutical company HT is that it has undergone years of scientific study. Although this is true, there has been little effort to make distinctions between different kinds of estrogens in particular. To a lesser degree but still true, there has not been much effort to distinguish between the various progestins (synthetic) and bioidentical progesterone. Whereas many alternative practitioners point to the superior safety profile of bioidentical estrogens over nonbioidentical estrogens, it cannot be stated with science-based facts that an equivalent dose of bioidentical estradiol is innately safer or better than the synthetic form or CEE. Whereas logic and common sense might lead us to assert that a bioidentical estrogen is more akin to the body's enzymatic pathways, bowel flora, and general physiology, thus leading to enhanced safety, we have yet to adequately prove this. For now it remains in the realm of hypotheticals and philosophical issues. There are however, some better safety profiles with bioidentical progesterone versus the progestins, to be discussed further.

The ability to individualize prescriptions with compounded bioidentical hormones can provide endless customized options with the ability to be flexible in dosing and delivery according to the needs of each woman. If for no other reason, this is compelling

enough reason to prescribe compounded bioidentical hormones. The combination of estriol with estradiol and the use of bioidentical progesterone and testosterone with the estrogens provides the potential maximum benefit and a more individualized approach for each patient. The hope is that there is less risk that nonbioidentical hormones in the case of combining the weaker estriol with estradiol/estrone. In the case of progestogens there is more than hope, there is some actual evidence of reduced risk.

Estriol seems to be helpful in treating many of the symptoms of menopause, such as hot flashes. Vaginal estriol for vaginal dryness is considered a potentially preferred form of vaginal estrogen owing to the dominance of estriol receptors in the vagina and vulva.

Alternative practitioners often use estriol to treat menopausal symptoms, as it is thought to have a better safety profile than estradiol and estrone. Estriol is about one fourth as potent as estradiol.[120]

Estriol can be taken orally in capsules or tablets and intravaginally as a cream. Vaginal estriol creams and suppositories have been shown to restore normal vaginal cytology[121] and to decrease the incidence of bladder infections.[122]

These creams most likely work by restoring the vaginal flora, improving vaginal and bladder health, and increasing lubrication, elasticity, and thickness of the vaginal epithelium. A common prescription is 1 mg of estriol per gram of cream inserted vaginally daily for 2 weeks and then twice a week for maintenance.

A popular practice for prescribing compounded bioidentical estrogens is to combine the lower dose and perhaps potentially safer effects of estriol with small doses of estradiol and estrone. Currently, those who prescribe a triple-estrogen compound typically use a formula composed of 80% estriol, 10% estradiol and 10% estrone. Progesterone is added to the formula at a minimum of 100 mg/day to protect the uterus from the potential effects of the estrogen in thickening the lining of the endometrium. Use of estrogen only, without the proper dose of progesterone, in women with a uterus might put them at risk for endometrial hyperplasia or even endometrial (uterine) cancer.

A biestrogen formulation, with estriol and estradiol, is increasingly popular because of concerns that estrone may be associated with more carcinogenic estrogen metabolites, which are associated with an increase in the risk of breast cancer. (Recommended dose ratios for both triestrogen and biestrogen formulations are discussed later.)

Progesterone

Progesterone is available with a prescription as oral capsules, sublingual drops, sublingual pellets, lozenges, transvaginal or rectal suppositories, and by injection. Progesterone is also available over the counter as a cream. Progesterone is added to a compounded biestrogen or triestrogen formulas at a minimum of 100 mg/day to protect the uterus.

For women with a uterus, a progestogen must be added to any estrogen preparation to prevent endometrial hyperplasia and uterine cancer. *Progesterone* is a natural hormone made by the ovaries and its main function is to support pregnancy. *Progestin* is the term applied to the synthetic derivatives, which differ in biochemical structure from progesterone. Progestins used in conventional HT and birth control pills often account for the side effects that patients experience, such as irritability, depression, bloating, and mood swings. Progestins tend to cause water retention, can effect brain chemistry, and alter other steroid pathways. *Progestogen* is the term applied to any substance possessing progesterone qualities. It can refer to progesterone or progestin.

The advantages of bioidentical progesterone over progestins are better validated than are the advantages of estrogens.

Bioidentical progesterone minimizes the side effects associated with progestogens and has a more favorable effect on lipid profiles and cardiovascular function.[123]

In some women, insomnia, fatigue, anxiety, and mood swings may be more responsive to progesterone than estrogen.

Progesterone Cream

Bioidentical progesterone by itself can also be used very effectively in perimenopause. Problems that can be addressed include regulation of the menstrual cycle, hot flashes, night sweats, mood swings, sleep disruption, and premenstrual symptoms.

A transdermal progesterone cream was studied for its ability to control vasomotor symptoms (hot flashes) and in order to evaluate its ability to prevent bone loss. In this study, 102 healthy women within 5 years of menopause were randomly assigned to receive either transdermal progesterone cream or a placebo.[124] Subjects were instructed to apply a 1/4 tsp of cream (this amount contained 20 mg progesterone or placebo) to the skin daily. Each also received a multivitamin and 1200 mg of calcium. Measurements included medical history, physical examination, DEXA scanning of the hip and spine, measurements of TSH and FSH, a lipids profile (cholesterol, etc.), and a regular blood chemistry profile. The women kept weekly symptom diaries and were seen every 4 months for 1 year. Bone density scanning and blood chemistry profiles were obtained again at the end of 1 year.

Before the initiation of the study, 30 of the 43 (69%) in the treatment group and 26 of the 47 (55%) in the placebo group had hot flashes. Twenty five of 30 (83%) women in the treatment group experienced improvement or resolution of the hot flashes, and 5 of 26 (19%) placebo subjects showed improvement or resolution. The numbers of women who showed a gain in bone mineral density did not differ in the two groups.

The latest randomized clinical trial compared the effect of a transdermal natural progesterone cream (32 mg/day) with a placebo cream. Eighty postmenopausal women in Australia were randomly assigned to each group. They were evaluated using the Greene Climacteric Scale and the Menopause Quality of Life Questionnaire; serum lipid levels and bone markers were also monitored over 12 weeks. No detectable change was seen in vasomotor symptoms, moods, libido, serum lipid levels, or metabolic markers of bone turnover. There was a slight elevation of blood levels of progesterone. The researchers concluded that the 32 mg of transdermal progesterone was not sufficiently absorbed into the bloodstream to achieve biological effects.[125]

Testosterone

The majority of women treated with estrogen replacement have resolution of their menopausal symptoms. For those who do not, and especially for those complaining of a loss of libido, estrogen with testosterone may be beneficial.

One study of early postmenopausal women (both natural and surgical) who were switched from estrogen alone to estrogen/testosterone therapy found that overall symptom relief was superior to estrogen-only therapy. Sex drive and satisfaction both increased.[126] A double-blind study of women dissatisfied with their HT regimens showed that sexual desire, satisfaction, and frequency of sexual activity were increased when they used the estrogen/testosterone combination.[127]

Other studies have shown that the combination of 1.25 mg of esterified estrogen and 2.5 mg of methyltestosterone given daily for 2 years after surgical menopause significantly reduced the

intensity of hot flashes and vaginal dryness in 81% and 73% of women, respectively.[128]

A trial comprising 814 postmenopausal women with hypoactive sexual desire revealed that a 300-g testosterone patch improved the frequency of satisfying sexual episodes and decreased their distress.[129]

In this study, the women were not treated with estrogen or progesterone. Three excess cases of breast cancer were detected but were not statistically significant. Formulations of CEE and methyltestosterone combined either 0.625 or 1.25 mg of CEE with 5 mg of methyltestosterone. Other preparations come as either 1.25 or 0.625 esterified estrogens combined with 2.5 or 1.25 mg of methyltestosterone respectively. At present, bioidentical testosterone can be obtained only from a compounding pharmacy, where 4 to 6 mg of bioidentical testosterone is generally formulated alone or together with the biestrogen or triestrogen formulation. Testosterone cream applied to the genital region can be used as an alternative delivery method. Common prescriptions are anywhere from 1 to 10 mg/g of cream. The cream is applied to the external genitalia just before sexual activity to enhance sensitivity to touch and orgasm. Such use should not occur more than twice a week to avert local testosterone side effects, such as clitoral enlargement. The NAMS concluded that "Postmenopausal women with decreased sexual desire who have no cause other than being postmenopausal, may be candidates for testosterone treatment." Other causes of low libido should be ruled out and laboratory testing of testosterone levels should be used to monitor for supraphysiologic levels before and during therapy. Testosterone therapy is contraindicated in women with breast or uterine cancer and in those with cardiovascular or liver disease. Testosterone should be given at the lowest dose for the shortest time that meets treatment objectives.

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a bioidentical hormone and another of the androgens. It is the most abundant circulating steroid in humans. DHEA is called a precursor hormone because it is produced in large amounts in the body and because other steroid hormones are made from DHEA, including estrogen and testosterone.

Many claims have been made about DHEA's effect on the immune system, and its antiaging properties are said to include better memory, less fatigue, more energy, relaxation, and increased ability to handle stress. It is also touted as having positive effects on bone density and helping to prevent cancer and cardiovascular disease. However, the exact effect DHEA has on the body's cells is unclear. Observationally, DHEA may increase energy, improve stress response, improve muscle mass, and occasionally increase libido. However, in the DAWN trial, DHEA supplementation of 50 mg/day did not improve well-being or cognitive performance in healthy older adults.[130] In a 1-year study with 10 mg/day of DHEA alone or in combination with HT in postmenopausal women, DHEA was able to restore the androgenic milieu and had a positive effect on estrognic tone in postmenopausal women.[131] (There also appears to be an insulin-sensitizing effect of DHEA, reducing abdominal visceral fat, lowering insulin level, and producing a significant increase in insulin sensitivity.)[132]

Perhaps the most intriguing use of DHEA in menopausal women is for vaginal atrophy and/or sexual dysfunction. One study used three doses of DHEA ovules (0.25%, or 3.25 mg DHEA; 0.5%, or 6.5 mg DHEA; and 1.0%, or 13 mg DHEA) in 54 women; this was applied daily intravaginally for 12 weeks.[133] All three doses induced a significant beneficial change in vaginal epithelial cells, pH, and bothersome symptoms at 2 weeks. These benefits were accomplished with no effect on endometrial histology, and no or minimal effects on serum estrogens and androgens and their metabolites. Another intravaginal DHEA study was a prospective randomized double-blind placebo-controlled trial that evaluated the effect of daily local intravaginal DHEA ovules for 12 weeks in postmenopausal women.[134] The main assessment criteria were sexual dysfunction parameters of libido, arousal, orgasm, and dyspareunia in postmenopausal women who had vaginal atrophy. In this study, 218 postmenopausal women were randomized to receive a daily ovule of either no DHEA, 3.25 mg DHEA, 6.5 mg DHEA or 13 mg of DHEA. At 12 weeks, compared with placebo, the 13-mg ovule showed 68% improvement in the abbreviated sexual function arousal/sensation domain, in the arousal/lubrication domain by 39%, in orgasm by 75%, and in dryness during intercourse by 57%. DHEA also fared better than placebo in the desire domain of menopause-specific quality of life by 49% to 23%.

Nonbioidentical Hormones

Nonbioidentical conventional HT includes estrogens manufactured by a pharmaceutical company that are not identical in chemical structure to an endogenous hormone. As examples, conjugated equine estrogens are derived from the urine of pregnant mares. Esterified estrogens are in part estrone sulfate and in part equilin sulfates. Progestins are synthetic substances.

Oral capsules containing 1 mg of bioidentical hormones are equivalent to 0.625 mg of conjugated equine estrogens (CEE). Estrogen patches that contain 0.05 mg of bioidentical estradiol are considered to be equivalent to 0.625 mg CEE (Premarin) or 0.625 mg of esterified estrogens and equivalent to 1 mg of oral bioidentical estradiol. Current available products are available through the NAMS.

Recommended dose ratios for triestrogen and biestrogen formulations with progesterone:

- A triestrogen formulation is considered comparable with 0.625 mg Premarin/2.5 mg Provera = estriol 1 mg/estradiol 0.125 mg/estrone 0.125 mg/Prog 50 mg 1 cap twice a day
 - Or estriol 2mg/estradiol 0.25 mg/estrone 0.25mg/Prog 100 mg 1 cap a day
- A biestrogen formulation is considered comparable with:
 - 0.625 mg Premarin/2.5 mg Provera = estriol 1 mg/ estradiol 0.250 mg/Prog 50 mg. 1 cap twice a day or estriol 2 mg/estradiol 0.50 mg/Prog 100 mg. 1 cap a day
 - Vaginal estriol**:** estriol cream 1mg/gm insert 1 gm nightly for 2 weeks then a maintenance of twice a week

Additional Medications

Nonhormonal options for hot flashes include clonidine, usually 0.1 to 0.2 mg daily at bedtime. The neuroleptic neurontin is administered at 300 mg three times daily. Venlafaxine and paroxetine have shown a reduction in hot flashes in studies using 37.5 to 75 mg and 10 to 20 mg daily respectively. However, selective serotonin reuptake inhibitors and selective norepiniphrine reuptake inhibitors have occasionally been shown to cause vasomotor symptoms in both men and women. Bellergal, an ergot and belladonna combination, was used for many years for vasomotor symptoms but is now available only from compounding pharmacies. There are no studies, and empirical reports show mixed results.

Perimenopause–Menopause Evaluation

The onset of perimenopause–menopause is an important time for a comprehensive health and lifestyle evaluation. A comprehensive medical history and complete physical examination are

essential prior to initiating menopausal HT of any kind. Assessment of risk factors for stroke, CHD, venous thrombolic embolism, osteoporosis, diabetes and breast/ovarian/uterine cancer is highly recommended. DEXA testing, lipid profiles, fasting glucose, and mammography should be performed according to national guidelines, age, and medical judgment. Other selected tests depend on age, symptoms, and other medical problems.

There is no one test for menopause. Tests to determine ovarian function are not routinely done because the diagnosis of perimenopause or menopause cans largely be made based on the medical history. Practitioners can use hormone testing on an individual basis, mostly to differentiate menopause from thyroid problems, abnormal causes of a lack of menses such as elevated prolactin levels, or premature ovarian failure (premature menopause). The follicle-stimulating hormone (FSH) test is not as accurate as one would like in a perimenopausal woman. The difficulty with FSH tests is that they can fluctuate immensely during perimenopause. What a woman's FSH is on any given day is not meaningful in diagnosing her symptoms as being due to menopausal changes or not. In a woman who is still having menses, especially irregular/random cycles, as is often the case in perimenopause, the FSH fluctuates unpredictably; it can easily be within normal range on one day and elevated on another. In fact, FSH tests are frequently normal in perimenopausal women and a physician with lack of experience in menopausal/midlife patients may mistakenly attribute symptoms to depression, anxiety, or unknowns rather than to perimenopause. There are two regular scenarios to consider for ordering an FSH: (1) If a woman is suspected to be perimenopausal or menopausal and is using contraception, the FSH can be useful in determining if she still needs contraception. A FSH above 30 mIU/mL that, when repeated 1 month later, is also above 30 mIU/mL would justify a diagnosis of menopause. It is important to continue the contraception during that 1-month period until this is determined. (2) If a woman is reporting irregular menses, irritability, fatigue, insomnia, and so on, an FSH and a thyroid-stimulating hormone (TSH) test will be helpful in sorting out her problems.

There is a popular notion, especially among alternative health care providers, that saliva or serum testing or urinary hormone testing can be done to determine hormone management. One major problem with this thinking is that there is little or no value in these tests in a perimenopausal woman for the purpose of diagnosing her hormone levels. What her levels are on the hour/day/days of the test is the only information that is gleaned, but this is not diagnostic of perimenopause and, as mentioned, it is highly variable. There is no scientific evidence to support claims of increased efficacy, enhanced safety, or need for testing in order to determine the dosing of the hormonal prescriptions. In particular, there are numerous problems with saliva testing of estrogen and progesterone: (1) there is only a very small amount of these hormones in the saliva, (2) there are high false-positive elevations in those already taking a sublingual hormone, (3) there may be contamination of the saliva collection tube if a patient is already using topical hormone creams/gels, (4) there is little proficiency testing, (5) varying technologies yield broad differences in results, (6) technical challenges are not adequately addressed by all laboratories conducting these tests, (7) there is a lack of scientifically proved accuracy, and (8) there are interfering components such as food, beverages, medications, and chewing gums.

Salivary testing of cortisol and DHEA levels holds more promise, as these do not fluctuate so much from day to day, we have a known daily rhythm of cortisol production, and there are naturally higher amounts of these in the saliva than of the hormones estrogen and progesterone.

Serum testing of estrogen, progesterone and testosterone has proven to be more accurate with standardized methods of measuring. However, it is not often that even these are necessary tests in perimenopausal and menopausal women. For one, the reference ranges are often wide, and with testosterone in particular we are not even sure what the normal reference range of testosterone is for women. Again, in a perimenopausal woman, estrogen levels in particular fluctuate from day to day and therefore are not valuable in diagnosis or management. In a postmenopausal woman, estrogen and progesterone levels are predictably low, as they are supposed to be.

Although saliva estrogen/progesterone testing has yet to prove its accuracy or efficacy, even if it were accurate, neither salivary nor serum hormone testing is necessary or even helpful for the perimenopausal woman, because it is difficult to draw conclusions from test results when the hormones are in such a fluctuating state. There are so many peaks and valleys and erratic hormone activity that testing offers little value in most situations. For the women taking HT, it is tempting to think that the blood or saliva could be tested to determine dose. This is a popular recommendation in some consumer menopause books. However, there is no mathematical grid or equation comparing values of estrogen or progesterone or testosterone levels in the blood or saliva and how that would equate with a certain dose of the comparable hormone. There are reference ranges for these hormones, but we do not know exactly what dose to give in order to keep a patient within the reference range. Women absorb and metabolize hormones differently. The form of the hormones and the delivery method—oral, transdermal, sublingual, injection—are also different from woman to woman. In very occasional and selective cases, serum testing may be a helpful guide, but these are generally cases in which a woman is on HT and not doing well and, despite our best efforts with a good medical history and adjusting the dose, she still does not feel well. The majority of the time, it requires the practitioner's experience and menopause expertise and time to listen to the patient, to know what dose to prescribe and what dosing adjustments and forms and deliveries of hormones may work best. Even if testing is done, it basically comes down to good clinical judgment and the willingness of the woman and her practitioner to try something else.

Urinary testing of estrogen metabolites can be considered in evaluating a woman's risk of health problems that may be associated with higher or lower levels of certain estrogen metabolites. Although such data are limited, the use of estrogen metabolism testing to try to gain some insight as to a patient's risk of cervical and breast cancer in particular or how to decrease the recurrence of these diseases is a preventive medicine practice that is hard to argue with. A complete discussion of the metabolites of the various forms of estrogen, progesterones, DHEA, and testosterone is beyond the scope of this chapter. As an example, the metabolites of one estrogen, estrone, are known to play both oncogenic and antioncogenic roles. Estrone's oncogenic metabolites, 4-hydroxyestrone (4-OH estrone), considered the most carcinogenic estrogen metabolite) and 16α-OH estrone (needed in small amounts because of its bone-building actions), are produced by phase I metabolism. Estrone's protective metabolites (2-hydroxyestrone [2-OH estrone], 2-methoxyestrone [2-CH3O-estrone], and estriol [E3]) are produced in phase II metabolism. The primary value of these tests is that they help the clinician to use nutrients, botanicals, and lifestyle modification to facilitate

the optimal metabolism of these hormones through the pathways that lead to the potential for the reduction of breast and cervical cancers.

Practitioners should be encouraged to rethink the use of salivary and serum estrogen/progesterone testing in the diagnosis and management of perimenopausal/menopausal symptoms. In the perimenopausal woman, these hormones fluctuate within a day and from day to day. In the postmenopausal woman not on hormones, I would also assert that this is a poor use of a woman's funds. Her estrogen and progesterone levels are low. She is a postmenopausal woman, and mother nature had this in mind. It is rarely necessary to test the estrogen levels of a postmenopausal woman on HT for prescription management; however, there are times when testing may help to determine absorption/delivery and dosing issues when there is a lack of response or an adverse response to customary prescriptions. For select and very difficult cases, it is likely more useful to use the testing of neurotransmitters, amino acids, and nutrients while ensuring that due diligence has been done with regard to the basics of history, physical examination, and conventional testing.

THERAPEUTIC APPROACH

Menopause is a normal and natural part of aging and each woman experiences it in her own way. However, premature, surgical, or medication-induced menopause is not normal and should be addressed with individual consideration as to the benefits and risks of each therapy. Using natural therapies, HT, other pharmaceuticals, or some combination of each is a personal decision for each woman. Our views of menopause and aging and our concerns about long-term health problems evolve over time. Balance is necessary and the over medicalization of menopause is inappropriate. The integrative provider can remind women that menopause can be a time of positive, life-changing insights, empowerment, and personal growth.

Many natural measures can help alleviate the most common symptoms of menopause. In most cases, HT either is not necessary or is needed for only 1 to 4 years. However, in women at high risk for osteoporosis and those who have already experienced significant bone loss and also have menopausal symptoms or do not tolerate osteoporosis medications, HT may be indicated. For women who have menopausal symptoms that they are not tolerating well, bHT, cbHT, or cHT can be used, with periodic attempts at reducing or discontinuing the hormones.

Diet

Consumption of foods that may provide modest symptom relief, such as soy foods, legumes in general, and flaxseeds should be increased. A whole-foods diet that addresses the prevention or management of cardiovascular disease, diabetes, and osteoporosis should also be attended to.

Supplements

- Vitamin E: 800 IU/day until symptoms have improved, then 400 IU/day
- Hesperidin: 900 mg/day; or PCOs from grape seed or pine bark: 200 mg/day
- Vitamin C: 1200 mg/day
- Consider gamma-oryzanol: 300 mg/day

Botanical Medicines

Choose one or more of the following for general symptom relief:
- Standardized extract of black cohosh: 40 mg to 80 mg/day
- Gelatinized maca extract: 1000 mg twice a day or dose equivalent to 3500 dried powdered maca root a day
- Red clover extract: 40 to 80 mg/day

Choose one of the following if symptoms of anxiety or depression are significant (can be used with the previous list):
- Hops extract standardized for 8-prenylnaringenin: 120 to 300 mg/day
- Kava extract: 45 to 80 mg of kavalactones three times a day
- St. John's wort extract standardized to 0.3% hypericin: 900 to 1800 mg/day

Choose the following if symptoms of vaginal atrophy do not respond after 2 months of treatment with other botanical(s):
- Kudzu: dried powdered root 20 to 50 mg a day

Choose the following if symptoms of menopausal migraine are significant:
- 100 mg *Angelica sinensis* extract, 60 mg soy isoflavones, and 50 mg of black cohosh extract a day.
- If symptoms do not sufficiently improve consider HT.

Lifestyle

Facilitate a regular exercise program, at least 30 minutes four times a week. For weight loss in midlife women, it is likely that 60 minutes of exercise every day will be needed to combat insulin resistance and achieve successful weight loss.

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CHAPTER 189

Menorrhagia

Tori Hudson, ND

DIAGNOSTIC SUMMARY

- Excessive menstrual bleeding—blood loss greater than 80 mL—occurring at regular cyclic intervals (cycles are usually but not necessarily of normal length).
- May be due to dysfunctional uterine bleeding (no organic cause); often due to local lesions (e.g., uterine myomas [fibroids], endometrial polyps, endometrial hyperplasia, endometrial cancer, adenomyosis, and endometritis); other causes are bleeding disorders and hypothyroid.

The diagnosis begins with the history and physical examination. The following tests and procedures are performed for diagnosis and management on an as-needed basis: pelvic examination, pelvic ultrasound and/or pelvic sonohystogram, cervical cytology, sexually transmitted infection testing, thyroid function studies, pregnancy test, complete blood count (CBC), ferritin measurement, liver function or coagulation studies, measurement of follicle-stimulating hormone (FSH) and luteinizing hormone (LD), hysteroscopy, dilation and curettage (D&C).

GENERAL CONSIDERATIONS

There are many types of abnormal uterine bleeding. This chapter focuses on menorrhagia (regular/normal intervals with excessive flow and duration). Other patterns of abnormal bleeding are oligomenorrhea (interval greater than 35 days), polymenorrhea (interval less than 21 days), metrorrhagia (irregular/frequent intervals with excessive flow and duration), menometrorrhagia (prolonged heavy bleeding at irregular intervals), and intermenstrual bleeding (variable amounts occurring between regular menses).

The normal menstrual cycle is defined as 28 days (±7 days) in length and 4 days (±4 days) in duration, with a blood loss of 40 mL (±20 mL).

The complaint of menorrhagia is largely subjective, because an objective measurement of blood loss is rarely made. Furthermore, there is a poor correlation between measured blood loss and a patient's assessment of her bleeding (discussed in more detail later). Studies that have measured blood loss have demonstrated that patients with menorrhagia have a considerable increase in menstrual blood flow during the first 3 days (up to 92% of their total menses being lost at this time). This finding suggests that the mechanisms responsible for cessation of menstruation are as effective in women who have menorrhagia as in normal women despite the very high blood loss.

Etiology

As with any disease, proper determination of the cause is essential for effective treatment. The appropriate methodology for ruling out pathologic causes is beyond the scope of this chapter and can be found in any good text on gynecology (Table 189-1).[1] It is important to be aware of the scope of causes so that one does not just assume that the problem is "dysfunctional uterine bleeding" (DUB)—defined as abnormal uterine bleeding without any demonstrable organic cause. Abnormal bleeding can include menorrhagia, oligomenenorrhea, polymenorrhea, metrorrhagia, menometrorrhagia, and intermenstrual bleeding. Abnormal bleeding is best understood by thinking in categories of abnormalities: hormonal, mechanical, and clotting. Hormonal causes include anovulation and luteal phase defects and stress,

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TABLE 189-1 **Pathologic Causes of Menorrhagia**

CAUSE	POSSIBLE ETIOLOGY
Anovulation	Excessive estrogen
	Failure of midcycle surge of luteinizing hormone
	Hypothyroidism
	Hyperprolactinemia
	Polycystic ovary disease
Intrauterine structural defects	Fibroids
	Polyps
	Cancer
	Ectopic pregnancy
	Intrauterine devices
Bleeding disorders	See Table 189-2

Data from Federman DD. Ovary. In Dale DC, Federman DD. Scientific American medicine. New York: Scientific American, 1997, 3:III:9-3:III:10.

exogenous hormones, hypothyroidism, and ovarian cysts. Mechanical causes include uterine polyps, uterine fibroids, endometrial hyperplasia, uterine cancer, intrauterine devices (IUDs), atopic pregnancy, pregnancy, endometriosis, and endometritis. Clotting abnormalities include vitamin K deficiency, drug-induced hemorrhage (heparin, warfarin, aspirin), dysproteinemias, disseminated intravascular coagulation, severe hepatic disease, primary fibrinolysis, and circulating inhibitors of coagulation; not all of these will cause menorrhagia; rather, they give rise to other abnormal bleeding patterns.

Abnormalities in Prostaglandin Metabolism

The etiology of functional menorrhagia is currently believed to involve abnormalities in the biochemical processes of the endometrium that control the supply of arachidonic acid for prostaglandin synthesis.[2,3] Menorrhagic endometrium incorporates arachidonic acid into neutral lipids to a much greater extent than normal, whereas its incorporation into phospholipids is lower. The greater arachidonic acid release during menstruation results in the higher production of series 2 prostaglandins, which are thought to be the major factor both in the excessive bleeding seen at menstruation and in the symptoms of dysmenorrhea. The excessive bleeding during the first 3 days appears to be due to the vasodilatory properties of prostaglandins (PGs) E_2 and PGI_2 and the antiaggregating activity of PGI_2, whereas the pain of dysmenorrhea is due to the overproduction of PGF_{2a}.

Thyroid Abnormalities

The association of overt hypothyroidism or hyperthyroidism with menstrual disturbances is well known. However, even minimal thyroid dysfunction, particularly minimal subclinical insufficiency as determined by testing the thyroid stimulating hormone (TSH), may be responsible for menorrhagia and other menstrual disturbances.[4] Patients with minimal thyroid insufficiency and menorrhagia have shown dramatic responses to thyroxine.[4] It has been recommended that patients with long-standing menstrual dysfunction (who have no obvious uterine disease) should be considered for TSH testing. This approach is preferable to the empiric use of thyroid hormone.

Estimating Menstrual Blood Loss

Physicians often believe that they can assess menstrual blood loss by asking the patient to estimate the number of pads or tampons used during each period and the duration of the period. However, studies have demonstrated that there is no correlation between measured blood loss and these assessments.[1,5,6] A woman's assessment of her blood loss is extremely subjective, as demonstrated by one study finding that 40% of women with a menstrual blood loss exceeding 80 mL considered their periods only moderately heavy or scanty, whereas 14% of those with a measured loss of less than 20 mL judged their periods to be heavy.[6]

Serum ferritin levels may be the best indicator of excessive menstrual blood loss, but their determination may not be practical in terms of immediate need to know. Despite inaccuracies of patient reporting, it is important for the clinician to make an attempt at understanding blood loss. Excessive blood loss should be a concern if a woman is bleeding longer than 7 straight days or more frequently than every 21 days and is changing a pad or tampon every hour for more than half a day. Women who are changing a pad and/or tampon every half hour or even more often require urgent, perhaps emergency attention. Symptoms of lightheadedness, dizziness, fainting, or the like are cause for immediate concern. Any amount of bleeding in a postmenopausal woman is considered abnormal.

THERAPEUTIC CONSIDERATIONS

Many women have been subjected to needless hysterectomies because of inadequate medical management of their heavy bleeding cycles. This practice was more common over 20 years ago, but it is still followed in varying and disturbing fashion in different parts of the country. Clearly, the standard of care in conventional medicine is not the same everywhere. The time for a hysterectomy should be determined by the inability to manage menorrhagia adequately with nonsurgical interventions, patient safety and health, lack of a clear diagnosis, and the stress and fatigue wearing on the patient so that she expresses a preference for the procedure. Although we recognize the need for hysterectomy in select circumstances, most cases of menorrhagia can be treated with nonsurgical therapies, including botanicals, nutritional interventions, and hormonal and pharmaceutical therapies. Less permanent surgical procedures than hysterectomy now spare the uterus—D&C, hysteroscopic resections and ablations, and uterine artery embolization.

Psychological Considerations

Stress affects bleeding patterns directly by influencing the hypothalamic/pituitary/ovarian axis. This influence causes anovulation and the subsequent lack of progesterone production. As a result, the endometrium is in an estrogen-dominant state and becomes thickened and plump without the opposing and stabilizing effect of progesterone. This state can then lead to heavy bleeding at the next menstrual cycle. Adolescents account for many of these cases, and the remainder are often perimenopausal women.

Nutrition

Iron Deficiency

A menstrual blood loss exceeding 60 mL per period is associated with negative iron balance in most cases.[7] Although

menstrual blood loss is well recognized as a major cause of iron-deficiency anemia in fertile women, it is not as well known that chronic iron deficiency can be a cause of menorrhagia. Taymor et al[8] have made such a suggestion on the basis of several observations:

- Response to iron supplementation alone in 74 of 83 patients (in whom organic disease had been excluded)
- High rate of organic disease (fibroids, polyps, adenomyosis, etc.) in the patients with no response to iron supplementation
- Associated rise in serum iron levels in 44 of 57 patients
- Decreased response to iron therapy when initial serum iron levels were high
- Correlation of menorrhagia with depleted tissue iron stores (bone marrow) irrespective of serum iron level
- A significant double-blind placebo-controlled study displaying improvement in 75% of those given iron supplementation compared with 32.5% of those given the placebo

Hematologic screening and serum ferritin determination (the first parameter to indicate decreased iron levels) should be performed for patients complaining of menorrhagia. In one study, women who were menorrhagic (according to subjective information) displayed significantly lower serum ferritin levels than controls, but hemoglobin concentration, mean corpuscular volume, and mean corpuscular hemoglobin were not significantly different between the two groups.[9] (The investigators in this study erroneously stated that such women do not require prophylactic iron supplementation since no hematologic abnormalities appeared despite significantly reduced iron stores.)

Iron supplementation, at a daily dose of 100 mg of elemental iron, has been recommended as a prophylactic therapy by several researchers because chronic iron deficiency appears to promote menorrhagia, and iron-containing enzymes are depleted before hematologic changes are observed. A decreased serum ferritin level is a good indication of the need for iron supplementation.

Vitamin A

In one study, serum retinol levels were found to be significantly lower in women with menorrhagia than in healthy controls. In this study, vitamin A was used as a treatment in 40 women diagnosed as having menorrhagia due to a number of different causes. In the group who received 60,000 IU of vitamin A for 35 days, menstruation returned to normal in 23 patients (57.5%) and was reduced in 14 (35%). Overall, the vitamin A was ineffective in only 3 of the 40 women (7.5%), and 92.5% of the 37 women had either complete relief or significant improvement.[10] Although potentially effective, this therapy should not be used in women at risk of pregnancy.

Vitamin C and Bioflavonoids

Capillary fragility is believed to play a role in many cases of menorrhagia. Supplementation with vitamin C (200 mg three times daily) and bioflavonoids (dose not specified) was shown to reduce menorrhagia in 14 of 16 patients.[11] One of the patients with no response had endometriosis and the other had metrorrhagia. Bioflavonoids, like vitamin C, can help strengthen the walls of capillaries. Bioflavonoids may also reduce heavy bleeding through their antiinflammatory effect. A natural antiinflammatory such as a bioflavonoid may be used to reduce heavy bleeding, just as conventional medicine uses nonsteroidal antiinflammatory agents.

Because vitamin C is known to significantly increase iron absorption, its therapeutic effect could also be due to enhanced iron absorption.

TABLE 189-2 **Acquired Generalized Hemorrhagic Disorders**

FACTOR	POSSIBLE CAUSE
Deficiency of vitamin K	Low intake, impaired absorption, antimicrobial inhibition of gut flora that synthesize vitamin K
Drug-induced hemorrhage	Heparin, warfarin
Dysproteinemias	Myeloma, macroglobinemia
Disseminated intravascular coagulation	
Severe hepatic disease	
Circulating inhibitors of coagulation	
Primary fibrinolysis	

Data from Gubner R, Ungerleider HE. Vitamin K therapy in menorrhagia. South Med J 1944;37:556-558.

Vitamin E

One group of investigators has suggested that free radicals have a causative role in endometrial bleeding, particularly in the presence of an intrauterine device.[12] Vitamin E supplementation (100 IU every 2 days) resulted in improvement in all patients by the end of 10 weeks.[13] Although vitamin E may have produced its effects via its antioxidant activity, it is equally plausible that the vitamin affected prostaglandin metabolism in a manner that reduced bleeding.

Vitamin K and Chlorophyll

Although bleeding time and prothrombin levels in women with menorrhagia are typically normal, the use of vitamin K (historically in the form of crude preparations of chlorophyll) has clinical and limited research support.[14,15] Also, some women are found to have an inherited or acquired bleeding disorder. Table 189-2 lists some causes of acquired hemorrhagic disorders.

Essential Fatty Acids

Menorrhagia is associated with the increased availability of arachidonic acid in the uterus.[16] It now appears that the majority of tissue arachidonic acid is derived from the diet. It is therefore possible that by reducing the intake of animal products and/or increasing the intake of linoleic, linolenic, and dihomo-gamma-linolenic acid, blood loss could be curtailed by decreasing the availability of arachidonic acid. Consuming larger proportions of fish, nuts, and seeds can have an effect over time in altering the production of arachidonic acid. The use of fish oils, flax oil, and other seed oils as supplements may produce this favorable effect more quickly.

Vitamin B Complex

There may be a correlation between a nutritional deficiency of B vitamins and menorrhagia. It has been shown that in vitamin B complex deficiency, the liver loses its ability to inactivate estrogen. Some cases of menorrhagia are due to an excess estrogen effect on the endometrium. Therefore, supplementing with a complex of B vitamins may normalize estrogen metabolism. A study conducted in the 1940s in a series of consecutive cases showed that a B-complex preparation led to "prompt" improvement in both menorrhagia and metrorrhagia.[17] The preparations used were thiamin 3 to 9 mg, riboflavin 4.5 to 9 mg, and niacin up to 60 mg.

Botanical Medicines

Zingiber officinale (Ginger)

Ginger has been shown to inhibit prostaglandin synthetase, the enzyme believed to be related to the altered prostaglandin-2 ratio associated with excessive menstrual loss.[18] The inhibition of prostaglandin and leukotriene formation could explain the traditional use of ginger as an antiinflammatory agent.

Vitex agnus castus (Chaste Tree)

Chaste tree is probably the best-known herb in all of Europe for treatment of hormonal imbalances and abnormal bleeding in women. Since at least the time of the Ancient Greeks, chaste tree has been used for the full scope of menstrual disorders, including heavy menses. It is mainly the seeds that are used for medicine in Europe and the United States. Chaste tree acts on the hypothalamus and pituitary glands. It increases LH production and mildly inhibits the release of FSH. The result is a shift in the ratio of estrogen and progesterone that effectively becomes a progesterone-like action. Chaste tree has been studied and been shown to effect improvements in amenorrhea, polymenorrhea, oligomenorrhea, and menorrhagia.[19–21] In a study observing 126 women with menstrual disorders, with the use of 15 drops of chaste tree liquid extract, the duration between periods lengthened from an average of 20.1 days to 26.3 days in the 33 women with polymenorrhea, and the number of heavy bleeding days was shortened in the 58 patients with menorrhagia.

Chaste tree is the most important herb for normalizing the menstrual flow, but it is not a fast-acting herb. Its effects may not be known for 3 or 4 months.

Traditional Astringent Herbs

Astringent herbs are used to reduce blood loss from the reproductive tract as well as the gastrointestinal tract, respiratory tract, and skin. The astringents most effective in uterine blood loss are often those that are high in tannins, although the tannins are most likely not the only constituent responsible. The following eight herbs are major astringent and hemostatic agents used in chronic and acute menorrhagia. These herbs are usually used in combination formulations for weeks or months before they produce results.

- Yarrow *(Achillea millefolium)*
- Ladies' mantle *(Alchemilla vulgaris)*
- Cranesbill *(Geranium maculatum)*
- Beth root *(Trillium erectum)*
- Greater periwinkle *(Vinca major)*
- Horsetail *(Equisetum arvense)*
- Goldenseal *(Hydrastis canadensis)*
- Shepherd's purse *(Capsella bursa pastoris)*

Shepherd's purse has a long history of use in the management of obstetric and gynecologic hemorrhage. Intravenous and intramuscular injections of this herb have been found to be effective (in uncontrolled studies) in menorrhagia owing to functional abnormalities and fibroids.[14,22] The hemostatic action of shepherd's purse is believed to be due to its high concentration of oxalic and dicarboxylic acids.

Traditional Uterine Tonics

Uterine tonics have enjoyed a long history of use in traditional herbal medicine for easing menstrual flow. Traditional and empiric views of uterine tonics hold that if the uterus is hypotonic, there may be heavy bleeding, and that improving uterine tone tends to normalize and regulate menstrual bleeding. Uterine tonics or amphoterics that regulate tone and potentially reduce bleeding are as follows:

- Blue cohosh *(Caulophyllum thalictroides)*
- Helonia *(Chamaelirium luteum)*
- Squaw vine *(Mitchella repens)*
- Raspberry leaves *(Rubus idaeus)*
- Life root *(Senecio aureus)*

Astringent and uterine tonic herbs can be used in combination formulations or for weeks to months as teas, liquid extracts, or powders in capsules. These herbs must usually be taken in combination formulations for weeks or months to produce results.

Traditional Herbs for Semi-acute and Acute Blood Loss When the Patient Is Stable

The traditional herbs listed here have dose-specific toxicities and should be used only after reference to a botanical reference text to ensure proper dosing. Cinnamon essential oil should be used at 1 to 5 drops every 3 to 4 hours. The other herbs should not exceed 20 drops every 2 hours or 1 capsule every 4 hours.

- Cinnamon essential oil *(Cinnamomum verum)*
- Life root *(Senecio aureus)*
- Canadian fleabane *(Erigeron canadensis)*
- Greater periwinkle *(Vinca major)*
- Shepherd's purse *(Capsella bursa pastorus)*
- Yarrow *(Achillea millefolium)*
- Savin *(Sabina officinalis)*
- Beth root *(Trillium erectum)*

These botanicals should be used as the sole treatment only in women who are stable. In unstable patients, they should be used only as adjuncts to intravenous estrogens or other pharmaceutical or surgical interventions. They can be used in patients with chronic menorrhagia who are stable and for semi-acute blood loss or acute blood loss if a patient shows no signs of instability and improves within 12 to 24 hours.

Bioidentical Hormones

Estrogens and progestogens, including bioidentical estradiol and progesterone, can be extremely effective in managing menorrhagia, in the same way as conjugated equine estrogens (CEEs) or synthetic estrogens and progestins are in conventional medicine. For control of an acute bleeding episode, the use of bioidentical estradiol should be just as effective as one of the dosing regimens of CEE. These hormones are prescription items and should be administered by a practitioner qualified to use them. Cyclic bioidentical progesterone can be used to correct recurring menorrhagia, and a short course of oral bioidentical progesterone can be used in many cases of acute menorrhagia. Bioidentical progesterone creams will not have as significant an effect as the higher-dose pills or oral micronized natural progesterone.

THERAPEUTIC APPROACH

Patients who are unstable—as evidenced by hypotension, dizziness, loss of consciousness, chills or fever, or passage of large amounts of tissue—require transfer to a hospital for intravenous estrogens, D&C, and/or hysterectomy or uterine ablation.

The first step in treating a woman with menorrhagia is to control the cause. When the excessive bleeding has been determined to be related to prothrombin time, hematologic status, or thyroid function, such abnormalities can be corrected. Mechanical causes of menorrhagia may be managed without removal of the cause, such as an endometrial polyp or uterine fibroid. But if no improvement occurs, conventional treatment, including surgery, may be

necessary. Endometrial hyperplasia requires definitive and proved progesterone or progestin treatment with biopsy-proved improvement. Endometrial cancer requires a hysterectomy. Infections of the uterus must be treated appropriately. Ectopic pregnancy with or without bleeding necessitates immediate conventional intervention. In cases of chronic menorrhagia or episodic acute blood loss that is effectively managed, a CBC and serum ferritin measurement can be used to help monitor the patient's anemia status.

Diet

The diet should be relatively low in sources of arachidonic acid (animal fats), high in fish oils (docosahexaenoic and eicosapentaenoic acids), and high in linolenic and linoleic acids (vegetable oil sources). Green leafy vegetables and other sources of vitamin K should be eaten freely. Fruits, vegetables, and spices with antiinflammatory effects include garlic, onions, cumin, pineapple, and citrus.

Supplements

High potency multiple vitamin and mineral formula
- Vitamin C: 1 g three times per day with meals
- Bioflavonoids (mixed from citrus): 1000 mg/day
- Chlorophyll: 25 mg/day (use a crude form) or 1 mg vitamin K_1
 If low serum ferritin is confirmed:
- Iron: 30 mg, bound to either pyrophosphate, succinate, glycinate, or fumarate, twice a day between meals (if this recommendation results in abdominal discomfort, take 30 mg with meals three times a day)

Botanical Medicines

For chronic recurring menorrhagia:
- *Vitex agnus castus (chaste berry):* The usual dosage of chaste berry extract (often standardized to contain 0.5 % agnuside) in tablet or capsule form is 175 to 225 mg/day. If using the liquid extract, the typical dosage is 2 to 4 mL (1/2 to 1 tsp)/day.

 For semi-acute cases, the following botanicals should be given:
- Botanical tincture of equal parts of each herb (20 to 30 drops every 2 to 3 hours): yarrow, greater periwinkle, shepherd's purse, life root
- Cinnamon oil: 1 to 5 drops every 3 to 4 hours

Bioidentical Hormones

- Oral micronized progesterone: 100 mg twice a day given in the luteal phase for 12 days per month for recurring menorrhagia; 200 to 400 mg per day for 7 to 12 days may be used for semi-acute blood loss, followed by a cyclic hormone product for 21 days on and 7 days off.
- Progesterone cream (a product that contains at least 400 mg of progesterone per ounce): 1/4 to 1/2 tsp twice a day for 12 days per month during the luteal phase for cases of mild recurring menorrhagia
- Bioidentical estradiol: High-dose regimen for acute bleeding is as follows: 4 mg estradiol every 4 hours for 24 hours, then a single daily dose of 1 mg for 7 to 10 days, followed by oral micronized progesterone 200 mg before bed for 7 to 12 days.

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CHAPTER 190

Migraine Headache

Nancy Sudak, MD

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DIAGNOSTIC SUMMARY

- Recurrent paroxysmal attacks of headache.
- Headache is typically pounding and unilateral but may become generalized.
- Attacks often preceded by psychological or visual disturbances (auras); accompanied by anorexia, nausea, and gastrointestinal upset; and followed by drowsiness.
- Physical examination typically reveals no focal neurologic deficit.

GENERAL CONSIDERATIONS

The lifetime prevalence of migraine headache is at least 18%.[1] Women are more frequently affected than men, and more than half of affected patients have a family history of migraine. Prevalence is highest in North America and lowest in Africa and Asia.[2] Although many migraines come on spontaneously, 10% to 20% of migraineurs may have warning symptoms (auras) before the onset of pain.[3] Typical auras last a few minutes and may include the following:

- Blurring or bright spots of vision
- Anxiety
- Fatigue
- Disturbed thinking
- Unilateral peripheral numbness or tingling

The pain of migraine headache results from sensory responses distinct from brain tissue because the brain itself is insensate. Cephalic pain arises from the meninges, large cranial vessels, proximal intracranial vessels, and the scalp vasculature and muscles when stretched or tensed.

Pathophysiology

The sequence of events producing migraine headache is unclear, but migraine headache is no longer believed to be a primary vascular event.[1,4,5] Considerable evidence supports an association between migraine headache and vasomotor instability, but vasomotor changes are now believed to be epiphenomena, and a singular pathophysiologic mechanism has not been identified. Despite the awareness of multiple pathways involved in migraine, a clear understanding of its pathogenesis is at present not within reach. However, many of the key elements involved are worth discussing, because they relate to prevention and treatment.

Vasomotor Activity

Migraineurs experience heightened central nervous system (CNS) activity, which appears to be mediated by the trigeminovascular system. Stimulation of the trigeminal ganglion results in the release of vasoactive neuropeptides, including substance P, calcitonin gene–related peptide, and neurokinin A. Release of these neuropeptides results in the process of neurogenic inflammation. The two main components of this sterile inflammatory response are vasodilation and plasma protein extravasation.

It has been clinically observed that superficial temporal vessels are visibly dilated during migraine, and local compression of these vessels or the carotid artery temporarily relieves migraine pain.[6] However, other types of extracranial vasodilation (e.g., heat- or exercise-induced) are not associated with migraine. Despite the extracranial vasodilation, the patient appears pale during the headache, suggesting

constriction of the small vessels. This observation is supported by the presence of a lower skin temperature on the affected side. The clinical manifestations of focal or diffuse cerebral or brainstem dysfunction have been attributed to intracranial vasoconstriction. Some studies measuring cerebral blood flow have demonstrated a reduction in flow, sometimes to very low and critical levels, during the prodromal stage. The aura of migraine is apparently caused by cortical spreading depression (CSD),[7-10] a process that produces transient depression of spontaneous and evoked neuronal activity. During this time, the brain fails to maintain normal ionic homeostasis and efflux of excitatory amino acids from neurons.[7] CSD may represent a significant link to the decrease in cerebral blood flow observed during a migraine aura.[11,12] This stage may be followed by a phase of increased blood flow, which can persist for more than 48 hours.

We are seeing increasing evidence that CSD may play a role in migraine pathophysiology and overall cerebral hyperexcitability. In addition, triggering CSD can require activation of the *N*-methyl-D-aspartate (NMDA) receptor, which augments depolarization.[13] In one study, CSD was prevented in the presence of ifenprodil, a selective NMDA receptor antagonist.[14] NMDA receptor antagonist therapy is suggested to be a potentially novel therapeutic approach.[15] The anticonvulsant topiramate has become a first-line treatment for migraine; its efficacy as a GABA-agonist and glutamate antagonist supports the concept of excessive cerebral excitability as related to NMDA receptor activation.[16] Calcitonin gene–related peptide (CGRP), among the most potent vasodilators known, is found to be elevated after migraine. CGRP antagonists have been demonstrated to be effective in relieving migraine pain without causing vasoconstriction and are being investigated for their therapeutic efficacy and safety.[17]

Evidence indicates that migraine patients have a functional abnormality of vasomotor control. Migraineurs suffer from syncope and orthostatic intolerance more often than patients who do not have migraine (who are without clear interictal signs of autonomic nervous system dysfunction)[18]; they also seem to be abnormally sensitive to the vasodilatory effects of physical and chemical agents.

Migraine also has complex relations with disorders of the cerebrovasculature, the cardiovascular system, and the heart. Right-to-left shunt, patent foramen ovale, and mitral valve prolapse are all associated with a higher prevalence of migraine headache. Migraine has also been shown to be associated with an increase in cardiovascular risk factors (ratio of total cholesterol to high-density-lipoprotein cholesterol >5), hypertension, and history of early-onset coronary heart disease or stroke). Although the risk for stroke is highest among young women who have migraine with aura, particularly if they smoke or use oral contraceptives, studies suggest that male and female migraineurs are at increased risk for ischemic stroke regardless of age.[20] It is additionally worth noting that migraine and epilepsy are comorbid disorders that share common physiologic mechanisms and treatments.[19]

Platelets and Serotonin

Serotonin is normally stored in platelets and released by platelet aggregation and in response to various stimuli, such as catecholamines. There is no difference in total serotonin content between normal platelets and the platelets of migraine patients. However, the quantity of serotonin released by the platelets of the migraine patient in response to serotonin stimulation, although normal or even subnormal immediately after an attack, becomes progressively higher as the next attack approaches.[21] The rise of plasma serotonin may not be causative in migraine but could represent a self-defense mechanism.[7] Platelet activation has been observed in electron micrographs during migraine, which may be a result of the neurogenic inflammation.[8] It is worth noting, on the other hand, that platelet deactivating agents—such as aspirin, feverfew, and essential fatty acids—appear to be effective in migraine prevention. Biochemical studies have shown that serotonin is a stress-response system that involves increased turnover during both acute and longer-term stress.[22]

The connection between serotonin and headaches began in the 1960s when researchers found that there was an increase in the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the urine during a migraine.[23] Initially, serotonin excess was implicated; however, newer information indicates that the factor responsible for the increase in 5-HIAA is more likely the increased breakdown of serotonin as a result of increased activity of monoamine oxidase (MAO).[24,25] Because migraineurs appear to have low levels of serotonin in their tissues, researchers began to refer to migraine as a "low-serotonin syndrome."[25] Low serotonin levels are thought to lead to a decrease in the pain threshold in patients with chronic headaches. This contention is strongly supported by over 35 years of research, including positive clinical results in double-blind studies with the serotonin precursor 5-hydroxytryptophan (5-HTP). Current understanding indicates that a low-serotonin state facilitates activation of the trigeminovascular nociceptive pathway, as induced by CSD.[26] For more information on the clinical studies with 5-HTP in migraine headaches, see Chapter 98.

The triptan family of drugs are the $5HT_{1b}$ and $5HT_{1d}$ receptor agonists. These agents constrict blood vessels, block neurogenic inflammation and neural peptide release, and may also inhibit neuronal activity within the trigeminovascular system.[27-29] The safety of these agents has been questioned, because the triptans activate serotonin receptors on cerebral vessels and, to a lesser extent, coronary arteries. The chest pain that is reported by 3% to 5% of patients taking oral triptans has generally not been associated with electrocardiographic changes and does not appear to be due to cardiac ischemia.[30] However, triptans should be avoided in patients with ischemic heart disease, uncontrolled hypertension, or cerebrovascular disease.[1] It is generally advisable to avoid the use of triptans, ergotamine-based drugs, and selective serotonin reuptake inhibitors (SSRIs) simultaneously, although the risk of serotonin syndrome appears to be low.[30] Extreme caution is advised in considering the use of an SSRI along with 5-HTP. Although SSRIs are sometimes used for migraine prophylaxis, the scientific effect is unknown, the quality of evidence poor, and the impression of clinical impact low.[22,31,32]

Neuronal Disorder

It has been suggested that the trigeminovascular neurons, which innervate the pial arteries, release calcitonin gene–related peptide and the peptide substance P, either directly from various cellular signals or secondarily to CNS activation.[33] Substance P is a key pain mediator and its release into the arteries is associated with vasodilation, mast cell degranulation, and increased vascular permeability. It is believed that the endothelial cells of the arteries respond to substance P and CGRP by releasing vasoactive substances such as arachidonic acid metabolites, purine compounds, or molecules containing carbonyl groups. This theory suggests that functional changes within the noradrenergic system constitute the threshold for migraine activation, and it is through modulation of sympathetic activity that potentiators exert their effects.[33] Chronic stress is a chief potentiator in this model.

Unified Hypothesis

The mechanism of migraine can be described as a three-stage process: initiation, prodrome, and headache. Although a particular stressor

may be associated with the onset of a specific attack, it appears that initiation is dependent on the accumulation over time of several stressors. These stressors ultimately affect serotonin metabolism (Box 190-1). Once a critical threshold of susceptibility is reached, a cascade of events is initiated. This susceptibility is probably based on a combination of decreased tissue serotonin levels, platelet modulation, alteration in the responsiveness of key cerebrovascular end organs, increased sensitivity of the intrinsic noradrenergic system of the brain, and the accumulation of histamine, arachidonic acid metabolites, or other mediators of inflammation. The platelet changes include increased adhesiveness, enhanced tendency to release serotonin, and increased levels of arachidonic acid in the membranes. Once platelets are stimulated to secrete serotonin, sequelae including platelet aggregation, vasospasm, and inflammatory processes lead to local cerebral ischemia. This is followed by rebound vasodilation and the release of peptide substance P and other mediators of pain. These events are summarized in Figure 190-1.

BOX 190-1 Factors that can Trigger Migraine Headaches

- Low serotonin levels
 - Genetics
 - Shunting of tryptophan into other pathways
- Foods
 - Food allergies
 - Histamine-releasing foods
 - Histamine-containing foods
- Alcohol, especially red wine
- Chemicals
 - Nitrates
 - Monosodium glutamate (MSG)
 - Nitroglycerin
- Withdrawal from caffeine or other drugs that constrict blood vessels
- Stress
- Emotional changes, especially letdown after stress, and intense emotions such as anger
- Hormonal changes—e.g., menstruation, ovulation, birth control pills
- Too little or too much sleep
- Exhaustion
- Poor posture
- Muscle tension
- Weather changes—e.g., changes in barometric pressure, exposure to sun
- Glare or eyestrain

THERAPEUTIC CONSIDERATIONS

Pharmacologic treatment of migraine headache tends to be inadequate because it fails to address the underlying cause. Modern first-line pharmaceuticals for prophylaxis in adults include propranolol, valproic acid, and topiramate, but a host of other drugs are helpful for migraine prevention. Despite their effectiveness, some preventive drugs can exacerbate other conditions. Flunarizine (unavailable in the United States), valproate, and amitriptyline, for example, should be used with caution or avoided in obese patients because they tend to cause weight gain. Amitriptyline and pizotifen can worsen glaucoma and urinary retention. Beta blockers can exacerbate asthma and diabetes a and topiramate can enhance the risk of renal calculi.[34] Most guidelines from European countries include a nondrug treatment section, which also includes behavioral and psychological techniques.[35] Medications are considered efficacious if they reduce migraine frequency by at least 50%.[36] This is an important consideration where nonpharmacologic treatment options are concerned. The first step in treating migraine headache is to identify the precipitating factor or factors. Although food intolerance/allergy is important, many other factors must be considered as either primary causes or contributors to the migraine process. In particular, it is very important to assess the role that headache medications may be playing, particularly in chronic headaches.

Drug Reaction

Medication-overuse headache (MOH), also known as analgesic rebound headache, drug-induced headache, and medication-misuse headache, deserves mention because it frequently precludes the successful treatment of the underlying primary headache disorder, most often migraine or tension-type headache. In some cases, MOH may be associated with the development or maintenance of a chronic daily headache syndrome.[37] After successful MOH treatment, preventive medications for the underlying primary headache disorder have a greater chance of success. Patients who were able to discontinue their daily use of symptom-modifying medications experienced improvement in their chronic headaches in addition to greater efficacy of their prophylactic medications.[38] All drugs used for symptomatic

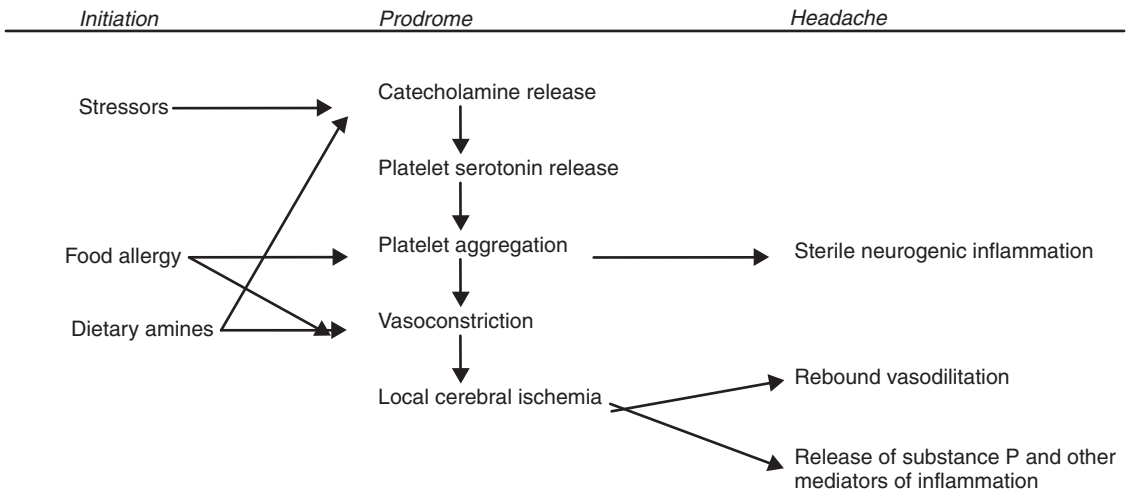


FIGURE 190-1 Suggested pathogenesis of migraine headache.

TABLE 190-1 **Food Allergy/Intolerance and Migraine Headache**

STUDY	PERCENTAGE RESPONDING	METHOD
Mansfield et al.[41]	30	Elimination
Carter et al.[42]	93	Oligoantigenic diet
Hughes et al.[43]	80	Fasting, rotation, elimination
Egger et al.[44]	93	Elimination
Monro et al.[45]	70	RAST*, elimination, sodium
Grant[46]	85	Elimination

*Radioallergosorbent Test (blood test for IgE mediated allergy)

relief on a regular basis can produce MOH, although the precise mechanism of action is unknown.[39] Central sensitization, changes in trigeminal pain processing, receptor downregulation, and biobehavioral factors have all been proposed as possibly leading to MOH. Drugs that carry the highest potential for causing MOH include opioids, butalbital-containing analgesics, and aspirin/acetaminophen/caffeine combinations. Triptans carry intermediate to high potential for causing MOH when used frequently, and nonsteroidal antiinflammatory drugs (NSAIDs) carry the lowest risk.[40] Ergotamine can cause MOH in addition to other symptoms when taken regularly. Regular use of ergotamine in migraine can result in a dependency cycle in which headaches escalate in severity on cessation of the medication. Ergotamine withdrawal predictably causes debilitating headaches, often accompanied by nausea and vomiting, generally resulting in an improved status by 72 hours. Ginger preparations can be helpful during ergotamine withdrawal.

MOH should be suspected in any patient with chronic headaches who is taking large or regular quantities of analgesics and who is experiencing daily predictable headache. Any medication used regularly for headache pain could be a causative agent and hence should be eliminated (opiates, barbiturates, and benzodiazepines must be withdrawn slowly, but NSAIDs, triptans, ergot alkaloids, and acetaminophen may be stopped abruptly). Although the logic may seem counterintuitive to patients, they may be pleasantly surprised by a sizable improvement in outcome. For those having trouble tolerating the transition, acupuncture may be offered. Agents that are sometimes used during the transition when medications are unavoidable include metoclopramide, dihydroergotamine mesylate, naproxen sodium, and prednisone.

Diet

Food Allergy/Intolerance

Food allergy/intolerance can play an important role in many cases of migraine headache. Double-blind placebo-controlled studies have demonstrated that the detection and removal of antigenic/intolerable foods will eliminate or greatly reduce migraine symptoms in the majority of patients. What is unclear is the percentage of migraine patients for whom food control is the most important factor. Table 190-1 summarizes the results of several clinical studies. Success ranges from 30% to 93%, with the majority of studies showing a remarkably high degree of success.[41-48]

A plausible explanation for the large difference between the results of Mansfield et al[41] and the others[42-48] is that the Mansfield design was carefully selected for food allergy only, whereas the others included food intolerance. These studies found the incidence of food allergy to be similar among the major types of migraine. Few studies have been performed since the 1980s, when much of the groundwork regarding the relationship between food intolerance and migraine was laid. The foods most commonly found to induce migraine headaches are listed in Table 190-2.

TABLE 190-2 **Foods that Most Commonly Induce Migraine Headaches**

FOOD	EGGER et al.[44] (%)	HUGHES et al.[43] (%)	MONRO et al.[45] (%)
Cow's milk	67%	57%	65%
Wheat	52	43	57
Chocolate	55	57	26
Egg	60	24	22
Orange	52	–	13
Benzoic acid	35	–	–
Cheese	32	–	–
Tomato	32	14	–
Tartrazine	30	–	–
Rye	30	–	–
Rice	–	–	30
Fish	22	29 (shell)	17
Grapes	12	33	–
Onion	–	24	–
Soy	17	24	–
Pork	22	–	17
Peanuts	12	29	–
Alcohol	–	29	9
Monosodium glutamate	–	19	–
Walnuts	–	19	–
Beef	20	14	–
Tea	17	–	17
Coffee	15	19	17
Nuts	12	19 (cashew)	17
Goat's milk	15	14	–
Corn	20	9	–
Oats	15	–	–
Cane sugar	7	19	–
Yeast	12	14	–
Apple	12	–	–
Peach	12	–	–
Potato	12	–	–
Chicken	7	14	–
Banana	7	–	–
Strawberry	7	–	–
Melon	7	–	–
Carrot	7	–	–

The mechanism by which food allergy/intolerance induces a migraine attack is still unknown. Several theories have been proposed:

- Idiopathic response to a pharmacologically active substance, such as tyramine
- Monoamine oxidase deficiency

- Platelet phenolsulfotransferase deficiency; immunologically mediated food allergy
- Platelet abnormalities

Egger et al[44] suggested that migraine headache may occur through chronic activation of the nonspecific responsiveness of cerebrovascular end organs as a result of long-term antigenic stimulation. This mechanism would be analogous to the bronchiolar response in asthma to exercise or cold after antigen contact. Allergic reactions to foods are known to cause platelet degranulation, with resultant serotonin release.[47]

In children, common migraine triggers include cheese, chocolate, citrus fruits, hot dogs, monosodium glutamate, aspartame, fatty foods, ice cream, caffeine withdrawal, and alcoholic drinks, especially red wine and beer. Tyramine, phenylethylamine, histamine, nitrites, and sulfites are involved in the mechanism of food intolerance headache, whereas immunoglobulin E–mediated food allergy is an infrequent cause.[49]

Several methods may be used to detect food allergies; most of these are described in Chapter 15. Laboratory testing can be convenient, but one major drawback of food intolerance testing with IgG antibodies can be a lack of reproducible findings with split blood samples among various laboratories. However, a study published in Mexico in 2007 found that when migraineurs removed foods to which they had mounted IgG responses, they experienced a robust improvement in their migraines, with 43 of 65 patients showing complete remission after 1 month of specific food elimination.[50] Elimination diets/challenge testing are reliable and experiential methods for detecting food intolerance, but they also have limitations: some foods evoke a delayed response, so that it may require several days of repeated challenge to elicit recognizable symptoms. Food triggers can also be inconsistent. Ingestion of large amounts of several foods may be necessary to detect those that are marginally reactive. The recommended procedure for the diagnosis and management of food allergy/intolerance is described in the section on "Therapeutic Approach."

Dietary Amines

Foods such as chocolate, aged cheese, pickled herring, sausages, sour cream, fermented foods, beer, and wine may precipitate migraine attacks because they contain histamine and/or other vasoactive compounds such as phenylethylamine that have a vasodilatory effect (Box 190-2).[48,51,52] Tyramine is a component of many of these foods and has long been regarded as an important migraine trigger, but controlled studies have yielded conflicting findings.[53] Red wine is more likely than white wine to trigger a headache because it contains 20 to 200 times the amount of histamine and also stimulates the release of vasoactive compounds by platelets.[21,51,54]

Red wine is additionally much higher in flavonoids, the antioxidant components shown to help prevent heart disease. These compounds can also inhibit the enzyme phenol sulfotransferase, which normally breaks down serotonin and other vasoactive amines in platelets. Many migraineurs have been found to have significantly lower levels of this enzyme,[53] although the implications are confusing. Because red wine contains substances that are potent inhibitors of this enzyme, it often triggers migraines in these individuals, especially if consumed along with foods high in high vasoactive amine content, like cheese or chocolate. A standard treatment for histamine-induced headaches is to use a histamine-free diet along with vitamin B_6 supplementation.[54,55]

The activity of the enzyme diamine oxidase, which breaks down histamine in the lining of the small intestine before it is absorbed into the circulation, appears to play a key role in determining reactivity to dietary histamine. Individuals sensitive to dietary histamine have lower levels (about 50%) of this enzyme in their tissues compared with control subjects.[51] Diamine oxidase is a vitamin B_6–dependent enzyme. Not surprisingly, compounds that antagonize vitamin B_6 also inhibit diamine oxidase.[51] These inhibitory factors include food coloring agents (specifically the hydrazine dyes, such as FD&C yellow #5), some drugs (isoniazid, hydralazine, dopamine, and penicillamine), oral contraceptives, alcohol, and excessive protein intake.

Vitamin B_6 supplementation (usually 1 mg/kg) has been shown to improve histamine tolerance, presumably by increasing diamine oxidase activity.[51,55] Women have lower levels of diamine oxidase, which may explain the higher incidence of histamine-induced headaches among them. Women are also much more frequently unable to tolerate red wine. Interestingly, the level of diamine oxidase in a woman increases by over 500 times during pregnancy.[56,57] It is very common for women with histamine-induced headaches to experience complete remission of their headaches during pregnancy.

BOX 190-2 Factors Involved with Histamine-Induced Headaches

Histamine levels increased by:
- Histamine in alcoholic beverages (particularly red wine)
- Histamine in food
- Histamine-releasing foods
- Food allergy
- Vitamin B_6 deficiency

Histamine breakdown inhibited by:
- Vitamin B_6 antagonists
 - Alcohol
 - Drugs
 - Food additives (e.g., yellow dye #5, monosodium glutamate)
- Vitamin C deficiency

Histamine release prevented by:
- Disodium chromoglycate
- Quercetin
- Antioxidants (e.g., vitamin C, vitamin E, selenium, etc.)

Histamine breakdown promoted by:
- Vitamin B_6
- Vitamin C

Miscellaneous Diet-Related Triggers

Hypoglycemia can be a trigger for migraine headache[58,59] and is modifiable by dietary manipulation. Glycemic dysregulation is common in the setting of the standard American diet, given a tendency to consume unregulated quantities of high-glycemic-index carbohydrates. Hypoglycemia may be a result of inappropriate carbohydrate intake, especially when insulin levels become elevated. Excessive sodium intake may also represent a migraine trigger,[60] perhaps as a consequence of increasing angiotensin levels in response to sodium ingestion. For individuals who are lactose-intolerant, avoidance of dairy products may afford improvement in the experience of migraine headache.[61] Aspartame, a common sweetener, may be associated with an increased likelihood of migraine incidence[62,63] and is easily avoided. Sucralose has become another commonly used artificial sweetener, and may be a migraine trigger.[64] Monosodium glutamate is a well-recognized migraine trigger that can directly activate the NMDA receptor.

Helicobacter pylori

Gasbarrini et al[65] demonstrated that migraine headaches improved dramatically in 100% of patients for whom *H. pylori* was identified and treated through standard measures. Further research has shown that the prevalence of *H. pylori* infection is significantly higher in migraineurs without aura compared with controls, indicating that *H. pylori* infection is a probable independent environmental risk factor for migraine without aura, especially in patients not genetically or hormonally susceptible.[66] It appears that incidental *H. pylori* positivity is more relevant in migraineurs compared with controls, because a high percentage experienced relief from migraines when the infection was eradicated.[67]

Nutritional Supplements

5-Hydroxytryptophan (5-HTP)

5-HTP, the molecular intermediate between tryptophan and serotonin, is readily absorbed when taken orally and easily crosses the blood-brain barrier. In addition to augmenting serotonin levels, it may also increase endorphin levels. The use of 5-HTP in the prevention of migraine headache offers considerable advantages over drug therapy. Although a number of drugs have been shown to be useful in the prevention of migraine headache, all of the currently used drugs carry with them a risk of significant adverse effects. 5-HTP is at least as effective as other pharmacologic agents used in the prevention of migraine headaches and is safer and better tolerated. Although some studies have employed a dosage of 600 mg/day or more,[68] 5-HTP can be effective at a dosage as low as 200 mg/day.[69] The clinical studies with 5-HTP in migraine headaches are discussed in Chapter 98.

Essential Fatty Acids

The role of essential fatty acids (EFAs) in the pathogenesis of migraine may be quite important but does not appear to have received much research attention. Considering the significance of platelet aggregation and arachidonic acid metabolites in the mediation of the events leading to the cerebral ischemia of migraine, manipulation of dietary EFAs may be very useful. It has been demonstrated that reducing the consumption of animal fats and increasing the consumption of fish will significantly modify platelet and membrane EFA ratios and decrease platelet aggregation.[70-72] It is also noteworthy that 60% of the brain is composed of lipids; therefore, appropriate consumption of the essential fats is mandatory for proper neurologic function. In two small placebo-controlled studies,[73,74] omega-3 fatty acids performed significantly better than placebo in reducing headache frequency and intensity. A small randomized double-blind crossover study of 27 adolescents with migraine[75] revealed marked improvement in migraine headache frequency, duration, and severity with fish oil, but patients were noted to respond equally well to olive oil supplements, the chosen placebo for this study. The proposed mechanisms of action of the omega-3 fatty acids include reduced platelet serotonin release, modulation of prostaglandin synthesis, and diminution of cerebral vasospasm.

Bic et al[76] proposed that free fatty acids are an important underlying factor in the development of migraine headache, because elevated blood lipids and free fatty acids are associated with increased platelet aggregability, decreased 5-HT, and increased prostaglandin levels, all of which may play a role in migraine. They list biological states that produce increased free fatty acids and lipids, including high dietary fat intake, obesity, insulin resistance, vigorous exercise, hunger, consumption of alcohol and caffeine, oral contraceptive use, tobacco abuse, and stress. These variables may be manipulated successfully through lifestyle practices, diet, and pharmacologic measures.

Riboflavin (Vitamin B_2)

A deficit of mitochondrial energy metabolism may play a role in migraine pathogenesis.[77] Riboflavin (vitamin B_2) is a precursor of flavin mononucleotide and flavin adenine dinucleotide, which are required for the activity of flavoenzymes involved in the electron transport chain. A randomized placebo-controlled double-blind study demonstrated that a daily oral dose of 400 mg of riboflavin was superior to placebo for migraine prophylaxis. The effect began at 1 month, with maximal effect after 3 months of therapy.[78] The hypothesis that vitamin B_2 benefits migraine by increasing complex I and II activity in mitochondrial energy metabolism can be tested by nuclear magnetic resonance spectroscopy. [78,79] Vitamin B_2 appears to improve mitochondrial function without changing neuronal excitability, which could explain the excellent tolerance and lack of CNS adverse effects. Diarrhea and polyuria may be associated with the administration of high-dose vitamin B_2.[65] It is notable that riboflavin is well tolerated, less expensive than typical migraine-targeted medications, and may provide protection from oxidative toxicity in the brain, making it an excellent therapeutic option.[80] In a study of riboflavin propyhylaxis for pediatric and adolescent migraine, 200 mg/day was an adequate dose, but it took 4 months to achieve optimal results.[81] Another study suggested lack of efficacy for riboflavin in children, but the inclusion and exclusion criteria were acknowledged to be very strict.[82] Other B vitamins, including folic acid, may also be instrumental in aborting or preventing migraine headache.[83]

Coenzyme Q10

CoenzymeQ10 (CoQ10) is a critical component of the electron transport chain and functions as an important antioxidant. Evidence supports the administration of CoQ10 in reducing the frequency of migraines by 61%.[84] After 3 months of receiving 150 mg of CoQ10 at breakfast, the average number of headache days decreased from 7 to 3 per month in 31 adults who completed an open-label study. A double-blind randomized study of 42 adult patients, using 100 mg of water-soluble CoQ10 three times daily, revealed similar results.[85] CoQ10 deficiency appears to be common in the pediatric and adolescent populations and can be an important therapeutic consideration in these age groups.[86] Like riboflavin, CoQ10 is well tolerated (although expensive), with little risk of toxicity. It is ideal for women of childbearing age and for children because of its excellent tolerability. Liquid gel formulations should be favored for their high bioavailability. CoQ10 must be used with caution in patients who also take warfarin, because, it may antagonize the anticoagulation effects of warfarin. It is also noteworthy that many medications can interfere with CoQ10 activity, including statins, beta blockers, and certain antidepressants and antipsychotics.[87]

Magnesium

The high frequency of magnesium deficiency is well established. Magnesium is the least abundant serum electrolyte and the second must abundant intracellular cation; it is integral to the metabolism of calcium, potassium, phosphorus, zinc, copper, iron, sodium, lead, calcium, hydrochloric acid, acetylcholine, nitric oxide, and many enzymes. Magnesium absorption depends on dietary adequacy, selenium, parathyroid hormone, and vitamins B_6 and D. Absorption is hindered by excess fat. Magnesium levels are depleted by a multitude of common factors, including stress, excess alcohol intake, high estrogen levels, low progesterone,

dietary excesses, certain drugs, hyperthyroidism, and hyperparathyroidism. Inadequate dietary intake of magnesium is likely in 75% of the U.S. population,[88] it is felt to be the most common micronutrient deficiency, manifested by a diverse range of associated pathologies.[89] Physiologic and psychological stress results in magnesium depletion, and both acute and chronic stress is associated with increased episodes of migraine.

Substantial documentation linking low magnesium levels to both migraine and tension headaches exists in the medical literature.[90-92] Low brain and tissue magnesium concentrations have been found in patients with migraine, indicating a need for supplementation. Among magnesium's central functions are to maintain vascular tone and prevent neuronal hyperexcitation.[90-93] Cerebrospinal fluid levels of magnesium have been found to be low in migraine, and low magnesium levels can predispose to many of the physiologic dysfunctions known to be prominent in migraine, such as induction of cerebral vasospasm; potentiation of the contractile response of blood vessels to vasoactive substances such as serotonin; enhancement of the sensitivity of NMDA receptors to glutamate; and an increase in platelet aggregation, leading to serotonin release.[94] Magnesium deficiency may play an important role in the pathogenesis of migraine by promoting CSD.[64]

Two notable double-blind studies have provided conflicting results on the prevention of migraines in people prone to recurrent migraine headaches. In the first study,[95] 250 mg of magnesium or placebo was given twice daily to 69 patients (35 received magnesium and 34 placebo) for 12 weeks. The number of responders was 10 in each group (28.6% with magnesium and 29.4% with placebo). There was no benefit with magnesium compared with placebo with respect to migraine frequency or intensity. In the other double-blind study,[94,96] patients experiencing recurrent migraines were given either 600 mg of oral magnesium daily for 12 weeks or placebo. By the ninth week, the frequency of attacks was reduced by 41.6% in the magnesium group, compared with only 15.8% in the placebo group. Drug consumption for symptomatic treatment per patient also decreased significantly in the magnesium group. In a newer study that sought to determine magnesium efficacy specifically in migraineurs without aura, 600 mg of magnesium citrate daily produced a statistically significant improvement in outcome compared with placebo and also produced an improvement in cortical blood flow.[97]

It appears that magnesium supplementation may specifically be effective in those individuals with low tissue or low ionized levels of magnesium. Low tissue levels of magnesium are common in patients with migraine, but most cases go unnoticed because physicians generally rely on serum magnesium levels to assess magnesium status. Because most of the body's magnesium is intracellular, serum levels are unreliable indicators. A low magnesium level in the serum reflects late-stage deficiency. More sensitive tests of magnesium status include erythrocyte magnesium levels or ionized magnesium, the most physiologically active form.

Hypothetically, patients with an acute migraine episode and low serum levels (<0.54 mmol/L) of ionized magnesium are more likely to respond to an intravenous infusion of magnesium sulfate ($MgSO_4$) than patients with higher levels of ionized magnesium in serum; this hypothesis has been tested.[98,99] Serum samples to determine levels of ionized magnesium were drawn immediately before infusion of 1 g of $MgSO_4$ in 40 patients with acute migraine headache. Pain reduction of 50% or more, as measured on a verbal pain intensity scale of 1 to 10, occurred within 15 minutes of infusion in 35 patients. In 21 patients, at least this degree of improvement or complete relief persisted for 24 hours or more. Pain relief lasted at least 24 hours in 18 of 21 patients (86%) with serum ionized magnesium levels below 0.54 mmol/L and in 3 of 19 patients (16%) with ionized magnesium levels at or above 0.54 mmol/L. The average ionized magnesium level in patients with relief lasting for at least 24 hours was initially significantly lower than that in patients with no relief or only fleeting relief.

Intravenous magnesium has been shown to be an extremely effective treatment in some cases of acute migraine, tension, and cluster headaches. A dosage of 1 to 3 g of intravenous magnesium (over a 10-minute period) generally results in a nearly 90% success rate in patients with low ionized magnesium levels[98-101] Patients treated with $MgSO_4$ typically observe complete elimination of migraine-associated symptoms such as nausea, photosensitivity, and phonosensitivity. Adverse effects are rare with the exception of a brief flushed feeling.

Another possible benefit of magnesium in migraineurs may be its ability to improve mitral valve prolapse, which is linked to migraines because it causes mechanical damage to platelets, promoting their release of vasoactive substances like histamine, platelet-activating factor, and serotonin. Because research indicates that 85% of patients with mitral valve prolapse have chronic magnesium deficiency, magnesium supplementation is advisable.[102] This recommendation is further supported by several studies demonstrating that oral magnesium supplementation improves mitral valve prolapse.

Supplementation is readily achieved by using magnesium bound to glycine, citrate, malate, aspartate, or another Krebs cycle intermediate (caution is advised relative to the possible neuroexcitatory effects of aspartate). Typical dosage ranges are from 200 to 800 mg/day, depending on bowel tolerance. Magnesium sulfates, oxides, and hydroxides are less predictably absorbed and may produce adverse gastrointestinal effects, but they can also be effective. The coadministration of vitamin B_6 is also ideal, since it facilitates magnesium transport into cells. Caution is advised in administering magnesium to patients with renal insufficiency.

Botanical Medicines

Botanical medicines have a lengthy history of use as traditional remedies for migraine headache. Although many botanicals have been used, feverfew *(Tanacetum parthenium),* ginger *(Zingiber officinalis),* and butterbur *(Petasides hybridus)* tend to be widely used for migraine prophylaxis and treatment.

Tanacetum Parthenium

Perhaps the most popular preventive treatment of migraine headaches is the herb feverfew. Scientific interest in feverfew began when a 1983 survey found that 70% of 270 migraine sufferers who had eaten feverfew daily for prolonged periods found that the herb decreased the frequency and/or intensity of their attacks.[103] Many of these patients had been unresponsive to routine medications. This survey prompted several clinical investigations that are supportive of the therapeutic and preventive effects of feverfew in the treatment of migraine frequency and intensity.[103-106] However, at least three crossover randomized controlled trials found no benefit with feverfew, although each study had limitations.[107] Noting that the stability of feverfew can be problematic, a randomized double-blind multicenter placebo-controlled study confirmed the efficacy of the carbon dioxide–based feverfew extract MIG-99 in migraine prophylaxis, using only 6.25 mg three times daily for up to 4 months.[108]

Feverfew has been suggested to inhibit serotonin release, inhibit prostaglandin synthesis and platelet aggregation, inhibit polymorphonuclear leukocyte degranulation and phagocytosis of neutrophils, inhibit mast cell release of histamine, promote cytotoxic activity against human tumor cells, and possess both antimicrobial activity and antithrombotic potential.[109] In vitro studies have

demonstrated that feverfew extract inhibits serotonin release from platelets.[104,110] The active constituent remains incompletely appreciated; the plant is rich is sesquiterpene lactones, the principal one being parthenolide. Given the diversity of feverfew's pharmacologic activity, parthenolide may not be the sole active principle. Feverfew should be avoided or used with caution in patients on anticoagulants because of its platelet-inhibitory effects.[85,86] Feverfew is generally well tolerated, but oral ulceration (especially for those who chew feverfew leaves) and gastrointestinal symptoms are the most common adverse events; these effects are mild and reversible with discontinuation. Because feverfew is in the same (Asteraceae) family as ragweed and chamomile, individuals with such allergies should avoid feverfew as well. Feverfew is not known to be safe in pregnancy and lactation and should be slowly tapered when discontinued.

Zingiber Officinalis

The common ginger root has been shown to exert significant effects in suppressing inflammation and platelet aggregation.[87-89] With respect to migraine headache, there is much anecdotal information and speculation about its usefulness based on its known properties. Ginger may be commonly used in clinical practice for migraine treatment, but little clinical investigation has been performed to date. The most active antiinflammatory components of ginger are found in fresh preparations and the oil.

Petasides Hybridus

Butterbur (*P. hybridus*) has been identified as an effective herbal therapy for migraine; its recorded use dates back at least 900 years. In the Middle Ages, it was used to treat fever and bubonic plague, and in the seventeenth century it was an oral treatment for cough and asthma and a topical treatment for skin wounds. It has vascular wall antispasmodic properties and an affinity for cerebral vessels; it also inhibits leukotriene synthesis and lipoxygenase activity.[114] Leukotriene synthesis is apparently inhibited by the active principles petasine and isopetasine, which also have a high affinity for blood vessels and produce vasodilation.[113] In a randomized, placebo-controlled double-blind study of 60 patients,[113] migraine frequency was decreased by 60% without adverse events (and dysmenorrhea incidentally improved markedly in 8 patients). It is administered prophylactically. Supplementation should be carried out daily for 4 to 6 months and tapered until migraine incidence begins to increase. Butterbur is generally well tolerated, but diarrhea has been reported in some individuals. No drug interactions have been identified, but it is not known to be safe during pregnancy or lactation. The plant's pyrrolizidine alkaloids are thought to be hepatotoxic and carcinogenic; for that reason, only extracts that have removed these specific alkaloids should be used.[114] The typical adult dosage ranges from 50 to 100 mg twice daily with meals, but 75 mg twice daily has performed better than 50 mg twice daily in some studies.[116] Butterbur has diverse properties and could be especially helpful for migraineurs who also experience dysmenorrhea and/or allergic rhinitis.[117] In one study, its efficacy was demonstrated in children and adolescents between the ages of 6 and 17 years.[118] Although no allergic reactions have been reported, patients who are hypersensitive to the Asteraceae family (e.g., ragweed, marigolds, daisies, chrysanthemums) should exercise caution because of a potential risk of cross-reactivity.

Hormones

Melatonin

Given the serotonergic involvement in migraine, it is logical to consider melatonin's function as well. Melatonin is the product of CNS serotonin, which is a downstream metabolite of dietary tryptophan. Nearly 90% of serotonin is produced in the walls of the gastrointestinal tract, stored in platelets, and distributed to the rest of the body except the CNS (serotonin cannot cross the blood-brain barrier).[119] Tryptophan and 5-hydroxytryptophan can cross the blood-brain barrier to be converted into serotonin in the pineal gland, which contains 90% of the CNS serotonin and most of the melatonin.[119] The pineal gland serves as an important interface between the environment and the CNS; as such, it may play a role in triggering a variety of external and internal effects such as reactions to certain foods, toxins/odors, flickering lights, sleep deprivation, travel through time zones, menses, and so on. Decreased levels of plasma and urinary melatonin have been observed in migraine patients.[120-122] Deficiency of melatonin appears to produce excessive stimulation of the trigeminovascular system.[119,123] Melatonin therapy is successful in some individuals, particularly those with delayed-sleep-phase syndrome,[124] and may resynchronize circadian rhythms to lifestyle, subsequently relieving triggers and symptoms.[120] In patients with migraine, the brain does not seem to tolerate the peaks and troughs of life well. Regular sleep, regular meals, exercise, avoidance of both excessive stimulation and relaxation, and evasion of dietary triggers can all help to reduce activation. Peres has studied the role of melatonin in migraine extensively and demonstrated in an open-label trial that a 3-mg dose of melatonin was effective in migraine prevention in 25 of 32 individuals with migraine by over 50%. Eight patients experienced 100% reduction of migraines.[125] Although the mechanism of action of melatonin is not understood, melatonin is known to possess the following properties as related to migraine: antiinflammatory activity, prevention of translocation of nuclear factor kappa B to the nucleus, free radical scavenging, inhibition of CGRP-induced vasodilatation, increasing inhibitory neurotransmitter activity, direct analgesic effects, inhibition of adhesion molecules, inhibition of nitric oxide synthase, and hypnotic effect from GABAergic upregulation.[126,127]

Sex Steroid Hormones

Studies have determined that the onset of migraine rises with menarche.[128] Episodes are linked to menstruation in 60% of female migraineurs, a condition described as menstrual migraine.[129] Menstrual migraine is particularly significant because many women report their menstrual migraines to be more disabling, longer-lasting, and less responsive to traditional abortive and preventive treatment.[130] Such headaches usually improve with pregnancy, perhaps owing to sustained estrogen levels.[131] None of the "21/7" contraceptive regimens benefits menstrual migraine, but skipping the placebo pills can prevent migraine in some patients.[132] Migraine incidence tends to decrease with advancing age but may either regress or worsen during perimenopause. It has been noted that headaches occur during and after the simultaneous decline of both estrogen and progesterone. There is no uniform agreement over the relation between hormone levels and migraine, although falling estrogen levels have been noted to be associated with menstrual migraine. DeLignieres et al used percutaneous estradiol gel perimenstrually with significant headache reduction.[133] In another study, when percutaneous estradiol was used during the luteal phase, postdosing rebound migraines were experienced.[134] Plasma taken from menstruating women and reinfused at another point of the menstrual cycle will reproduce menstrual symptoms, including headache; this phenomenon may be indicative of the presence of a prostaglandin-generating factor in plasma.[129] Transdermal progesterone therapy has been anecdotally successful in preventing migraine for some patients, although published studies are lacking. Hysterectomy or oophorectomy has not been demonstrated to be helpful.[129]

Although estrogen therapy can be effective for menstrual migraine, it is important to remember that migraineurs (especially those with aura) are at higher risk for ischemic strokes; using estrogen replacement therapy in these women, particularly in the setting of coagulopathy or other factors that promote coagulation, could be risky.[132] Additional medications or supplements used daily for a portion of the luteal phase have also successfully prevented menstrual migraine; these include naproxen, magnesium, and triptans.[135]

Manual Medicine

Purveyors of manual medicine seem to achieve success in reducing headache through various techniques such as spinal manipulation, massage, myofascial release, and craniosacral therapy. Manual medicine practitioners frequently identify loss of mobility in the cervical and thoracic spine in migraineurs. Although many forms of physical medicine seem helpful in shortening the duration and intensity of an episode of migraine,[136] literature support has been somewhat sparse with regard to manipulation as a modality to prevent recurrent migraine episodes. However, a randomized controlled trial of chiropractic spinal manipulation performed in the year 2000 revealed a significant improvement in migraine frequency, duration, disability, and medication use in 83 treatment-group participants.[137] In another study of 218 patients, spinal manipulation performed as favorably as amitriptyline for migraine prophylaxis.[138] A Cochrane Review performed in 2004 suggested, based on some of the evidence presented here, that spinal manipulation may have a place in migraine headache prophylaxis.[139] Tension headache may also respond favorably to these techniques, because of the structural component involved in muscular tension. The incidence of migraine in patients with temporomandibular joint (TMJ) dysfunction is similar to that in the general population, whereas the incidence of tension headache in patients with TMJ dysfunction is much higher than in the general population.[140] Physical therapy for migraine tends to be most effective when it is combined with other treatments, such as thermal biofeedback, relaxation training, and exercise.[141]

Acupuncture

Sufficient evidence exists to support use of acupuncture to relieve migraine pain.[142-148] Interestingly, the mechanism of relief is not clearly endorphin mediated. One study found that the injection of saline or naloxone did not affect the efficacy of the therapy,[143] and another found that whereas acupuncture increased endorphin levels in controls, the low levels of serum endorphins found in migraine patients did not rise with treatment.[149] The mechanism of action may instead involve normalization of serotonin levels. One study found that acupuncture was effective in relieving pain when it normalized serotonin levels but was ineffective in relieving pain and in raising serotonin levels in patients with very low levels of serotonin.[150]

Although limitations in experimental design make interpretation difficult, acupuncture appears to be successful in reducing the frequency of migraine episodes, generally by around 50%. Patients may be blinded with "sham" acupuncture treatments, but practitioners cannot be blinded. Interestingly, clinical outcomes between verum and sham acupuncture were similar in two studies.[151,152] Other studies and systematic reviews[153-156] shed a favorable light on acupuncture in spite of the difficulties posed by study design.

Biofeedback and Relaxation Therapy

Today the physiologic impact of emotional stress is commonly accepted. Stress is and always has been a part of life; our objective must be to find ways to reduce stressful circumstances when possible and to learn techniques allowing us to cope with unavoidable stressors more effectively. Practitioners who take the time to ask patients to describe their emotional stressors typically find that they have deeply enhanced the therapeutic relationship simply by sending a message of caring. They also validate the effects of stress by talking to patients about their lives rather than dismissing symptoms as "just stress." Patients must be taught that stress management is a critical component of each individual's daily maintenance needs and not just an occasional luxury. It is also sometimes helpful to ask patients why they think they are experiencing their particular condition. Their comments can be extremely elucidating, often allowing for a breakthrough in therapy.

Traditional peripheral biofeedback has produced grade A evidence for effectively treating migraines.[157] Thermal biofeedback uses the temperature of the hands to help the individual learn that inducing the relaxation response will raise hand temperature and facilitate other positive physiologic changes in the body. Learning how to take more active control over the body may reduce headache frequency and severity. The effectiveness of biofeedback and relaxation training in reducing the frequency and severity of migraine headaches has been the subject of dozens of clinical studies,[154] revealing that these techniques can be as effective as beta blockers for headache prevention but without the adverse effects. A recent article concluded that biofeedback is costly and no more effective than employing simpler relaxation techniques in migraine and tension headache.[158] Other relevant modalities to consider include cognitive behavioral therapy, neurolinguistic programming, hypnotherapy, transcutaneous electrical nerve stimulation, electromyographic (EMG) biofeedback, massage, and laser therapy.[159,160] In particular, there is grade A evidence for relaxation training, thermal biofeedback combined with relaxation training, EMG biofeedback, and cognitive behavioral therapy for migraine prophylaxis.[161] Neurofeedback, a technique that uses electroencephalographic feedback to teach patients how to alter brainwave activity, was effective in an open-label trial of 37 patients, with efficacy sustained on average for 14.5 months after discontinuation of treatment.[157] Given the safety and efficacy of these techniques, strong consideration should be given to including them routinely in the care of patients with migraine headaches.[162]

Exercise should not be overlooked as a helpful modality in migraine headache. Thirty-six patients with migraine who exercised for 30 minutes three times a week over 6 weeks experienced significant improvement in headache parameters. Preexercise β-endorphin levels in these individuals were inversely proportional to the degree of improvement in their postexercise headache parameters.[163]

Finally, the role of education in the setting of migraine is paramount to the delivery of quality care. In an open-label prospective study involving a total of 284 migraineurs, 46% of subjects reported a 50% or greater reduction in headache frequency when they were provided with educational materials that included general information about migraine headache, a headache diary, instructions on how to do range-of-motion stretching exercises, and biofeedback tapes. Subjects who tended to worry about impending migraines experienced a significant degree of benefit from the program.[164] Patients reported higher self-efficacy and coping skills after exposure to the educational program.

THERAPEUTIC APPROACH

Migraine headache is a multifaceted condition and should be understood as a symptom rather than a disease. Symptoms are often debilitating, frequently interfering significantly with an

individual's quality of life. A holistic, multidisciplinary approach is necessary for a satisfactory outcome. The challenge for the clinician is to determine which of many factors are responsible for each patient's migraine process. Identification and avoidance of precipitating factors is important in reducing the frequency of headaches. Avoidance of initiators is particularly significant considering that they are cumulative in effect.

Owing to the high incidence (80%-90%) of food allergy/intolerance in patients with migraine headache, diagnosis and management may begin with at least a 1-week trial (depending on migraine headache frequency) of careful avoidance of all foods to which the patient may be allergic or intolerant. This may be accomplished through supervised modified fasting or the use of elimination diets. All other possible allergens (e.g., vitamins, unnecessary drugs, herbs, etc.) should also be avoided. During this procedure, food-sensitive patients are likely to exhibit a significant exacerbation of symptoms early in the week, followed by almost total relief by the end of the fast/modified diet. This sequence has to do with the addictive characteristic of the reactive foods. Once the patient is symptom-free, one new food is reintroduced (and eaten several times) each day while symptoms are carefully recorded. Some authors recommend reintroduction on a 4-day cycle. Suspected foods (symptom onset ranges from 20 minutes to 2 weeks) are eliminated, and apparently safe foods are rotated throughout a 4-day cycle (see Chapter 46). Once a symptom-free period of at least 6 months has been established, the 4-day rotation diet should no longer be necessary.

An oligoantigenic diet, in which common food triggers are eliminated, may also be used successfully by some patients, but a longer trial (4-8 weeks) is typically necessary, depending on the frequency of episodes. Foods that are commonly eliminated during this period include dairy products, gluten-containing grains, eggs, corn, chocolate, peanuts, coffee, black tea, soft drinks, alcoholic beverages, and all processed foods. Some clinicians employ food allergy immunoglobulin testing, with mixed results.

It is worth noting that the cause of migraine headache is often not a simple matter of food intolerance. Aberrations in digestive function and detoxification may also complicate the picture. Metabolic waste products of pathogenic organisms may produce distant symptoms such as headache, and foundational care for patients with migraine headache should include correcting intestinal dysbiosis if identified clinically or in the laboratory through stool culture, organic acids analysis, or intestinal permeability assessment.

Toxic overload or suboptimal function of detoxification enzymes may theoretically trigger headaches and should be addressed if suspected.[165] Susceptibility to toxicity is produced by excessive environmental exposures, genetic polymorphisms in detoxification enzyme production, and depletion of nutrient cofactors catalyzing phase I and/or phase II detoxification reactions.[166]

Diet

As discussed above, all food allergens must be eliminated and a 4-day rotation diet used until the patient is symptom free for at least 6 months. Foods containing vasoactive amines should initially be eliminated. After symptoms have been controlled, such foods can be carefully reintroduced. The primary foods to eliminate initially are alcoholic beverages, cheese, chocolate, citrus fruits, and shellfish. The diet should be low in sources of arachidonic acid (land-animal fats) and high in foods that inhibit platelet aggregation (e.g., vegetable oils, fish oils, garlic, and onion).

Supplements

- Magnesium: 250 to 800 mg a day in divided doses, titrated to symptoms and bowel tolerance
- Vitamin B_6: 50 to 75 mg a day balanced with B complex
- 5-HTP: 100 to 200 mg once or twice a day
- Vitamin B_2 (riboflavin): 400 mg once a day balanced with B complex
- Coenzyme Q10: 150 mg once a day

Hormonal Therapies

- Trial of melatonin 0.3 to 3 mg at bedtime
- Trial of estradiol, carefully individualized to clinical picture

Botanical Medicines

- *Tanacetum parthenium* (feverfew): 0.25 to 0.5 mg parthenolide twice a day
- *Zingiber officinalis* (ginger):
 - Fresh ginger: approximately 10 g/day (a 6-mm slice)
 - Dried ginger: 500 mg four times a day
- Extract standardized to contain 20% of gingerol and shogaol
 - 100 to 200 mg three times a day for prevention and 200 mg every 2 hours (up to six times a day) in the treatment of an acute migraine
- *Petasides hybridus* (butterbur): 75 mg two times a day with meals

Physical Medicine and Relaxation Therapies

- Transelectrical nerve stimulation (TENS) to control secondary muscle spasm
- Acupuncture to balance meridians
- Biofeedback
- Guided imagery

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CHAPTER 191

Multiple Sclerosis

Lynne Shinto, ND, MPH, Vijashree Yadav, MD, MCR, Laurie K. Mischley, ND, and Dennis N. Bourdette, MD, FAAN

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DIAGNOSTIC SUMMARY

- Episodic neurologic symptoms, depending on the parts of the central nervous system (CNS) affected
- Typical onset is in adults between ages 20 and 55 years
- Symptomatology not consistent with a single neurologic lesion

GENERAL CONSIDERATIONS

Multiple sclerosis (MS) is a disease of the central nervous system (CNS) characterized by neurologic symptoms that relapse and remit. Symptoms depend on the parts of the CNS that are affected and patients have varying levels of permanent disability. Pathologically, MS is an inflammatory disease of the CNS in which there is multifocal destruction of the myelin sheaths, referred to as demyelination, and axons within the brain, spinal cord, and optic nerves.

MS is the most common disabling neurologic disease of young and middle-aged adults in North America and Europe.[1] Physicians have recognized its pathologic and clinical features since the mid–nineteenth century. MS pathology consists of multifocal areas of demyelination, referred to as plaques, in the brain, spinal cord, and optic nerves. In these areas there is destruction of the myelin sheath around axons with relative sparing of axons, although axonal damage also occurs in MS. Inflammatory cells composed of macrophages and lymphocytes are present when there is active demyelination within MS plaques, indicating that MS is an inflammatory disease. Magnetic resonance imaging (MRI) provides a means of visualizing MS lesions within the brain and spinal cord (Figure 191-1). Clinically, MS can cause various neurologic problems, depending on the location and severity of MS plaques (Table 191-1). In about 85% of cases, MS starts with a relapsing-remitting course.[2] Patients experience relapses or attacks of MS during which they develop a new neurologic problem, return of an old problem that had resolved, or worsening of preexisting symptoms. Relapses develop over a few days or weeks, followed by a period of improvement and stability. In between relapses, patients are clinically stable, although they may have residual permanent neurologic symptoms from previous relapses. However, relapses that cause *symptoms* represent only the "tip of the iceberg" of disease activity at this stage of the illness. Serial MRI studies in MS patients have disclosed that new, asymptomatic MS lesions appear within the brain 5 to 10 times more commonly than symptomatic lesions, and these cause permanent damage that contributes to the overall MS disease burden.[3]

About 50% of patients with relapsing-remitting MS (RRMS) enter a progressive phase of the disease 10 to 15 years after onset. Steady worsening characterizes this phase of the illness, called secondary progressive MS. Patients with secondary progressive MS may or may not continue to have relapses. About 15% of MS patients have progressive worsening from the onset of their illness, a form of MS referred to as primary progressive MS. Although MS is rarely fatal, it is often disabling, with about one third of patients losing the ability to walk 15 to 20 years after onset. In benign forms of MS, comprising up to 15% of patients, patients never develop any permanent disability from MS. Most patients, however, develop varying degrees of permanent neurologic disability.

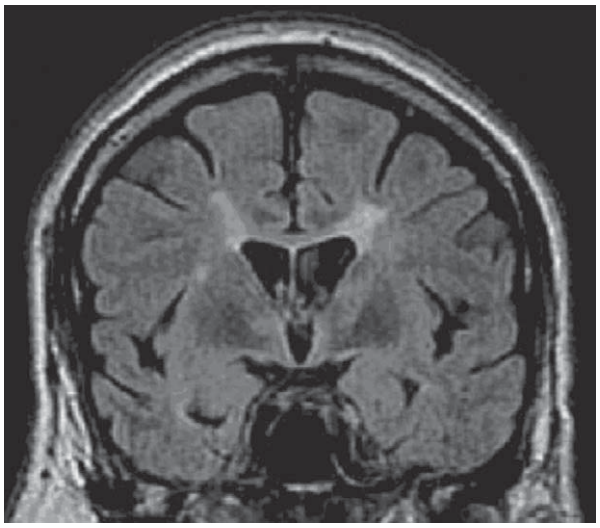


FIGURE 191-1 Coronal section through the brain of a patient with multiple sclerosis (MS). With this imaging sequence, the MS lesions appear as large areas of increased signal intensity or white "spots" adjacent to the lateral ventricles.

TABLE 191-1 **Symptoms of Multiple Sclerosis and Their Neurologic Causes**

SYMPTOMS	CAUSES
Weakness and numbness and tingling in legs and arms; stiffness in legs	Spinal cord lesions
Urinary urgency, retention, incontinence and recurrent infections	Spinal cord lesions
Constipation	Spinal cord lesions; diet
Sexual dysfunction	Spinal cord lesions
Blurred vision and blindness	Optic nerve lesions
Double vision	Brainstem lesions
Imbalance	Spinal cord and cerebellar lesions
Tremor of arms	Cerebellar lesions
Impaired memory and concentration	Cerebral lesions
Fatigue	Effects of inflammatory cytokines on neuronal function; nerve fiber fatigability resulting from demyelination
Heat sensitivity	Sensitivity of demyelinations to elevations in body temperature
Depression and other mood changes	Cerebral lesions and changes/ disorders in neurotransmitters

Epidemiology

MS affects about 1 of 1000 persons in the United States, Canada, and northern Europe. MS typically begins between the ages of 20 and 55 but may occur at any age. Women are more commonly affected than men, with about 60% of cases being female. A strong racial influence on the risk of developing MS exists: it is most common among whites, particularly those of northern European descent.[4,5] Typical MS is rare among Asians and black Africans but is relatively common among black Americans. The racial predilection of MS is one piece of evidence indicating the strong influence of genes on the risk of developing MS. In addition to racial influences, there is also an interesting geographic distribution of the disease. Areas with the highest prevalence are located in higher latitudes, in both the northern and southern hemispheres.[6,7] These high-risk areas include the northern United States, Canada, Great Britain, Scandinavia, northern Europe, New Zealand, and Tasmania.[8,9]



FIGURE 191-2 Model of acute multiple sclerosis plaque. (1) Activated T cells enter the central nervous system (CNS) by passage through the blood-brain barrier. (2) Pathogenic T cells then recognize antigens within the CNS, which may be fragments of myelin proteins or viral antigens expressed as part of a latent infection. (3) The activated T cells then release proinflammatory cytokines (lymphotoxin [LT], tumor necrosis factor-alpha [TFN-α], and interferon gamma [IFN-γ]), which directly injure myelin and activated macrophages. (4,5) Activated macrophages release cytokines, free radicals, and proteases, which injure myelin and axons. (6) Plasma cells within the CNS release antimyelin antibodies, which bind to myelin and cause demyelination by complement activation or by assisting myelin phagocytosis by macrophages. Regulatory T cells entering the CNS release regulatory cytokines (transforming growth factor-beta [TGF-β], interleukin-4 [IL-4]; and IL-10), which downregulate pathogenic T cells and help to "turn off" the acute inflammatory response. (From "Multiple Sclerosis" Continuum Vol 5 [5], 1999, p 16.)

Pathogenesis

All of the signs and symptoms of MS relate to damage to the brain, spinal cord, and optic nerves.

Macrophages can cause damage by releasing soluble inflammatory mediators such as cytokines and free radicals or by actively stripping myelin from the axon sheath. Activated T cells can also release proinflammatory cytokines, which can contribute to tissue damage. Finally, antimyelin antibodies can damage myelin either by initiating complement-mediated demyelination or assisting the phagocytosis of myelin by macrophages. The disease process is "turned off" by apoptosis of the disease-initiating T cells and by the recruitment of regulatory T cells into the CNS. This model of the acute MS lesion is consistent with the most prevalent theory about the MS, namely that it is an immune-mediated disease (Figure 191-2).

Risk Factors

Genes

Substantial evidence indicates that genetic background influences the risk of developing MS.[10,11] Race is a strong influence on this

risk, with whites and blacks being much more at risk of developing MS than Asians. Having a first-order relative (parent or sibling) with MS increases the risk of developing the disease by fivefold to tenfold. Perhaps the most compelling evidence of the genetic influence on the risk of developing MS comes from studies of twins where at least one twin has MS.[12] Among nonidentical twins, the chances of the second twin having MS are 1% to 2%, which is similar to the risk of nontwin sibling pairs. Among identical twins, the chance of the second twin having MS is 25%, indicating the strong influence of genetic background. An estimated 10 to 15 different genes may affect the risk of developing MS, and major research efforts are under way to identify these. Thus far, only the human leukocyte antigen DR2 gene has been definitively shown to be associated with an increased risk of developing MS among individuals of northern European descent.

Viruses

Considerable interest lies in identifying the target or targets of the pernicious inflammatory response in MS.[13] Viruses and microbial agents have been postulated to be associated with an increased risk of developing MS. For decades there has been interest in the possibility that one or more viruses or other microbial infections might cause MS. This interest stems from the inflammatory nature of MS and the apparent influence of environment on the risk of developing MS, both suggesting the possibility of an infectious etiology. However, although various infectious agents have been reported to be associated with MS—including measles, Epstein-Barr virus, distemper virus, coronavirus, retrovirus, herpes simplex, human herpesvirus-6, and *Chlamydia pneumoniae*—there is no convincing evidence at present of a linkage between any infectious agent and MS.[14] The lack of evidence does not exclude the possibility that an infectious agent causes MS, but as of now there is no widely accepted evidence associating MS with any specific virus or other microbe.

Environment

Geographic and Seasonal Influences. The association with latitude and MS prevalence has shown mixed results and is confounded by factors that include migration, lifestyle habits, biological influences, and social factors. However, in general there is an increased prevalence of MS in northern latitudes (high risk) and a decreased prevalence in southern latitutdes (low risk). People who move from a low-risk to a high-risk area before age 15 acquire a higher risk of developing MS, whereas those who make the same move after adolescence retain a lower risk.[9,15] These observations suggest that an environmental exposure in the first two decades of life influences the risk of developing MS. They also suggest that early sunlight exposure, which is correlated to serum vitamin D levels, may influence the risk for developing MS.[16]

Although not consistent to all geographic areas,[17] there are several European epidemiologic studies showing an association between season of birth and risk of developing MS [18,19] These studies indicate that there is a lower risk for MS for births occurring after summer and a higher risk for MS for births occurring after winter. The authors reporting these findings suggest that maternal levels vitamin D during the third trimester of pregnancy may influence the risk for MS, lower risk when maternal vitamin D levels are high (summer months) and higher risk when maternal vitamin D levels are low (winter months). Taken together, there is some evidence to suggest that sunlight exposure and vitamin D levels at a young age may have an influential role in the risk of developing MS.

Diet. Diet may play a role as an environmental risk factor for acquiring MS. The first investigations into diet and MS centered around trying to explain why inland farming communities in Norway had a higher incidence than areas near the coastline. It was discovered that the diets of the farmers were much higher in animal and dairy products than the diets of the coastal dwellers, whose diet was enriched by cold-water fish.[20] Additional studies have since correlated consumption of animal fat, animal protein, and meat from nonmarine mammals with the risk for MS.[21]

In a review of epidemiologic data reporting the relationship between diet and MS from 1952 through 1995, the authors concluded that multiple studies suggested that the risk of MS was significantly correlated with the following parameters: consumption of animal fat, animal protein, and meat from nonmarine mammals.[21] However, a large prospective cohort study using data from the Nurses' Health Study and Nurses' Health Study II found no evidence linking risk of MS with intake of saturated fats. The authors did note, however, that intake of linolenic acid, an omega-3 fatty acid, but not fish oils or docosahexanoic acid, was associated with a trend toward a lower risk for MS.[22]

Using data from the same cohorts, this same group also found no relationship between intake of fruits and vegetables and risk of MS.[23] A case-control study in Canada assessing the relationship between nutritional factors and risk of MS in 197 incident cases of MS and 202 frequency-matched controls found a positive association between animal fat intake and risk of MS.[24] Taken together, these studies suggest that there is a modest influence of diet on the risk of developing MS.

Summary of Risk Factors

Although there is general agreement that MS is an immune-mediated disease, why people develop MS remains uncertain. Epidemiologic studies suggest that there is a complex relationship between genetic and environmental factors that can influence both the risk of acquiring MS and MS disease progression.



DIAGNOSTIC CONSIDERATIONS

MS remains a clinical diagnosis.[25] No single test such as a blood test, MRI examination, or cerebrospinal fluid (CSF) study "diagnoses" MS. The diagnosis rests on a knowledgeable physician taking a history, performing a neurologic examination, conducting various tests, and then making a diagnosis on the basis of all the data. In general, only neurologists have sufficient training and experience to make an accurate diagnosis. The diagnosis of MS rests on the *objective* demonstration of two or more areas of demyelination in the CNS that have occurred more than one time, and a diagnosis cannot be based only on a patient's symptoms.

Means of "objective" demonstration of areas of demyelination include the neurologic examination, MRI of the brain and spinal cord, and electrophysiologic tests (called evoked potentials) that assess visual, auditory, and somatosensory pathways. CSF examination can also be useful in establishing the inflammatory nature of a given patient's condition. In evaluating patients for possible MS, the CSF is evaluated for the presence of plasma cells that are producing immunoglobulins (IgGs) within the CNS by assessing for qualitative (oligoclonal bands) and quantitative (total IgG, IgG index, and IgG synthesis rate) IgG changes. Excluding the presence of other disorders that can masquerade or be misdiagnosed as MS is also important, such as unusual causes of cerebrovascular disease, vitamin B_{12} deficiency, spinal cord compression

from tumors, herniated disks or spinal canal stenosis, vascular malformations of the spinal cord, Lyme disease, and various other disorders. Although MS was formerly difficult to diagnose, MRI scanning has significantly improved the ability to diagnose MS in its early stages, because it allows imaging of areas of demyelination in the brain and spinal cord and also helps exclude the presence of other diseases that might explain the patient's symptoms.

THERAPEUTIC CONSIDERATIONS

Conventional Treatments

The conventional approach to treating MS includes the use of medications to control disease activity and rehabilitation interventions designed to alleviate symptoms resulting from damage to the CNS. Medications that help decrease disease activity (also called disease-modifying agents, or DMTs) in RRMS include human recombinant interferon-β (Avonex, Betaseron, and Rebif); glatiramer acetate (Copaxone), a random polymer of four amino acids that stimulates protective T cells; a monoclonal antibody against α-4 integrin (Tysabri); fingolimod (Gilenya), the only oral agent that prevents activated lymphocytes from entering the CNS by sequestration in lymph nodes[25a,25b]; and a chemotherapy agent (Novantrone).[26-31]

Compared with placebo, these medications decrease the relapse rate by 30% to 50%, decrease new lesion formation in the brain as detected by MRI, and decrease the risk of developing permanent neurologic disability. An immunosuppressant (chemotherapy agent), mitoxantrone (Novantrone), has also been shown to decrease disease activity in patients with rapidly progressive forms of MS.[32] A monoclonal antibody (Tysabri) that prevents inflammatory cells from entering the CNS has been shown to decrease the rate of MS exacerbations and reduce disease activity (MRI lesions) compared with placebo.[26,27] Fingolimod (Gilenya), that was FDA approved in 2010, reduces CNS inflammation and axonal damage by retaining lymphocytes in the lymph nodes so fewer are able to enter the CNS. Fingolimod has been shown to reduce relapse rates by 50%, decrease rate of disease progression, and decrease disease activity (MRI lesions).[25a,25b] Corticosteroids, such as methylprednisolone, given in high doses can decrease the duration of relapses of MS but do not affect the degree of eventual recovery for relapses.[33] A number of different medications are useful for treating various symptoms of MS, such as fatigue, bladder dysfunction, and spasticity, but these medications do not reverse damage that has already occurred or decrease disease activity.

Although conventional medications are able to reduce disease activity in RRMS, they have limitations, which include the following: only a modest effect on prolonging time to disability, cost (average cost is $28,000-$48,000 per year), and side effects (e.g., injection site reactions, neutralizing antibodies for interferon beta; bradycardia, arrhythmia for fingolimod). All except Novantrone are FDA-approved for RRMS. Given these considerations, an effort to identify natural therapies that have benefit for people with MS is warranted.

Natural Medicine Therapeutic Considerations

From a natural medicine standpoint, there are four major approaches to treating MS:

- Dietary therapy
- Nutritional supplements
- Exercise
- Stress management

Including all four provides the most comprehensive natural medicine treatment plan and should be used in combination with appropriate conventional therapies.

Diet Therapy

Swank/Low-Saturated-Fat Diet

Dr. Roy Swank has provided evidence that a diet low in saturated fats maintained over a long period of time tends to retard the disease process, reduce the number of attacks, and decrease mortality.[34-36] Swank began treating patients with his low-fat diet in 1948. The approach to using a low-fat diet supplemented with cod liver oil is based on epidemiologic studies that found a decreased incidence of MS in populations that had a low consumption of animal fats with a high consumption of cold-water fish.

Based on current knowledge of the pathogenesis of MS, the rationale of using the Swank diet or other diets low in saturated fats in patients with MS relates to the general health benefits of such a diet and the antiinflammatory and perhaps neuron membrane–stabilizing effects of a diet enriched with omega-3 fatty acids. Although the consumption of red meat is significantly restricted on the Swank diet, fish appears to be particularly indicated owing to its excellent protein content and, perhaps more importantly, its high content of omega-3 fatty acids. Cold-water fish such as mackerel, salmon, and herring are rich in omega-3 fatty acids, which include eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA). As reviewed under the "Nutritional Supplements," section, omega-3 fatty acids have antiinflammatory effects that may be of benefit in MS. In addition, because optimal neuronal functioning depends on cell membrane fluidity, which in turn depends on lipid composition, optimal essential fatty acid (EFA) levels may be important in exerting neuroprotective effects by maintaining healthy neuronal functioning.[37-39] Decreasing animal fats and increasing omega-3 fatty acids in the diet thus may improve neuronal function by modulating neuronal lipid composition.

Since Dr. Swank's observational studies, two pilot studies evaluating diet in MS have been conducted. An open-label study evaluated the effects of a diet low in saturated fats combined with fish-oil supplementation and vitamin B complex and vitamin C in newly diagnosed RRMS.[40] Beside dietary modifications, subjects were advised to reduce their intake of sugar, coffee, tea, and alcohol and to stop smoking. Diet was monitored over 2 years by a 4-day dietary record at the end of each year and plasma fatty acid levels were monitored at baseline, year 1, and year 2.

A significant increase occurred in the intake of fish, and a reduction in food items containing saturated fats occurred after 2 years. A significant increase occurred in plasma levels of omega-3 fatty acids, and a significant decrease occurred in plasma omega-6 fatty acids. Over the 2 years of the study, patients had significant reductions in both relapse rates and disability. This study, however, had significant limitations because there was no comparison group.

Although caution is warranted in interpreting the results of this small open-label study, its outcome does concur with Dr. Swank's long-term studies on diet and fish-oil supplementation for people with MS.

A partially blinded, randomized controlled study evaluated the effect of low-fat dietary intervention with omega-3 fatty acid supplementation in 31 subjects with RRMS.[41] The intervention lasted for 12 months and the primary outcome was quality of life, using the Short Form Health Survey Questionnaire (SF-36). Subjects were randomized into one of two groups: the "low-fat

diet/fish oil" group and the "diet/olive oil" group. The low-fat diet/fish oil group followed a diet that did not exceed 15% of saturated fats (percent of totally daily calorie intake) plus fish-oil capsules (daily doses of EPA 1.98 g and DHA 1.32 g). The diet/olive oil group followed the American Heart Association's step I diet, 30% saturated fats (percent of total daily calorie intake) plus olive-oil capsules (6 capsules of 1 g of olive oil per day). The subjects were followed for an average of 11 ± 2.9 months and the low-fat diet/fish oil group maintained better quality-of-life scores for physical well-being (although not statistically significant) than the group using olive-oil supplementation. The mental health component scores were similar in the two intervention groups. At the 6-month time point, the olive-oil group reported an improvement in fatigue as compared with the fish-oil group ($P = 0.035$), which continued for 12 months. For both intervention groups, relapse rates were reduced as compared with the year prior to entering the study. This study suggests that a diet low in saturated fats with fish-oil supplementation might promote better physical and mental health for people with MS. Because all subjects improved after 12 months, the study also suggests that diet modification in addition to supplementation with a "good oil" (fish oil or olive oil) may be beneficial in people with MS.

The epidemiologic studies suggesting a link between a high-fat diet and an increased risk of MS coupled with the results from the three low-fat-diet studies reviewed show a consistency in identifying a low-fat diet as a therapy that may benefit people with MS. A person with MS following a low-fat diet will gain general health benefits. A diet enriched in omega-3 fatty acids, which have immunomodulatory effects, may also provide more specific disease-modifying benefit.

Nutritional Supplements

Essential Fatty Acids. EFAs are divided into two major groups, the omega-3 fatty acids and the omega-6 fatty acids.

Omega-3 Fatty Acids. There is a good rationale for supplementation with EPA and DHA, the so-called marine lipids, in the treatment of MS. General agreement exists that MS results from an acquired immune dysregulation and aberrant immune activation, leading to T cell–driven inflammatory processes in the CNS that cause demyelination and axonal damage. Increased levels of proinflammatory cytokines such as TNF-α, interferon IFN-γ, and IL-2 have been found in the peripheral blood, cerebrospinal fluid (CSF), and brain lesions of MS patients.[42-47] Numerous reports document the association between these cytokines and disease activity, thus implicating them as mediators of the immunopathogenesis of MS.[48-51]

Matrix metalloprotenase-9 (MMP-9) has been implicated in the pathogenesis of MS. MMPs are a family of proteases that aid in the remodeling of the extracellular matrix, basement membrane, and other tissues in the body by digesting collagen components in these tissues. MMPs are thought to play a significant role in the transmigration of inflammatory cells into the CNS by aiding in the disruption of the blood–brain barrier.[52,53] Several studies have shown higher serum levels of MMP-9 in MS patients.[54-56] There is one open-label study in RRMS patients ($n = 10$) group that showed a significant decrease in MMP-9 levels secreted from unstimulated immune cells after supplementing with fish-oil concentrate at 8 g/day (containing 2.9 g EPA and 1.9 g DHA) for 3 months. All subjects showed a decrease in MMP-9 levels whether or not they were on MS disease modifying medication.[57]

It is important to find agents that can suppress inflammatory cytokines and MMP-9 levels in order to develop new therapies for altering the course of MS. The immunomodulatory effects of omega-3 fatty acids have been well documented. In vitro, animal, and ex vivo human studies have reported a decrease in mRNA and protein levels of a number of cytokines, including TNF-α, IFN-γ, IL-1, IL-2, and VCAM-1.[58] One published study documented the effects of supplementation with fish oils enriched with the omega-3 fatty acids EPA and DHA on cytokine secretion in MS.[59] In this study, levels of IL-1-β, TNF-α, IL-2, IFN-γ, prostaglandin E2 (PGE2), and LTB4 secreted from unstimulated and stimulated immune cells in people with MS and healthy controls was evaluated. Twenty subjects with MS and 15 age-matched healthy controls were supplemented with 6 g/day of fish oil containing 3 g EPA and 1.8 g DHA for 6 months. All MS subjects had a stable course of MS for at least 3 months before enrollment, had not modified their diet as a consequence of developing MS, and were not on any disease-modifying therapies.

Outcome measures compared baseline levels of the cytokines mentioned to levels after 3 and 6 months of supplementation in both MS subjects and healthy controls. After 3 and 6 months of fish-oil supplementation, there was a significant decrease in the levels of soluble IL-1β ($P = 0.03$), TNF-α ($P = 0.02$), IL-2 ($P = 0.002$), and IFN-γ ($P = 0.01$) in the unstimulated peripheral blood mononuclear cells (PBMC) of both groups. A significant difference was observed after 3 and 6 months of supplementation in the levels of soluble IL-1β ($P = 0.01$), TNF-α ($P = 0.02$), IL-2 ($P = 0.003$), and IFN-γ ($P = 0.005$) from stimulated immune cells of both groups. Cytokine levels returned to baseline values after a 3-month washout period.

One study has examined the use of omega-3 fatty acid supplementation in MS.[60] This was a large ($n = 312$) double-blind placebo-controlled trial in which MS patients were randomized to receive either 20 capsules of fish oil per day or olive oil containing 72% oleic acid for 2 years. The total daily dose of EPA was 1.71 g, and the total daily dose of DHA was 1.41 g. This study reported a trend in improvement in the omega-3–treated subjects compared with controls ($P = 0.07$). Although the results did not achieve statistical significance favoring omega-3 fatty acid supplementation, the study was not optimally designed. Both groups in the study were advised to follow a diet low in animal fats and high in polyunsaturated fatty acids. Importantly, both groups developed changes in serum fatty acid content over the 2 years of the study. The lack of comparing fish-oil supplementation with a placebo in patients who did not have other dietary modifications may have affected the ability of the study to detect a statistically significant therapeutic benefit of omega-3 fatty acid supplementation.

Although the only clinical trial of fish-oil supplementation in MS failed to show a statistically significant benefit over placebo, this study showed a strong trend favoring fish-oil supplementation. Based on the studies reviewed, there is evidence to support using omega-3 fatty acids supplementation to decrease proinflammatory cytokines and MMP-9, both of which are associated with MS pathogenesis.

Omega-6 Fatty Acids. There is less evidence to support the effects of omega-6 supplementation on decreasing proinflammatory cytokines, although some evidence supports omega-6 in decreasing relapses in MS. Supplementation of omega-6 fatty acids significantly increased the production of transforming growth factor beta-1 (TGF-β1) in the peripheral blood mononuclear cells of healthy subjects.[61] TGF-β1 is an antiinflammatory cytokine that might be beneficial for MS.[62] Two studies in an animal model of MS reported that supplementation with linoleic acid, which is rich in omega-6 fatty acids, decreased the severity of disease[63] and reduced inflammation

in the CNS.[64] Thus, there is some experimental basis for considering supplementation with omega-6 fatty acids.

Linoleic acid supplementation for the treatment of MS has been investigated in at least three double-blind clinical trials.[65-67] Although the results of the studies were mixed (two showed a positive effect and one did not), combined analysis indicates that patients supplemented with linoleic acid had a smaller increase in disability and reduced severity and duration of relapses compared with patients supplemented with olive oil as a control.[68] These studies used a sunflower seed oil emulsion at a sufficient dosage to provide a daily supplementation of 17.2 g of linoleic acid. Unlike the trial using fish-oil supplementation, subjects in these studies were not advised to alter their diets.

Evening primrose oil, which is rich in the omega-6 fatty acid gamma-linoleic acid, is commonly used by MS patients. Gamma-linolenic acid might be more effective than linoleic acid owing to its easier incorporation into brain lipids and its possibly greater effect on immune function.[69] However, evening primrose oil contains low levels of gamma-linolenic acid and the product is relatively expensive. Large and prohibitively expensive amounts of evening primrose oil would have to be used to obtain adequate supplementation. In addition, a single pilot trial of evening primrose oil in MS failed to demonstrate any benefit.[70] Despite its common use by MS patients, we do not recommend the use of evening primrose oil as a supplement.

In summary, evidence from clinical trials indicates that supplementation with the omega-6 fatty acid linoleic acid has a modest benefit in the treatment of MS.

Vitamin D. Epidemiologic studies have found that low vitamin D intake and low serum levels of vitamin D may increase the risk of MS.[71,72] A recent study looked at the serum levels of vitamin D in people with MS (n = 199) and found 84% of them to be deficient.[73]

Studies of vitamin D in the animal model of MS have shown that vitamin D has the ability to decrease immune cell–mediated inflammation and prevent disease.[74,75] MS studies in animal models suggests that vitamin D may have a beneficial role in MS by affecting the ability of inflammatory cells to enter the CNS.[76]

There have been a number of pilot studies in humans evaluating both vitamin D supplementation and associations between serum vitamin D levels and biomarkers of MS disease progression. In an open-label study, oral calcitriol at a target dose of 2.5 mcg/dL was found to be safe and tolerable in 16 MS patient for up to a year of supplementation.[77] Another study examined the seasonal variation in the serum levels of vitamin D in people with MS (n = 103) and healthy controls (n = 110) and found these levels to be significantly higher in summer compared with winter in both cohorts.[77] This study also observed that higher circulating levels of vitamin D in women were correlated with lower MS-related disability. A pilot study evaluating 29 RRMS subjects found a positive correlation between serum vitamin D levels and levels of the antiinflammatory cytokine interleukin-4.[78]

Thus, there is emerging evidence from both animal studies and pilot human studies that vitamin D may have potential beneficial effects in MS. Larger clinical trials are warranted to evaluate vitamin D's therapeutic effect in MS. Given that 30% to 50% of the general population may be deficient in vitamin D,[79] it makes sense to evaluate serum levels of vitamin D to assess and treat vitamin D deficiency in MS.

Antioxidants

Alpha-Lipoic Acid. Alpha-lipoic acid (ALA) and its reduced form, dihydrolipoic acid (DHLA), are potent antioxidants with multiple modes of action. ALA/DHLA can regenerate other antioxidants such as glutathione, vitamin C, and vitamin E; serve as a reactive oxygen species scavenger; repair oxidative damage; and chelate metallic ions involved in oxidative injury. DHLA acts by restoring reduced levels of other antioxidants such as glutathione and by repairing oxidative damage.[80-82] ALA is absorbed from the diet and synthesized de novo; it converts readily intracellularly to DHLA. Both ALA and DHLA are present in both extracellular and intracellular environments.[83] In studies evaluating ALA effects in an animal model of MS, ALA has been shown to supress the development of disease by preventing inflammatory T cells from entering the CNS.[84-86] The immunomodulatory effects of ALA include inhibition of T-cell production of MMP-9, inhibition of the expression of the adhesion molecules ICAM-1 and VCAM-1, and stimulation of cAMP by the prostagladin receptors EP2 and EP4.[84,85,87]

There is one pilot double-blind placebo-controlled study evaluating doses of oral ALA in RRMS. Thirty-seven subjects were randomized to one of four groups: (1) placebo, (2) ALA 600 mg twice a day, (3) ALA 1200 mg once a day, (4) and ALA 1200 mg twice a day. The study found that ALA given at 600 mg twice a day was barely measurable in serum, whereas ALA given at the dose of 1200 mg once daily showed significantly higher serum levels. The study also found an association between higher ALA serum levels and lower MMP-9 levels and higher ALA serum levels with lower soluble ICAM-1 levels. The investigators concluded that oral ALA between 600 and 1200 mg can be measured in serum and that higher serum levels of ALA are associated with increased immunomodulatory activity that may benefit people with MS.[88]

Evidence from animal studies and the one human study shows that ALA has beneficial immunomodulatory effects and that it may be beneficial for people with MS.

Botanical Medicine

Ginkgo biloba

Cognitive impairment affects up to 40% to 50% of people with MS,[89,90] and currently there are no effective symptomatic therapies for cognitive dysfunction in MS.

G. biloba has been evaluated for cognitive impairment in Alzheimer's disease, with mixed findings. A recent meta-analyses of these studies reports that *G. biloba* is safe, but benefits for cognitive impairment and dementia are not predictable.[91]

There is one randomized placebo-controlled pilot study evaluating the effects of a standardized *G. biloba* extract on cognitive performance in 43 subjects with MS.[92] Subjects were randomized to receive 120 mg of *G. biloba* twice a day or placebo for 12 weeks. The outcomes of the study included several neuropsychological tests including the Stroop test, which is a measure of attention and executive function. Subjects receiving *G. biloba* showed significantly improved performance on the Stroop test as well as improvement in subjective reports of cognitive deficits when compared with the placebo group. This pilot study also showed that *G. biloba* extract was safe and well tolerated. Although the studies evaluating *G. biloba* in people with dementia have shown mixed results, this supplement has been shown to be safe and well tolerated in many clinical trials. The pilot study in MS also demonstrated that *G. biloba* standardized extract given at 120 mg twice a day for 12 weeks was safe in people with MS. Given its safety profile and limited evidence on improving attention and executive function in MS, *G. biloba* standardized extract may benefit MS patients with cognitive impairment.

Cannabis

The major psychoactive constituent in cannabis is delta-9-tetrahydrocannabinol (THC). THC binds to cannabinoid receptors (CB) in the CNS and acts as a partial agonist to both CB1 and CB2 receptors. Cannabidol (CBD) is a nonpsychoactive constituent in cannabis and the major constituent in the plant. It is thought to decrease the clearance of THC by affecting liver metabolism. It binds to both CB1 and CB2 receptors in the CNS, with a higher affinity to the CB2 receptor.

In a review of six controlled studies evaluating a combination of THC-CBD (Marinol) for spasticity in MS, it was found that THC-CBD was well tolerated and improved patient self-reports of spasticity, although objective measures for spasticity such as the Ashworth score did not show significant improvement compared with placebo.[93] The authors report that side effects were mild in both the treatment and placebo groups. The authors concluded that there was significant improvement in patient-reported spasticity with the combination of THC-CBD and that THC-CBD was well tolerated in MS. Unlike the dietary supplements discussed, Marinol is a controlled substance and requires a prescription in the United States.

OTHER CONSIDERATIONS

Exercise

In the past, MS patients were often advised not to exercise because increased body temperature and nerve fiber fatigue resulting from exercise were thought to induce transient symptomatic worsening and provide no long-term benefit. However, research has since shown that regular exercise is beneficial for people with MS.[94-100] Four studies and two meta-analyses reported that compared with an MS nonexercise group, the MS exercise group demonstrated improvement in the subjects' reports of fatigue, quality of life, well-being, and walking ability.[95,96,99-102] In summary, evidence indicates that regular exercise is beneficial in MS and should be part of any natural medicine approach to treating MS.

Stress and Multiple Sclerosis

MS patients often report that stress worsens their MS symptoms and consequently triggers an exacerbation. In a review of the scientific literature reporting associations between psychological stress and worsening of MS symptoms, an expert panel concluded that there was a possible relationship between antecedent stress and either MS onset or exacerbations.[103] A prospective longitudinal study of MS patients designed to examine the relationship between stressful life events, psychological stress, and disease activity as measured by MRI found that increased conflicts and disruptions in routine were followed by an increased risk of developing new brain lesions 8 weeks later.[104] Perceived stress in patients with MS has been associated with MS exacerbations in a number of studies.[105]

Given the emerging evidence that antecedent stressors may contribute to the development of new lesions in MS and that perceived stress is associated with MS exacerbations, therapies that reduce stress are highly recommended in MS.

Mind–Body

There are very few scientific studies evaluating mind-body interventions such as yoga, meditation, and prayer in MS.[106] Mind-body techniques using meditation, yoga, and slowed breathing to reduce stress in cancer patients have shown that these therapies are effective in decreasing stress, improving quality of life, and improving sleep.[107]

There are two reported pilot studies evaluated the use of Tai Chi in people with MS.[97,98] To evaluate the effects of training in the principles of "mindfulness of movement" from Tai Chi/Qi Gong in MS, 16 secondary progressive MS patients were divided into 8 matched pairs. Each pair was randomized into a "mindfulness" group or a "usual care" group (standard medical care for MS). Although there was no difference between groups in measures of balance, there was a significant improvement in the mindfulness group in self-reported measures of MS-related symptoms.[97] In a nonrandomized uncontrolled pilot study, 19 people with MS underwent Tai Chi training twice weekly for 8 weeks. Outcomes measures compared pretraining to posttraining scores. Posttraining outcomes demonstrated an improvement in walking speed, hamstring flexibility, and subjects' reports of well-being and quality of life.[98]

There has been one randomized controlled study evaluating yoga in MS.[108] Sixty nine subjects were randomized to one of three groups: (1) wait-list control (n = 22), (2) exercise (n = 26), and (3) yoga (n = 21). The intervention lasted for 6 months. After 6 months, the subjects were randomized to either the exercise or yoga group. Those in the yoga group showed significant improvements in quality of life and physical measures compared with those randomized to the exercise or wait-list control group. There has been one randomized study evaluating a Mindfulness Based Intervention in MS.[109] One hundred and fifty subjects were randomized to a mindfulness based intervention (MBI) (n = 76) or usual care (n = 74) with an intervention period of 8 weeks and a 6-month post-intervention follow-up. Subjects randomized to MBI underwent training that closely followed the protocol of Jon Kabat-Zinn's Mindfulness Based Stress Reduction Program[110] that consists of a two and a half hour session, once a week, for eight weeks, and one seven hour session on Saturdays. Subjects in usual care were offered MBI training after completing outcome assessments at the time equivalent of the MBI intervention and the 6-months post-intervention. Compared with the usual care group, subjects randomized to MBI showed significant improvements in quality of life, fatigue, anxiety, and depression. Mind-body interventions show promise of benefit in MS and offer a nonpharmacologic therapy that can be effective in reducing stress, improving fatigue, and improving quality of life in MS.

THERAPEUTIC APPROACH

Treatment of MS with diet, nutritional supplementation, exercise, and stress reduction should be the basis for the natural medicine approach to MS. Although this approach (employing combined therapies) has not been proved to be beneficial for MS in randomized controlled trials, it should help to improve the general health of patients and may provide specific benefit to help control the disease and improve symptoms. This approach also can be used in conjunction with conventional therapies that have been proved in controlled trials to be beneficial for MS.

Diet

The Swank/low-saturated-fat dietary protocol is recommended:

- 15 g/day or less of saturated fat intake
- An unsaturated fat intake of a minimum of 20 g/day and maximum of 50 g/day

- No red meat consumption for the first year (this includes dark meat of turkey and chicken); following the first year, only 3 oz of red meat weekly
- White-meat poultry, fish, and shellfish are permissible in any amounts as long as they are low in saturated fats
- Elimination of dairy products containing 1% butterfat or more
- One multivitamin/multimineral daily is recommended

The Swank diet recommends supplementation with one to four capsules of nonconcentrated cod-liver oil, or patients can use fish-oil concentrate for cod-liver oil at 3 to 4 capsules daily. Fresh whole foods should be emphasized, and animal foods (with the exception of cold-water fish) should be reduced if not completely eliminated.

Nutritional Supplements

High-potency Multiple-vitamin-and-mineral Formula

- Fish oils: 3000 mg EPA+DHA a day
- Vitamin C: 500 to 1000 mg/day
- Vitamin D_3: 2000 to 8000 IU/day with the goal of achieving an ideal range of 50 to 80 ng/mL 25-hydroxy D3
- Alpha-lipoic acid: 600 to 1200 mg once a day with meals.

Choose one of the following:

- Grape seed extract (>95% procyanidolic oligomers): 150 to 300 mg/day
- Pine bark extract (>90% procyanidolic oligomers): 150 to 300 mg/day
- Proteolytic enzymes such as mixed enzyme preparations or pancreatin (8-10 × USP): 350 to 750 mg between meals three times a day; or Bromelain: 250 to 750 mg (1800 to 2000 MCU) between meals three times a day

Botanical Medicine

- Ginkgo biloba extract (24% ginkgo flavonglycosides): 120 to 160 mg twice a day is recommended for patients with cognitive impairment

Exercise

The type and amount of exercise should be tailored to the patient. Mild to moderate exercise for at least 30 minutes three times a week is recommended. Exercises that can cause overheating in an MS patient should be avoided. Types of exercises recommended for MS include walking, stretching, bicycling, low-impact aerobics, stationary bicycling, swimming or water aerobics, yoga, and Tai Chi.

Stress Reduction

As with exercise, the therapy used to reduce stress should be tailored to the patient. Exercise can be used as a stress-reduction therapy. Stress-reduction therapies recommended for MS include yoga, exercise, meditation, deep breathing or breathing exercises, and prayer.

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CHAPTER 192

Obesity

Michael T. Murray, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

Obesity is defined as the following:

- Having a body-mass index greater than 30
- Having a body-fat percentage greater than 30% for women and 25% for men

GENERAL CONSIDERATIONS

Obesity is a major contributor to mortality and morbidity, having surpassed smoking as the number one cause of premature death in the United States.[1,2] The simplest definition of obesity is an excessive amount of body fat. It must be distinguished from overweight, which refers to an excess of body weight relative to height. A muscular athlete may be overweight yet have a low percentage of body fat. With this in mind, it is obvious that using body weight alone as an index of obesity is not entirely accurate. Nonetheless, a simple measure known as the body-mass index (BMI) is now the accepted standard for classifying individuals with regard to their body composition (Table 192-1). BMI generally correlates well with a person's total body fat. The BMI is calculated as follows:

$$\text{BMI} = (\text{lb} \times 703) / \text{in}^2 \text{ (lb = pounds; in = inches)}$$

$$\text{Metric: BMI} = \text{kg}/\text{m}^2 \text{ (kg = kilograms; m = height in meters)}$$

Despite promotion of the BMI within the medical community as the definitive measure of adiposity, height and weight indices are still popular measurements made in this regard. The indices in widest use are the tables of desirable weights for height provided by the Metropolitan Life Insurance Company. However, the Metropolitan tables are often criticized for three major shortcomings:

- The stated weight ranges merely reflect the weights of those with the lowest mortality of insured persons, which may not reflect the U.S. population.
- Weight ranges for lowest mortality do not necessarily reflect optimal healthy weight for height.
- The standard values make it difficult to assess the degree of obesity (e.g., a person within the proper weight range may have excess body fat and lower-than-optimal lean body mass, or an individual with increased muscular development may be "overweight" despite having a low percentage of body fat). Again, it is important to recognize that weight alone is a poor reflector of body-fat composition.

PREVALENCE

The prevalence of obesity has reached epidemic proportions and has steadily increased over the years among both genders, all ages, all racial/ethnic groups, and all educational levels. From 1960 to 2008, the prevalence of overweight (BMI between 25 and 30) increased from 31.5% to 34% among U.S. adults ages 20 to 74. The prevalence of obesity (BMI >30) during this same time period more than doubled, from 13.3% to 34%, with most of this rise occurring in the past 20 years. From 1960 to 2008, the prevalence of extreme obesity (BMI > 40) increased from 0.8% to 5.7%. Childhood and adolescent obesity has also increased dramatically. Results from the 2007-2008 NHANES, using measured heights and weights, indicate that an estimated 16.9% of children and adolescents ages 2 to 19 years are obese. Given the health challenges associated with obesity, as shown in Box 192-1, the significance of these increases is staggering.[3-5]

TABLE 192-1 **Classification of Body-Mass Index**

Underweight	<18.5
Normal	18.5-24.9
Overweight	25-29.9
Obesity	30-39.9
Extreme obesity	>40

BOX 192-1 **Morbidity Associated with an Increased Risk Due to Obesity**

Cardiovascular
- Angina
- Atherosclerosis
- Congestive heart failure
- Deep vein thrombosis
- Heart attack
- High blood pressure
- High cholesterol levels
- Pulmonary embolism
- Stroke

Dermatology
- Cellulitis
- Hirsutism
- Intertrigo
- Lymphedema
- Stretch marks

Endocrinology and Reproduction
- Complications during pregnancy
- Diabetes mellitus
- Infertility
- Menstrual disorders
- Intrauterine fetal death
- Polycystic ovary syndrome

Gastrointestinal
- Gastroesophageal reflux disease
- Cholelithiasis
- Fatty liver disease

Neurology
- Carpal tunnel syndrome
- Dementia
- Idiopathic intracranial hypertension
- Migraine headaches
- Multiple sclerosis

Oncology
- Cancer

Psychiatry
- Depression
- Social stigmatization

Respiratory
- Asthma
- Obstructive sleep apnea

Rheumatology and Orthopedics
- Chronic low back pain
- Gout
- Osteoarthritis

Urology and Nephrology
- Chronic renal failure
- Erectile dysfunction
- Hypogonadism
- Urinary incontinence

Obese individuals have an average of a 5- to 7-year shorter life expectancy compared with normal-weight individuals (BMI 20 to 25), with a greater relative risk for mortality associated with a greater degree of obesity.[1,6] Most of the increased risk for mortality is due to cardiovascular causes, as obesity carries with it a tremendous risk for type II diabetes, elevated cholesterol levels, high blood pressure, and other risk factors for atherosclerosis. In 2009 the estimated annual medical spending due to overweight and obesity was estimated to be $147 billion.[7]

DETERMINATION OF BODY COMPOSITION

The importance of determining body-fat composition and classifying obesity accurately cannot be overstated, since it offers valuable monitoring, prognostic, and therapeutic information. In terms of body-fat percentage, obesity is defined as greater than 30% body fat for women and 25% body fat for men. Because direct analysis of body composition cannot at this time be performed on live subjects, indirect methods must be employed, such as those listed in Box 192-2.

BOX 192-2 **Indirect Methods of Analyzing Body Fat Composition**

- Visual observation (somatotypes)
- Anthropometric measurements
- Height and weight
- Circumferences and diameters
- Skinfold thickness
- Isotope or chemical dilution
- Body water
- Body potassium
- Body fat
- Body density and body volume
- Conductivity
- Total-body electrical conductivity
- Bioelectric impedance
- Neutron activation
- Imaging techniques
- Ultrasound
- Computer tomography
- Nuclear magnetic resonance
- Nuclear magnetic spectroscopy

Visual Observation

Superficial visual observation is often all that is required for a qualitative analysis of obesity. One popular way of classifying body types is somatotyping—a physical, anthropologic classification of physique based on body size and proportion:
- The endomorph has a relatively large body and short arms and legs.
- The mesomorph has a large, muscular chest that dominates the abdomen and has prominent bony joints.
- The ectomorph has a relatively small frame (a slender, delicate bone structure) and long arms and legs.

The endomorph is at greatest risk for developing obesity, the mesomorph is at moderate risk, and the ectomorph is extremely unlikely to develop obesity.

The distribution of body fat is also important in the classification of obesity. Two basic distribution patterns exist: gynecoid and android, or female- and male-patterned obesity. These types are discussed in greater detail below, under "Types of Obesity."

Skinfold Thickness

The amount of total body fat can be estimated by measuring the thickness of the subcutaneous fat (skinfold or fatfold thickness). Skinfold thickness is measured with skinfold calipers at several sites on the body to improve accuracy. The most common measurement sites are the triceps, biceps, subscapular, and suprailiac skinfolds.

Although skinfold thickness measurements are easy to obtain and are generally accurate in estimating body-fat percentage, their limitations include the inability to control intersubject and intrasubject variations in skinfold compressibility, the inability to palpate the fat-muscle interface, and the impossibility of obtaining interpretable measurements on very obese individuals. Additionally, interobserver variability as well as the use of different types of skinfold calipers may contribute to measurement errors.

However, for most clinical purposes, skinfold measurements provide the easiest and least expensive method for estimating body fat percentage. For more precise estimations, other methods (e.g., bioelectrical impedance, ultrasound, total body electrical conductivity, and hydrostatic weighing) offer significant advantages.

Body Density

Measurement of body density provides a quantitative technique for measuring body fat. Density is determined from the specific gravity, which is calculated by measuring the different weights of the body in and out of water. In this procedure, individuals are weighed under water and out of water, taking into account the residual volume of the lungs. This information is used to fractionate the body into its fat and nonfat components, because fat is lighter than water and other tissues are heavier than water. The method is relatively simple if appropriate facilities are available. The major limitation of hydrostatic weighing is that it requires considerable cooperation from the subject, who must exhale completely and then submerge totally under water up to 10 times, making the method impossible to use with elderly, ill, or hospitalized patients.

With the advent of more sophisticated body composition analyzers, the hydrostatic weighing procedure has generally fallen out of favor, although many experts still consider it to be the gold standard of body composition determination. However, dual-energy x-ray absorptiometry (DEXA) is fast becoming the new gold standard because it provides greater precision with only one measurement and can show exactly where fat is distributed throughout the body. DEXA is based on a three-compartment model that divides the body into total body mineral, fat-free soft (lean) mass, and fat tissue mass. DEXA uses a whole-body scanner that has two low-dose x-ray beams from different sources reading bone and soft tissue mass simultaneously. The sources are mounted beneath the table with a detector overhead. The scanner passes across a person's reclining body with data collected at 0.5-cm intervals. A scan takes between 10 and 20 minutes.

Bioelectric Impedance

The bioelectrical impedance method for determining body composition is based on measuring the conduction of an applied electrical current through body tissues. In biological structures, application of a constant low-level alternating current results in a frequency-dependent impedance to the flow of the current, according to the type of tissue. Intracellular and extracellular fluids behave as electrical conductors, whereas the cell membranes act as electrical condensers. At low frequencies, such as 1 kHz, the current mainly passes through the extracellular fluids, whereas at higher frequencies, such as 500 to 800 kHz, it penetrates the intracellular and extracellular fluids. Thus, body fluids and electrolytes function as electrical conductors while cell membranes behave as capacitors.

Because fat-free mass has a much greater conductivity than does fat, there is a strong relationship between conductance and lean body mass. Body composition analysis, as determined by bioelectrical impedance, is a safe, noninvasive procedure that provides rapid measurements. Home scales equipped with bioelectrical impedance units to assess body fat percentage as well as weight are now available. These scales typically cost between $50 and $200 (Table 192-2).

TABLE 192-2 **Body-fat Rating Chart for Use With a Body-fat Measuring Scale**

AGE	RISKY	EXCELLENT	GOOD	FAIR	POOR
Male					
19-24	<6%	10.8%	14.9%	19%	23.3%
25-29	<6%	12.8%	16.5%	20.3%	24.4%
30-34	<6%	14.5%	18%	21.5%	25.2%
35-39	<6%	16.1%	19.4%	22.6%	26.1%
40-44	<6%	17.5%	20.5%	23.6%	26.9%
45-49	<6%	18.6%	21.5%	24.5%	27.6%
50-54	<6%	19.8%	22.7%	25.6%	28.7%
55-59	<6%	20.2%	23.2%	26.2%	29.3%
60	<6%	20.3%	23.5%	26.7%	29.8%
Female					
19-24	<9%	18.9%	22.1%	25.0%	29.6%
25-29	<9%	18.9%	22%	25.4%	29.8%
30-34	<9%	19.7%	22.7%	26.4%	30.5%
35-39	<9%	21%	24%	27.7%	31.5%
40-44	<9%	22.6%	25.6%	29.3%	32.8%
45-49	<9%	24.3%	27.3%	30.9%	34.1%
50-54	<9%	26.6%	29.7%	33.1%	36.2%
55-59	<9%	27.4%	30.7%	34%	37.3%
60	<9%	27.6%	31%	34.4%	38%

TYPES OF OBESITY

Obesity is divided into several categories on the basis of the size and number of fat cells and also on how the fat is distributed in the body (e.g., in the abdomen vs. the hips).

In hyperplastic obesity, there are increased numbers of fat cells throughout the body. The number of fat cells that a person has depends primarily on the diet of the mother while the individual was still in the womb as well as on early infant nutrition. An excess of calories during these early stages of development can lead to the formation of an increased number of fat cells for the rest of that individual's life. Because it is harder to develop new fat cells in adulthood, hyperplastic obesity usually begins in childhood. Fortunately this type of obesity tends to be associated with fewer serious health effects than other types of obesity.

Hypertrophic obesity is characterized by an increase in the size of each fat cell and is linked to diabetes, heart disease, high blood pressure, and other serious disturbances of metabolism.[5] With hypertrophic obesity, the fat distribution is usually around the waist. This type of distribution is referred to as male-patterned or "android" because it is typically seen in the obese male. If the waist is larger than the hips, a person is said to have android obesity. If the hips are larger, then a person has female-patterned or "gynecoid" obesity.

The waist-to-hip ratio is determined by measuring the circumference of the waist about ½ in. above the navel and measuring the circumference of the hips at the greatest protrusion of the buttocks. The waist circumference is then divided by the hip circumference. A waist-to-hip ratio above 1 for men and above 0.8 for women is associated with the metabolic syndrome (also known as syndrome X) and increases the risk of developing type II diabetes, high blood pressure, coronary heart disease, stroke, and gout.

Finally, in hyperplastic-hypertrophic obesity, there is an increase in both the number and size of fat cells.

CAUSES OF OBESITY

Although there may or may not be a specific "obesity gene," the tendency to be overweight is definitely inherited. Nonetheless, even high-risk individuals can avoid obesity, indicating that

dietary and lifestyle factors (primarily little or no physical activity) are chiefly responsible for obesity. In looking at possible causes beyond diet and lifestyle, researchers have focused on both psychological and physiologic factors.

Psychological Factors

In the past, psychological factors were thought to be largely responsible for obesity. An early popular theory proposed that overweight individuals were insensitive to internal signals for hunger and satiety while simultaneously being extremely sensitive to external stimuli (sight, smell, and taste) that could increase the appetite. One source of external stimuli that has definitely been shown to be associated with obesity is watching television.

Watching television has been demonstrated to be linked to the onset of obesity, and there is a dose-related effect. Increased television viewing and decreased physical activity are thought to be primary causes of the growing prevalence of obesity among children in the United States. Television viewing in childhood and adolescence is associated not only with being overweight but also with poor fitness and the presence of obesity, smoking, and elevated cholesterol levels in adulthood, indicating that excessive television viewing has long-lasting adverse effects on health.[8]

In addition to leading to childhood obesity, television viewing also contributes to overweight in adults. In one study, 50,277 women with BMIs below 30 completed questions on physical activity and sedentary behaviors at baseline. During 6 years of follow-up, 3757 (7.5%) of these women became obese (their BMIs were at or above 30), and 1515 new cases of type II diabetes occurred. Time spent watching television was positively associated with the risk of obesity and type II diabetes. Each 2-hour-per-day increment in television watching was associated with a 23% increase in obesity and a 14% increase in risk of diabetes. In contrast, each 2-hour-per-day increment in sitting at work was associated with a 5% increase in obesity and a 7% increase in diabetes.[9]

Although watching television fits nicely with the psychological theory (increased sensitivity to external cues), several physiologic effects of watching television promote obesity, such as reducing physical activity and the actual lowering of resting (basal) metabolic rate to a level similar to that experienced during trance-like states. These factors clearly support the physiologic view.

Physiologic Factors

Although the psychological theories primarily propose that obese individuals have a decreased sensitivity to internal cues of hunger and satisfaction, an emerging theory of obesity states almost the opposite—that obese individuals appear to be extremely sensitive to specific internal cues.[4] Unfortunately, these cues relate to dysfunctional appetite control due to a combination of genetic, dietary, and lifestyle factors. At the center of this dysfunction in many cases is resistance to the hormone insulin as a result of a conditioned reaction to a high glycemic diet. The development, progression, and maintenance of obesity is a vicious positive feedback cycle consisting of insulin resistance, central adiposity, alterations in adipokine secretion by adipocytes and gut-derived hormones, impaired diet-induced thermogenesis, and low brain serotonin levels. All of these factors are interrelated and support the theory that obesity is primarily an adaptive physiologic response that is out of control. Failure to address these underlying areas and provide proper psychological support results in only temporary weight loss at best.

The "Set Point"

Body weight is closely tied to what is referred to as the set point—the weight that a body tries to maintain by regulating the amount of food and calories consumed. Research with animals and humans has found that each person has a programmed set-point weight. It has been postulated that individual fat cells control this set point: when the enlarged fat cells in obese individuals become smaller, they either send powerful messages to the brain to eat or they block the action of appetite-suppressing compounds like leptin.

The existence of this set point helps to explain why most diets do not work. Although the obese individual can fight off the impulse to eat for a time, eventually the signals become too strong to ignore. The result is rebound overeating, with individuals often exceeding their previous weight. In addition, their set point is now set at a higher level, making it even more difficult to lose weight. This has been termed the "ratchet effect" and "yo-yo dieting."

The key to overcoming the fat cells' set point appears to be increasing the sensitivity of the fat cells to insulin. This sensitivity apparently can be improved, and the set point lowered, by exercise, a specially designed diet, and several nutritional supplements (discussed later). The set-point theory suggests that a diet that does not improve insulin sensitivity will most likely fail to provide long-term results.

When fat cells, particularly those around the abdomen, become full of fat, they secrete a number of biological products (e.g., resistin, leptin, tumor necrosis factor, free fatty acids) that dampen the effect of insulin, impair glucose utilization in skeletal muscle, and promote glucose production by the liver. Also important is that as the number and size of fat cells increase, they lead to a reduction in the secretion of compounds that promote insulin action, including a novel protein produced by fat cells known as adiponectin. Adiponectin is not only associated with improved insulin sensitivity but also has antiinflammatory activity, lowers triglycerides, and blocks the development of atherosclerosis. The net effect of all of these actions by fat cells is that they severely stress the mechanisms governing blood sugar control and also lead to the development of the major complication of diabetes—atherosclerosis. Because of all of these newly discovered hormones secreted by fat cells, many experts now consider the adipose tissue a member of the endocrine system.[10,11]

Adipokines and Gut-Derived Hormonal Alterations

It could be argued that obese individuals are more sensitive to internal signals to eat. Appetite reflects a complex system that has evolved to help humans deal with food shortages. Therefore it is extremely biased toward weight gain. It makes sense that the people who survived famines were those who were more adept at storing fat than burning it. So there is a built-in tendency in many people to overeat even though food is readily available in developed countries.

To combat the tendency to eat more than is required, it is important to accentuate the normal physiologic processes that curb the appetite. An elaborate system exists that is supposed to tell the hypothalamus when the body requires more food as well as when enough food has been consumed. In addition, adipokines like leptin, a strong signal of appetite control, actually originate from the gastrointestinal tract. In addition to nerve signals feeding back to the central nervous system is a growing list of gut-derived hormones and peptides, such as neuropeptide Y and the analogs ghrelin and cholecystokinin.[12] For example, peptide YY 3-36 (or PYY for short) dramatically reduced appetite in both obese and normal-weight individuals.[13] The subjects consumed about 30% less at an "all-you-can-eat" buffet after receiving an infusion of this

hormone than they did when they were given only saline solution. The subjects also ate significantly less over the next 24 hours.

Unlike PYY, the stomach-derived hormone ghrelin increases appetite. Ghrelin levels are highest when the stomach is empty and during calorie restriction. Obese individuals tend to have elevated ghrelin levels to begin with, and when they try to lose weight, their ghrelin levels increase. Part of the success of gastroplasty in producing permanent weight loss is thought to be due to significantly reduced ghrelin levels. For example, a diet-induced weight loss of 17% of initial body weight was associated with a 24% increase in the area under the curve (AUC) for the 24-hour ghrelin profile. However, despite a 36% weight loss after gastric bypass, the AUC for the ghrelin profile in the gastric-bypass group was 77% lower than in normal-weight controls and 72% lower than in matched obese controls.[14]

Although it is possible to use various appetite regulators as therapeutic agents in human obesity, preliminary studies seem to indicate that in humans, compensatory actions may negate the effect. The perfect drug or natural product to affect appetite must be able to increase insulin sensitivity and produce a targeted effect of reducing factors that increase appetite while simultaneously increasing factors that decrease appetite. Highly viscous dietary fiber may prove useful in this application.

Gut-Derived Appetite Regulators

The main hormones inhibiting food intake are cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), oxyntomodulin, and PYY, while hormonal stimulators of appetite include ghrelin and orexin A.[12] It could be strongly argued that secretion of these regulators, as well as overall enteroendocrine cell function, is regulated by the presence or absence of highly viscous dietary fiber, especially since the main targets for these neurotransmitters are vagal afferent neurons and the appetite-inhibiting effects of CCK are enhanced by the mechanical effects of dietary fiber (gastric distention). Brief descriptions of these gut-derived appetite regulators follow.

Cholecystokinin. The role of CCK as a regulator of protein and fat digestion in the upper small intestine has been recognized for several decades. CCK determines the capacity for digestion by controlling gastric emptying as well as the delivery of enzymes from the pancreas. The inhibition of appetite by CCK has been demonstrated in human studies.[12,15] The reduction of food intake by low-dose exogenous CCK is enhanced with moderate gastric distention, implying synergistic interactions between CCK and the stimulation of gastric mechanoreceptors. Not surprisingly, viscous dietary fiber has been shown to increase the secretion of CCK.[16,17]

Glucagon-like Peptide-1. The distal intestinal glucagon-like peptide-1 (GLP-1) is derived from different regions of the glucagon precursor. Infusion of GLP-1 inhibits food intake, decreases sensations of hunger, and inhibits plasma ghrelin (discussed further below). The secretion of GLP-1 is clearly influenced by food intake, but the specific food components, as well as the role of dietary fiber, have not yet been determined.[18]

Oxyntomodulin. Oxyntomodulin (OXM) is released from the gut postprandially in proportion to food volume and energy content. Circulating levels of OXM are elevated in several conditions associated with anorexia. Injection of OXM reduces food intake presumably by suppressing ghrelin. Elevated levels of endogenous OXM associated with disorders of the gastrointestinal tract may contribute to anorexia.[19]

Peptide YY. Peptide YY (PYY) is secreted by enteroendocrine cells of the ileum and colon, while a related compound pancreatic polypeptide is secreted by the pancreas.[20] In obese subjects, basal and postprandial plasma concentrations of PYY are reduced compared with normal subjects. Administration of PYY inhibits food intake, with effects lasting up to 24 hours after a 2-hour infusion, suggesting that PYY exerts significant long-term appetite-suppressing action.[21] Like CCK, viscous dietary fiber likely raises PYY.

Ghrelin. Ghrelin is an interesting peptide that originates from X-cells in the stomach lining. This compound makes the stomach rumble, and it is a powerful appetite stimulator.[22] Not surprisingly, plasma concentrations of ghrelin are depressed in patients with anorexia nervosa and elevated in obesity. Concentrations of ghrelin decrease on feeding, especially with meals containing dietary fiber. However, because this effect is mediated by insulin, resistance to insulin is associated with higher ghrelin levels.[23]

Orexin A. The peptide orexin A has been most intensively studied in the hypothalamus, but it also occurs in enteric neurons and in gut endocrine cells, particularly enterochromaffin cells. Orexin A is a stimulator of appetite and is thought to inhibit CCK-stimulated excitation of vagal afferent fibers (thereby negating the appetite-suppressing effect of CCK). Plasma concentrations of orexin A increase with fasting and may contribute to overeating during or immediately after a meal by suppressing satiety signaling by CCK.[12]

Diet-Induced Thermogenesis

Another physiologic difference between obese and thin people is how much of the food consumed is converted immediately to heat. This process is known as diet-induced thermogenesis (heat production). Researchers have found that a meal may stimulate up to a 40% increase in diet-induced thermogenesis in lean individuals. In contrast, overweight individuals often display only a 10% or less increase.[24] In overweight individuals, the food energy is stored instead of being converted to heat, as it is in lean individuals.

A major factor for the decreased thermogenesis in overweight people is, once again, insulin insensitivity.[25] Therefore, the enhancement of insulin sensitivity may go a long way toward reestablishing normal thermogenesis as well as resetting the set point in overweight individuals.

Researchers have also shown that even after weight loss has been achieved, individuals predisposed to obesity still have decreased diet-induced thermogenesis compared with lean individuals.[26] Therefore, it is important to continue to support insulin sensitivity and proper metabolism indefinitely if weight loss is to be maintained.

In addition to insulin insensitivity and reduced sympathetic nervous system activity, another factor determines diet-induced thermogenesis—the amount of brown fat. Most fat in the body is "white fat," consisting of an energy reserve containing triglycerides stored in a single compartment. Tissue composed of white fat looks white or pale yellow. Brown fat cells contain multiple fat storage compartments. The triglycerides are localized in smaller droplets surrounding numerous mitochondria. An extensive blood vessel network and the density of the mitochondria give the tissue its brown appearance as well as its increased capacity to metabolize fatty acids.[27]

Brown fat does not metabolize fatty acids to ATP as efficiently as other tissues of the body, including white fat. This inefficiency results in increased heat production. Brown fat plays a major role in diet-induced thermogenesis.

Some theories suggest that lean people have a higher ratio of brown to white fat than overweight individuals. Evidence supports

this theory. The amount of brown fat in modern humans is extremely small (estimates are 0.5%-5% of total body weight); but because of its profound effect on diet-induced thermogenesis, as little as 1 oz of brown fat (0.1% of body weight) could make the difference between maintaining body weight or putting on an extra 10 lb/year.[27]

Lean individuals also tend to respond differently to excess calories than those who are overweight. In one experiment, lean individuals were overfed to increase their weight. In order to maintain the excess weight, they had to increase their caloric intake by 50% over their previous intake.[28] The opposite appears to be the case in overweight and formerly overweight individuals. In addition to requiring fewer calories to gain and maintain their weight, studies have shown that in order to maintain a reduced weight, formerly obese persons must restrict their food intake to approximately 25% less than a lean person of similar weight and body size.[29]

Individuals predisposed to obesity because of decreased diet-induced thermogenesis have been shown to be extremely sensitive to marked weight gain when consuming a high-fat diet compared with lean individuals.[30] These individuals are not only more sensitive to the weight gain–promoting effects of a high-fat diet but also tend to consume much more dietary fat than lean individuals and to exercise less.

The Low-Serotonin Theory

A considerable body of evidence demonstrates that brain serotonin plays a major role in influencing eating behavior. Initial studies showed that when animals and humans are fed diets deficient in tryptophan, appetite is significantly increased, resulting in the binge eating of carbohydrates.[31,32] The diet low in tryptophan leads to low brain serotonin levels, a condition the brain interprets as starvation, so that the appetite control centers are stimulated to prefer carbohydrates. Feeding animals or humans a carbohydrate meal leads to increased tryptophan delivery to the brain, resulting in the elevated manufacture of serotonin. This scenario has led to the idea that low serotonin levels lead to "carbohydrate cravings" and play a major role in the development of obesity.

Furthermore, it has been demonstrated that concentrations of tryptophan in the bloodstream and subsequent brain serotonin levels plummet with dieting.[33] In response to severe drops in serotonin levels, the brain simply puts out such a strong message to eat that it cannot be ignored. This explains why most diets do not work.

Cravings for carbohydrates due to low serotonin levels can be mild or severe. They may range in severity from the desire to nibble on a piece of bread or a cookie to uncontrollable binging. At the upper end of the spectrum of carbohydrate addiction is bulimia, a potentially serious eating disorder characterized by binge eating and purging of the food through forced vomiting or the use of laxatives. The medical consequences of bulimia can be severe (e.g., rupture of the stomach, erosion of the dental enamel, and cardiac disturbances due to loss of potassium).

THERAPEUTIC CONSIDERATIONS

Over the long term, the control of obesity is one of the greatest clinical challenges. Few people want to be overweight, most express a strong desire to lose weight, yet only 5% of obese individuals can attain and maintain "normal" body weight for a year or more, whereas 66% of those just a few pounds or so overweight are able to do the same.

The successful program for obesity is consistent with the basic foundations of good health—a positive mental attitude, a healthy lifestyle (regular exercise being especially important), a health-promoting diet, and supplementary measures. All of these components are interrelated, creating a situation where no single component is more important than any other. Improvement in one facet may be enough to result in some positive changes, but incorporating all components yields the greatest results.

Literally hundreds of diets and diet programs claim to be the answer to the problem of obesity. Dieters are constantly bombarded with new reports of yet another "wonder" diet. However, the basic equation for losing weight never changes. In order for an individual to lose weight, energy intake must be less than energy expenditure. This goal can be achieved by decreasing caloric intake or by increasing the rate at which calories are metabolized.

To lose 1 lb, a person must consume 3500 fewer calories than he or she expends. The loss of 1 lb each week requires a negative caloric balance of 500 calories/day. This can be achieved by decreasing the amount of calories ingested or by exercise. Reducing a person's caloric intake by 500 calories is often difficult, as is increasing metabolism by an additional 500 calories/day by exercise (accomplished by a 45-minute jog, playing tennis for an hour, or a brisk walk for 1.25 hours). The most sensible approach to weight loss is to both decrease caloric intake and increase energy expenditure through exercise.

Most individuals begin to lose weight if they decrease their caloric intake below 1500 calories/day and exercise for 15 to 20 minutes three to four times a week. Starvation and crash diets usually result in rapid weight loss (largely muscle and water) but cause rebound weight gain. The most successful approach to weight loss is gradual weight reduction (0.5 to 1 lb/week) by adopting long-standing dietary and lifestyle habits that promote health and the attainment and maintenance of ideal body weight. Exercise is critical to maintaining muscle mass, bone mineral density, and preventing the accumulation of visceral fat both during active weight loss as well as after weight loss has been achieved.[34,35]

Although many obese individuals may require the loss of considerable weight to achieve their long-term goals, it is important to stress that even modest reductions in body weight can produce significant health benefits. For example, a 5% to 10% reduction in weight is accompanied by clinically meaningful improvements in cholesterol, blood pressure, blood glucose, and other health indices.

Behavioral Therapy

Although clinical studies indicate that behavioral approaches to the management of obesity are often successful in achieving clinically significant weight loss, the lost weight is generally regained. The great majority of patients return to their pretreatment weight within 3 years. In order to provide the best insights on effective interventions, it is important to examine the psychological characteristics of people who have lost significant amounts of weight and regain only minimal weight.[36] Three main behavioral characteristics have been identified in individuals who avoid regaining significant weight:

- High levels of physical activity (approximately 1 hour daily)
- Eating a low-calorie, low-fat, low-glycemic diet
- Eating breakfast regularly
- Self-monitoring weight
- Maintaining a consistent eating pattern across weekdays and weekends
- Avoiding depression

These characteristics are intertwined within a whole host of additional factors that provide the necessary leverage for successful

weight loss. For example, most patients presenting for treatment of obesity want to lose 20% to 30% of their initial body weight. Because only modest weight loss is generally achieved, many patients quickly lose the motivation and determination to keep the weight off. However, if there is a significant boost to self-esteem and self-confidence, as well as improved appearance, the feeling of being more attractive, and being able to wear more fashionable clothing, it can provide tremendous impetus for continued weight loss until the initial goals are achieved or weight loss is maintained.

It is important to remember that the majority of people want to lose weight for the sake of changes in their physical appearance, not for the health benefits. Although there is widespread awareness that being overweight is associated with increased health risks, the reality is that relatively few patients give this as their reason for seeking treatment. Identifying the primary goals of weight loss in patients is a key step in helping them achieve success.

Dietary Strategies

The dietary strategy that we recommend for obesity is the same as that given in Chapter 44. The principles and goals detailed there reinforce some of the key goals of weight loss and the maintenance of ideal body weight. The importance of adequate protein consumption should be stressed. We recommend 2.0 g of protein per 2 lb body weight unless a patient is showing signs of renal failure.

The importance of higher protein consumption was demonstrated in the Diogenes study. The name Diogenes is an acronym standing for "Diet, Obesity and Genes." This 5-year program involved a consortium of 29 world-class centers in diet and health studies, epidemiology, dietary genomics, and food technology across Europe. Over 700 overweight adults from eight European countries who had lost at least 8% of their initial body weight with an 800-calorie diet were randomly assigned to one of five ad libitum diets to prevent weight regain over a 26-week period: a low-protein and low-glycemic-index diet, a low-protein and high-glycemic-index diet, a high-protein and low-glycemic-index diet, a high-protein and high-glycemic-index diet, or a control diet. Fewer participants in the high-protein and the low-glycemic-index groups than in the low-protein-high-glycemic-index group dropped out of the study (26.4% and 25.6%, respectively, vs. 37.4%). The mean initial weight loss with the low-calorie diet was 11 kg. In the analysis of participants who completed the study, only the low-protein-high-glycemic-index diet was associated with subsequent significant weight regain (1.67 kg). In an intention-to-treat analysis, the weight regain was 0.93 kg less in the groups assigned to a high-protein diet than in those assigned to a low-protein diet and 0.95 kg less in the groups assigned to a low-glycemic-index diet than in those assigned to a high-glycemic-index diet. The groups did not differ significantly with respect to diet-related adverse events.[37]

Water

It is well established that water consumption can acutely reduce caloric intake at mealtimes, especially among middle-aged and older adults. In the most recent study, 48 adults aged 55 to 75 years with a BMI between 25 and 40 were assigned to one of two groups: (1) a hypocaloric diet with 500 mL water prior to each daily meal (water group) or (2) a hypocaloric diet alone (nonwater group). Weight loss was approximately 2 kg greater in the water group than in the nonwater group, and the water group showed a 44% greater decline in weight over the 12 weeks than the nonwater group. Thus, when combined with a hypocaloric diet, consuming 500 mL water prior to each main meal leads to greater weight loss than a hypocaloric diet alone in middle-aged and older adults.[38]

The Atkins Diet

Although literally hundreds of fad diets have been promoted over the years, we would be remiss if we did not mention the most famous weight-loss diet of all time—the "Atkins Diet." This high-protein, high-fat, low-carbohydrate diet was developed by Robert Atkins during the 1960s. In the early 1990s, Atkins brought his diet back into the nutrition spotlight with the publication of his best-selling book *Dr. Atkins' New Diet Revolution*. An estimated 50 million people or more worldwide have tried the Atkins Diet, which emphasizes the consumption of protein and fat. Individuals following the Atkins Diet are permitted to eat unlimited amounts of all meats, poultry, fish, eggs, and most cheeses.

The Atkins Diet is divided into four phases: induction, ongoing weight loss, premaintenance, and maintenance. During the induction phase (the first 14 days of the diet), carbohydrate intake is limited to no more than 20 g per day. No fruit, bread, grains, starchy vegetables, or dairy products except cheese, cream, and butter are allowed during this phase. During the ongoing weight-loss phase, dieters experiment with various levels of carbohydrate consumption until they determine the most liberal level of carbohydrate intake that allows them to continue to lose weight. Dieters are encouraged to maintain this level of carbohydrate intake until their weight loss goals are met. Then, during the premaintenance and maintenance phases, dieters determine the level of carbohydrate consumption that allows them to maintain their weight. To avoid regaining weight, dieters must stick to this level of carbohydrate consumption, perhaps for the rest of their lives.

Although we agree with the underlying principle of the Atkins Diet, that diets high in sugar and refined carbohydrates cause weight gain and ultimately lead to obesity, we disagree with the solution. One of the big reasons why the Atkins Diet is so attractive to dieters who have tried unsuccessfully to lose weight on low-fat, low-calorie diets is that while on the Atkins Diet, they can eat as many calories as desired from protein and fat as long as carbohydrate consumption is restricted. Therefore many Atkins dieters are spared the feelings of hunger and deprivation that accompany other weight-loss regimens. However, we do not agree that such a diet is conducive to long-term health.

Despite its enormous popularity, the Atkins program was not evaluated in a proper clinical trial until 2003. In this initial study, although people following the Atkins Diet did experience initial weight loss—though likely as a result of water loss rather than true fat loss—in the long run they gained it all back, plus more. In the study, 63 obese men and women were randomly assigned to the Atkins Diet or a low-calorie, high-carbohydrate, low-fat diet. Professional contact was minimal, so as to replicate the approach used by most dieters. Although subjects on the Atkins Diet had lost more weight than subjects on the conventional diet at 6 months, the difference at 12 months was not significant. Adherence was poor, and attrition was high in both groups.[39]

Since this initial clinical evaluation, other studies have shown similar results. For example, in one study of 34 adults with impaired glucose tolerance, 12 weeks of a low-fat (18% of total calories), high–complex carbohydrate (more than 62% of total calories) diet alone (High-CHO) or paired with an aerobic exercise training program (High-CHO+Ex) was compared with the effects of an Atkin's-style diet (41% fat, 14% protein, 45% carbohydrate of total calories; the control group). Fiber intake averaged 58 to 61 g/day in the two high-carbohydrate groups versus 18.5 g/day in the control

group. Participants engaged in aerobic exercise for 45 minutes a day, 4 days per week, at 80% of peak oxygen consumption in the High-CHO+Ex group. All participants were instructed to consume food ad libitum. Although caloric intake was similar in all three groups, both High-CHO groups (with and without exercise) lost more weight (mean loss 10.5 lb with exercise and 7 lb without exercise than the control group (mean loss: a fraction of 1 lb). Similarly, a higher percentage of body fat was lost by the High-CHO+Ex (3.5%) group and the High-CHO without exercise group (2.2%) than by controls (0.2% increase in body fat). Thigh fat area also decreased significantly in both of the High-CHO groups but not in the control group. Resting metabolic rate and rate of fat oxidation were not decreased in the High-CHO or control groups.[40]

In another study, 132 obese adults (BMI >35), of whom 83% had type II diabetes or metabolic syndrome, were counseled to consume either an Atkins-like diet limited to less than 30 g of carbohydrates per day or to a diet restricted by 500 kcal per day with less than 30% of these calories coming from fat. Although initially the Atkins Diet did promote weight loss during the first 6-month period, this effect began to disappear during the second 6-month period. At 12 months, the difference between average weight loss in the two groups was no longer statistically significant (11 lb in the Atkins group vs 7 lb in the low-fat group), although changes in triglyceride levels favored the Atkins Diet (–57 mg/dL vs. +4 mg/dL), as did reductions in hemoglobin A_{1c} (–0.7 vs –0.1%) in the patients with type II diabetes.[41]

Another study worth commenting on was funded by the Atkins Foundation. In this study, 120 overweight but otherwise healthy adult subjects with elevated lipid levels followed either the Atkins Diet or a diet containing fewer than 30% calories from fat, 10% or fewer calories from saturated fat, less than 300 mg cholesterol, and a deficit of 500 to 1000 calories. At 24 weeks, the Atkins group had lost a mean of 26 lb versus a mean loss of 14 lb in the reduced-fat group. Triglyceride levels fell more in the Atkins group (–74 mg/dL) than in the restricted-fat group (+28 mg/dL) as well, and high-density-lipoprotein cholesterol (HDL-C) levels increased in the Atkins group (by 5.5 mg/dL) and decreased in the low-fat group (by 1.6 mg/dL). The main criticism of this study was that the "low-fat" group received almost 30% of their caloric intake from fat, and the dietitians administering the dietary recommendations made no clear attempt to significantly restrict sugar and refined carbohydrates. Thus, the control diet with which the Atkins Diet was compared was significantly less than ideal.[42]

The findings from these clinical trials indicate that while adhering strictly to the Atkins Diet (dramatically reducing carbohydrate intake while allowing free access to high-fat and high-protein foods) can lead to more weight loss in the first 6 months, eating a more healthful diet, as described in Chapter 44, is associated with equal efficacy in the long run and is considerably more health-promoting. The low-carbohydrate diet was associated with a greater improvement in some risk factors; however, on the basis of the current evidence, we do not recommend the Atkins Diet. Furthermore, because the high protein content of the Atkins Diet places stress on the liver and kidneys, we do not recommend it for anyone with impaired liver or kidney function.

Natural Weight-Loss Aids

Several natural weight loss aids can be useful in helping either to reduce appetite or enhance metabolism. In decreasing order of efficacy, we rate these items as follows:

- Meal-replacement formulas
- Fiber supplements
- Chromium
- Medium-chain triglycerides
- Hydroxycitrate
- 5-hydroxytryptophan (5-HTP)

Meal-Replacement Formulas

Meal replacement formulas are a popular weight-loss strategy, and their effectiveness has been confirmed in several clinical trials.[43-46] In these studies, dietary compliance and convenience were viewed more favorably by participants who consumed meal-replacement (MR) formulas than by those in a conventional weight-loss program. Ideally, these formulations should provide high-quality nutrition; they should be high in protein, low in glycemic load; and high in viscous, soluble fiber. A protein target of 2.2 g protein/kg lean body mass (LBM) per day produces greater fat loss than 1.1 g protein/kg LBM per day.[47]

Medifast is a popular physician-supervised weight-loss program that relies heavily on MR formulas. In one 40-week randomized controlled clinical trial that included 90 obese adults with a BMI between 30 and 50, subjects were randomly assigned to one of two weight loss programs for 16 weeks and then followed for a 24-week period of weight maintenance. The dietary interventions consisted of an MR program (Medifast) or a self-selected isocaloric food-based (FB) meal plan. The Medifast plan included 5 MRs (90-110 kcal/each), 5 to 7 oz lean protein, 1½ cups of nonstarchy vegetables, and up to two fat servings daily (providing 800-1000 kcal). The MRs used in this study were low in fat, low in glycemic index (GI), and low in sugar, providing a balanced ratio of carbohydrates to proteins; they were based on either soy and/or whey protein. The food-based plan included 3 oz of grains, 1 cup of vegetables, 1 cup of fruit, 2 cups of milk, 5 to 7 oz of lean protein, and 3 tsp of fat daily (providing about 1000 kcal/day). The FB group was also instructed to take a multivitamin and additional calcium to ensure that micronutrient needs were met. Weight loss at 16 weeks was significantly better in the Medifast group (MD) versus the food-based group (FB), 12.3% versus 6.9%, respectively. Significantly more of the MD participants lost 5% or more of their initial weight at week 16 (93% vs. 55%) and week 40 (62% vs. 30%). Significant improvements in body composition were also observed in MD participants compared with those in the FB group at weeks 16 and 40. At week 40, a mean body fat percentage decrease in the MD group was 2.9%, whereas the FB group decreased by 1.8%. Moreover, lean muscle mass as a percent of total weight was significantly increased by 4.5% from baseline to week 40 in the MD group, whereas the FB group did not experience any significant change. Blood pressure also dropped. At week 40, systolic blood pressure had dropped by 6.0 mm Hg (4.5%) in the MD group and 8.3 mm Hg in the FB group. Diastolic blood pressure was decreased by 5.5 mm Hg (6.2%) in the MD group and 0.9 mm Hg (0.45%) in the FB group. One advantage for the FB group was in the reduction of C-reactive protein (CRP). At week 40, CRP levels in the FB group decreased by a mean of 4.1 (30.1%) while in the MD group they decreased by a mean of 3.1 (40.7%).[48]

Fiber Supplements

A tremendous amount of clinical evidence indicates that increasing the amount of dietary fiber promotes weight loss. The best supplemental fiber sources for weight loss are PGX (discussed below), glucomannan, gum karaya, psyllium, chitin, guar gum, and pectin, because they are viscous, water-soluble fibers. When taken with water before meals, these fiber sources bind to the water in the stomach to form a gelatinous mass that induces a sense of satiety. As a result, individuals are less likely to overeat.

TABLE 192-3 **Clinical Studies With Dietary Fiber Supplements**

FIBER	NO. OF SUBJECTS	LENGTH OF STUDY	DOSAGE (g/day)	CALORIE RESTRICTION	AVERAGE WEIGHT LOSS (FIBER, LB)	AVERAGE WEIGHT LOSS (PLACEBO GROUP)	REFERENCE
Guar	9	2 mo	20	None	9.4	No placebo group	51
Guar	7	1 yr	20	None	61.9	No placebo group	52
Guar	21	2.5 mo	20	None	15.6	No placebo group	53
Guar	33	2.5 mo	15	None	5.5	0.9 lb in placebo group	54
Glucomannan	20	2 mo	3	None	5.5	Weight gain of 1.5 lb	55
Glucomannan	20	2 mo	3	None	8.14	0.44 lb in placebo	56
Citrus pectin	14	4 wk	5.56	Yes	12.8	No placebo group	57
Mixture A	60	12 wk	5	Yes	18.7	14.7 lb in placebo group	58
Mixture A	89	11 wk	10	Yes	13.9	9.2 lb in placebo group	59
Mixture B	45	3 mo	7	Yes	13.6	9 lb in placebo group	60
Mixture B	97	3 mo	7	Yes	10.8	7.3 lb in placebo group	61
Mixture B	52	6 mo	7	Yes	12.1	6.1 lb in placebo group	62

Mixture A = 80% fiber from grains, 20% fiber from citrus; mixture B = 90% insoluble and 10% soluble fiber from beet, barley, and citrus.

The benefits of fiber go well beyond this mechanical effect, however. Fiber supplements have been shown to enhance blood sugar control, decrease insulin levels, and reduce the number of calories absorbed by the body. In some of the clinical studies demonstrating weight loss, fiber supplements were shown to reduce the number of calories absorbed by 30 to 180 per day. Although modest, this reduction in calories would, over the course of a year, result in a 3- to 18-lb weight loss.[49,50]

Several studies have used guar gum, a water-soluble fiber obtained from the Indian cluster bean *(Cyamopsis tetragonoloba),* with good results (Table 192-3).[51-62] In one study, nine women weighing between 160 and 242 lb were given 10 g of guar gum immediately before lunch and dinner. They were told not to consciously alter their eating habits. After 2 months, the women reported an average weight loss of 9.4 lb. Reductions were also noted for cholesterol and triglyceride levels.[51]

Studies with soluble fiber in the treatment of elevated cholesterol levels have shown a dose-dependent effect.[49,50] Dietary fiber supplements appear to exert a dose-dependent effect in weight loss studies as well. Therefore, to achieve the greatest benefit, the dosage should be as high as possible. Because water-soluble fibers are fermented by intestinal bacteria, a great deal of gas can be produced, leading to increased flatulence and abdominal discomfort. Patients should be advised to start out with a dosage between 1 and 2 g before meals and at bedtime and to gradually increase the dosage to 5 g.

Several studies have used PGX (PolyGlycopleX), a novel natural polysaccharide matrix composed of three natural compounds (glucomannan, alginate, and xanthan gum) combined in a proprietary process that leads them to coalesce and form an entirely new matrix that is the most viscous fiber known to date.[63,64] Detailed clinical studies have now shown PGX to exert the following benefits:

- Reduce appetite and promote effective weight loss[65,66]
- Increase the level of compounds that block the appetite and promote satiety[67]
- Decrease the level of compounds that stimulate overeating[65]
- Reduce postprandial (after-meal) and delayed (second meal) postprandial blood glucose levels when added to or taken with foods[68,69]
- Reduce the glycemic index of any food or beverage by 15% to 70%[68,69]
- Increase insulin sensitivity and decrease blood insulin levels[70]
- Stabilize blood sugar control in the overweight and obese
- Lower blood cholesterol and triglycerides[65,66]

PGX is available in a soft gelatin capsule, as granules to be added into food and beverages, and in a meal-replacement drink mix. The typical dosage is 2.5 to 5 g before each meal. PGX has an excellent safety profile.[71] As with other sources of dietary fiber, to avoid minor side effects—such as increased gas, bloating, loose stools, or constipation—it is best to start with small amounts and then gradually increase the dosage within a few days to a week.

Chromium

One of the key goals for enhancing weight loss is to increase the sensitivity of body cells to insulin. Chromium plays a key role in cellular sensitivity to insulin. In some clinical studies in diabetics, supplementing the diet with chromium has been shown to decrease fasting glucose levels, improve glucose tolerance, lower insulin levels, and decrease total cholesterol and triglyceride levels while also increasing the levels of HDL-C (see Chapter 161). Chromium supplementation has been demonstrated to lower body weight yet increase lean body mass, presumably as a result of increased insulin sensitivity. In one study, patients were given chromium bound to picolinic acid (chromium picolinate) in one of three doses daily for 2.5 months: placebo, 200 mcg, or 400 mcg.[72] Patients taking the 200- and 400-mcg doses lost an average of 4.2 lb of fat. The group taking the placebo lost only 0.4 lb. Even more impressive was the fact that the chromium groups gained more muscle (1.4 lb vs 0.2 lb) than those taking the placebo. The results were most striking in elderly subjects and in men. The men taking chromium picolinate lost more than seven times the amount of body fat as those taking the placebo (7.7 lb vs 1 lb). However, an increase in lean body weight percentage with chromium supplementation may be limited to men, because two clinical trials in women involved in an exercise program did not show any significant changes in body composition with chromium supplementation.[73,74] The 400-mcg dosage is more effective than the 200-mcg dosage (Table 192-4). Several recent studies with chromium picolinate at dosages of 1000 mcg/day did not show any benefits, indicating that the effect of chromium is probably limited to restoring and maintaining optimal tissue concentrations of chromium versus any pharmacologic effect.[75,76] Higher dosages are not likely to show any greater effect than 400 mcg daily.

TABLE 192-4 **Effects of 200 Versus 400 mcg/day of Chromium Picolinate for 2.5 Months**

DOSAGE	FAT LOSS	MUSCLE GAIN	TOTAL WEIGHT LOSS
200 mcg chromium picolinate	−3.3 lb	+1.5 lb	−1.8 lb
400 mcg chromium picolinate	−4.6 lb	+1.1 lb	−3.5 lb

Medium-Chain Triglycerides

Medium-chain triglycerides (MCTs) are saturated fats (extracted from coconut oil) that range in length from 6 to 12 carbon chains. MCTs are used by the body differently from the long-chain triglycerides (LCTs), which are the most abundant fats found in nature. LCTs are the storage fats for both humans and plants and range in length from 18 to 24 carbons. This difference in length makes a substantial difference in how MCTs and LCTs are metabolized. Unlike regular fats, MCTs appear to promote weight loss rather than weight gain.

MCTs may promote weight loss by increasing thermogenesis and energy expenditure.[77,78] In contrast, the LCTs are usually stored in the fat deposits and because their energy is conserved and a high-fat diet tends to decrease the metabolic rate. In one study, the thermogenic effect of a high-calorie diet containing 40% fat as MCTs was compared with one containing 40% fat as LCTs. The thermogenic effect (calories wasted 6 hours after a meal) of the MCTs was almost twice as high as that of the LCTs—120 versus 66 calories. The researchers concluded that the excess energy provided by fats in the form of MCTs would not be efficiently stored as fat but rather wasted as heat. A follow-up study demonstrated that MCT oil given over a 6-day period can increase diet-induced thermogenesis by 50%.[80]

In another study, researchers compared single meals of 400 calories composed entirely of MCTs or LTCs.[81] The thermic effect of MCTs over 6 hours was three times greater than that of LCTs. In addition, while the LCTs elevated blood fat levels by 68%, MCTs had no effect on the blood fat level. Researchers concluded that the substitution of MCTs for LCTs would produce weight loss as long as the caloric level remained the same.

In one double-blind study, 101 hypertriacylglycerolemic subjects were randomly assigned to ingest 25 to 30 g/day of MCT or LCT oil as the only cooking oil for 8 consecutive weeks. As compared with subjects having BMIs between 24 and 28 in the LCT group, corresponding subjects in the MCT group showed significantly greater decreases in body weight, BMI, body fat, waist circumference (WC), ratio of WC to hip circumference (HC), total fat area and subcutaneous fat area in the abdomen, as well as blood triglycerides and low-density-lipoprotein cholesterol (LDL-C) levels at week 8.[82]

In order to gain the benefit from MCTs, a diet must remain low in LCTs. MCTs can be used as oils for salad dressing, bread spreads, or simply taken as supplements. A good dosage recommendation for MCTs is 1 to 2 tbsp/day.

Diabetic patients and individuals with liver disease should be monitored closely when using MCTs, as they may develop ketoacidosis.

Hydroxycitrate

Hydroxycitrate (HCA) is a natural substance isolated from the fruit of the Malabar tamarind *(Garcinia cambogia).* This is a yellowish fruit about the size of an orange with a thin skin and deep furrows, similar to an acorn squash. It is native to southern India, where it is dried and used extensively in curries. The dried fruit contains about 30% hydroxycitric acid.

HCA has been shown to be a powerful lipogenic inhibitor in animals.[83,84] Whether or not it demonstrates this effect in humans has not yet been proved. The weight loss–promoting effects in animals are perhaps best exemplified in a study that shows HCA producing a "significant reduction in food intake, and body weight gain" in rats.[85] HCA may be not only a powerful inhibitor of fat production but also an appetite suppressant. It is critical, when using an HCA formula, that a low-fat diet be maintained, as HCA only inhibits the conversion of carbohydrates into fat.

By itself, HCA may offer a safe, natural aid for weight loss when taken at a dosage of 1500 mg three times daily. In two clinical trials, a total of 90 moderately obese subjects (ages 21 to 50, BMI > 26) were randomly divided into three groups. Group A was administered HCA 4667 mg; group B was administered a combination of HCA 4667 mg, niacin-bound chromium 4 mg, and *Gymnema sylvestre* extract 400 mg; whereas group C was given a placebo daily in three equally divided doses 30 to 60 minutes before meals. All subjects were provided with a diet of 2000 kcal/day and participated in a supervised walking program for 30 min/day, 5 days/week. Eighty-two subjects completed the study. At the end of 8 weeks, both body weight and BMI decreased by 5.4% in group A, LDL-C and triglycerides were reduced by 12.9% and 6.9%, respectively, while HDL-C levels increased by 8.9%, serum leptin levels decreased by 38%, serotonin levels increased by 44.5%, and urinary excretion of fat metabolites increased by 32% to 109%. Group B demonstrated similar beneficial changes, but generally to a greater extent. Specifically, group B reduced body weight and BMI by 7.8% and 7.9%, respectively, food intake was reduced by 14.1%, total cholesterol, LDL-C, and triglyceride levels were reduced by 9.1%, 17.9%, and 18.1%, respectively, while HDL-C and serotonin levels increased by 20.7% and 50%, respectively. Serum leptin levels decreased by 40.5% and enhanced excretion of urinary fat metabolites increased by 146% to 281%. No significant adverse effects were observed in either trial.[86]

5-Hydroxytryptophan

More than three decades ago, researchers demonstrated that the administration of 5-HTP to rats genetically bred to overeat and be obese resulted in a significant reduction in food intake. Further research revealed that these rats had decreased activity of tryptophan hydroxylase, which converts tryptophan to 5-HTP, itself subsequently converted to serotonin. In other words, these rats were fat as a result of a genetically determined low level of activity of the enzyme that starts the manufacture of serotonin from tryptophan. Hence, these rats never got the message to stop eating until they had consumed far greater amounts of food than normal rats. Circumstantial evidence indicates that many humans are also genetically predisposed to obesity, a predisposition, which may involve the same mechanism as that in rats genetically predisposed to obesity (i.e., decreased conversion of tryptophan to 5-HTP and, as a result, decreased serotonin levels). By providing preformed 5-HTP, this genetic defect is bypassed and more serotonin is manufactured. (For a complete discussion of this interesting nutrient, see Chapter 98.)

The early animal studies with 5-HTP as a weight-loss aid have been followed by a series of three human clinical studies in overweight women.[87-89] The first study showed that 5-HTP was able to reduce caloric intake and promote weight loss despite the fact that the women made no conscious effort to lose weight.[87] The average amount of weight lost during the 5-week period of 5-HTP supplementation was a little more than 3 lb.

The second study sought to determine if 5-HTP helped overweight individuals adhere to dietary recommendations.[88] This

12-week study was divided into two 6-week periods. For the first 6 weeks there were no dietary recommendations, and for the second 6 weeks the women were placed on a 1200-calorie diet. As shown in Table 192-5, the women taking the placebo lost 2.28 lb, whereas the women taking the 5-HTP lost 10.34 lb.

As in the previous study, 5-HTP appeared to promote weight loss by promoting satiety, leading to the consumption of fewer calories at meals. All the women taking 5-HTP reported early satiety.

The third study with 5-HTP was similar to the second study: for the first 6 weeks there were no dietary restrictions, and for the second 6 weeks the women were placed on a diet of 1200 calories per day.[89] The group receiving the 5-HTP lost an average of 4.39 lb after the first 6 weeks and an average of 11.63 lb after 12 weeks. In comparison, the placebo group lost an average of only 0.62 lb after the first 6 weeks and 1.87 lb after 12 weeks. The lack of weight loss during the second 6-week period in the placebo group obviously reflects the fact that the women had difficulty adhering to the diet.

Early satiety was reported by 100% of the subjects during the first 6-week period. During the second 6-week period, even with severe caloric restriction, 90% of the women taking 5-HTP reported early satiety. Many of the women receiving the 5-HTP (300 mg three times daily) reported mild nausea during the first 6 weeks of therapy. However, the symptom was never severe enough for any of the women to drop out of the study. No other side effects were reported.

TABLE 192-5 **Impact of 5-HTP on Weight Loss**

	PLACEBO	5-HTP GROUP
Weight (lb)		
Baseline	207.68	229.46
After 6 weeks	206.58	225.94
After 12 weeks	205.4	219.12
Total Weight Loss (lb)		
After 6 weeks	1.1	3.52
After 12 weeks	2.28	10.34

THERAPEUTIC APPROACH

A successful program for weight loss must be consistent with the four cornerstones of good health:

- Proper diet
- Adequate exercise
- A positive mental attitude
- The right support for the body through natural measures

All of these components are critical and interrelated.

Diet

The recommendations given in Chapter 44 should be followed. Adequate protein is very important, 2 g per kg of body weight.

Psychological Support

Referral to counseling should be considered. Overweight individuals tend to suffer heavy assaults on their self-esteem and self-image.

Lifestyle

Exercise is absolutely critical to an effective weight loss program. Recommendations are given in Chapter 36.

Supplements

- Viscous, soluble fiber (e.g., PGX): 2.5 to 5 g before meals
- 5-HTP: begun at 50 to 100 mg 20 minutes before meals for 2 weeks and then doubled (to a maximum of 300 mg) if weight loss is less than 1 lb/week. Higher dosages of 5-HTP (e.g., 300 mg) are associated with nausea, but this symptom disappears after 6 weeks of use.
- Chromium: 200 to 400 mcg/day
- Medium-chain triglycerides: 1 to 2 tbsp incorporated into the diet

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- Hydroxycitrate (from *G. cambogia*): 1500 mg three times a day

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CHAPTER 193

Osteoarthritis

Michael T. Murray, ND

DIAGNOSTIC SUMMARY

- Clinical symptoms—mild early-morning stiffness, stiffness following periods of rest, pain that worsens on joint use, and loss of joint function
- Clinical signs—local tenderness; soft tissue swelling; joint crepitus; bony swelling; restricted mobility; Heberden's (proximal interphalangeal joints) or the less common Bouchard's (distal interphalangeal joints) nodes or both; and other signs of degenerative loss of articular cartilage
- X-ray findings—narrowed joint spaces, osteophytes, increased density of subchondral bone, subchondral sclerosis, bony cysts, soft tissue swelling, and periarticular swelling

GENERAL CONSIDERATIONS

Osteoarthritis (OA), or degenerative joint disease, is characterized by joint degeneration, loss of cartilage, and alterations of the subchondral bone. It is by far the most common form of arthritis. It is estimated that more than 40 million Americans have OA, and OA is believed to be responsible for 25% of all office visits to primary care physicians. Whereas 80% of persons above 50 years of age will have x-ray evidence of significant OA, only 60% will experience symptoms. Men and women are equally affected, but symptoms occur earlier and appear to be more severe in women. OA incidence increases dramatically with age and body-mass index (especially OA of the knee).[1-3] Table 193-1 lists some of the diseases that are now thought to be OA of specific joints.

The weight-bearing joints and peripheral and axial articulations are the joints principally affected by the degenerative changes associated with OA. Much destruction of hyaline cartilage occurs, followed by hardening and the formation of large bone spurs (calcified osteophytes) in the joint margins. Pain, deformity, and limitation of joint motion result from this degeneration. Inflammation is usually minimal.

OA is divided into two categories, primary and secondary.[4] In primary OA, the degenerative "wear-and-tear" process occurs after the fifth and sixth decades, with no apparent predisposing abnormalities. The cumulative effects of decades of use lead to degenerative changes by stressing the collagen matrix of the cartilage. Damage to the cartilage results in the release of enzymes that destroy collagen components. With aging, the ability to restore and synthesize normal collagen structures decreases.

Secondary OA is associated with some predisposing factors that can be responsible for the degenerative changes. Such factors include the following:

- Congenital abnormalities in joint structure or function (e.g., hypermobility and abnormally shaped joint surfaces)
- Trauma (e.g., obesity, fractures along joint surfaces, surgery)
- Crystal deposition
- Presence of abnormal cartilage
- Previous inflammatory disease of the joint (e.g., rheumatoid arthritis, gout, septic arthritis)

Box 193-1 summarizes the many factors involved in the pathogenesis of OA.

One of the most interesting clinical features of OA is the lack of correlation between its severity as determined by a radiograph and the degree of pain. In some cases the joint appears normal, with little if any joint-space narrowing, yet the pain can be excruciating. Conversely, there are cases in which there is tremendous deformity yet little if any pain. In fact, about 40% of individuals with the worst x-ray

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TABLE 193-1 **Diseases Thought to be Osteoarthritis of Specific Joints**

JOINT	DISEASE
Hands	Heberden's and Bouchard's nodes
Hip	Malum coxae senilis
Temporomandibular joint	Costen's syndrome
Knee	Chondromalacia patellae
Spine	Ankylosing hyperostosis (interstitial skeletal hyperostosis)

BOX 193-1 **Multifactorial Etiology of Osteoarthritis**

- Hypermobility/joint instability
- Age-related changes in collagen matrix repair mechanisms
- Hormonal and gender factors
- Altered biochemistry
- Genetic predisposition
- Inflammation
- Fractures and mechanical damage
- Inflammatory joint disease
- Acromegaly
- Others

classification for OA are pain-free.[5] The exact cause of the pain in OA is still not well defined, but there are numerous potential causes (Box 193-2). Depression and anxiety appear to increase the experience of the pain of OA.

DIAGNOSIS

The onset of OA can be subtle. Morning joint stiffness is often the first symptom. As the disease progresses, pain on motion of the involved joint is worsened by prolonged activity and relieved by rest. There are usually no obvious signs of inflammation.

The specific clinical picture varies with the joint involved. Disease of the hands leads to pain and limitation of use. Knee involvement produces pain, swelling, and instability. OA of the hip causes local pain and a limp. Spinal OA (which is common) may result in compression of nerves and blood vessels, causing pain and vascular insufficiency.

The classic presentation of OA is easy to distinguish from other arthritides, especially rheumatoid arthritis, which is usually associated with much more inflammation of surrounding soft tissues. After a detailed medical history and physical examination, the best diagnostic tool to confirm the diagnosis of OA is a radiograph of the suspected joint. The classic finding in joints affected with OA is joint-space narrowing, loss of cartilage, and the presence of bone spurs (osteophytes). Box 193-3 lists important causes of the misdiagnosis of OA.

THERAPEUTIC CONSIDERATIONS

Data collected from the earliest lesions to the most advanced stages of clinical OA suggest that the cellular and tissue response is purposeful and aimed at repair of the anatomic defects. The process contributing to OA appears to be arrestable and sometimes reversible. The major therapeutic goal should be to ultimately enhance repair of the collagen matrix and regeneration by the connective tissue cells.[6,7]

BOX 193-2 **Potential Causes of Pain in Osteoarthritis**

Bone
- Periosteal elevation by osteophytes
- Trabecular microfractures
- Pressure on subchondral bone
- Hypertension in bone marrow

Articular misalignment or surface damage
- Synovial inflammation
- Pinching of synovial villi
- Joint capsule distention

Periarticular inflammation
- Ligament damage
- Muscle spasm
- Bursitis

Psychological factors
- Anxiety
- Depression
- Lack of social support
- Secondary gain

Physical demands
- Occupational trauma
- Obesity
- Neuromuscular integrity
- Protective reflexes
- Muscle weakness

Several studies have attempted to determine the "natural course" of OA.[7,8] One group of researchers studied the course of OA of the hip over a 10-year period. All subjects had pseudocystic changes suggestive of advanced OA, yet the researchers reported marked clinical improvement and radiologic recovery of the joint space in 14 of 31 hips.[8] The authors purposely applied no therapy and regarded their results as reflecting the natural course of the disease. These results, as well as others, raise the serious concern that medical intervention may actually promote disease progression.

Conventional Pharmacologic Treatment

Nonsteroidal antiinflammatory drugs (NSAIDs) have become the main treatment of OA in conventional medicine. Although these drugs provide short-term symptomatic relief, they may actually increase the rate of degeneration of the joint cartilage. Experimental studies have shown that aspirin and other NSAIDs inhibit collagen matrix synthesis and accelerate the destruction of cartilage.[9] Some retrospective clinical studies have shown that NSAID use is associated with acceleration of OA and increased joint destruction.[10-13] Simply stated, NSAIDs appear to suppress the symptoms but accelerate the progression of OA. Furthermore, a patient is unlikely to die from OA, but NSAID use is associated with significant risk for mortality. With older NSAIDs the risk is primarily related to gastrointestinal bleeding, whereas the newer cyclooxygenase-2 (COX-2) inhibitors celecoxib (Celebrex) and rofecoxib (Vioxx) were associated with an increase in cardiovascular events.

Physical Therapy

Skewed musculoskeletal dynamics play a role in abnormally stressing involved joints. Despite this relatively simple concept, it is only recently that this idea has been researched. An 18-month study of 230 patients with tibiofemoral osteophytes and at least some difficulty with knee-requiring activity revealed conclusively that patients with varus alignment had a fourfold increased risk of medial OA progression.[14] Similarly, those with valgus alignment showed almost five times the risk of lateral OA progression. Not

BOX 193-3 Important Causes of the Misdiagnosis of Osteoarthritis

The source of the pain is not osteoarthritis (OA), but one of the following:
- Arthritis of other origin
- Pathologic changes of the adjacent bone (e.g., tumor, osteomyelitis, metabolic bone disease)
- Mechanical injuries
- Pathologic fractures
- Referred pain of neuritis, neuropathy, or radiculopathy
- Other neurologic disorders causing stiffness of the joints

The source of the pain is OA, but not at the joint suspected:
- OA of the hip, pain localized to the knee
- OA of the cervical spine, causing pain in the shoulder
- OA of the lumbar spine, causing pain in the hip, knee, or ankle
- OA of the shoulder, causing pain in the elbow

The source of pain is caused by secondary soft tissue alterations of OA:
- Tendinitis or ligamentitis (especially of the knee)
- Enthesopathy or tendinopathy due to joint contracture
- Bursitis

Misinterpretation of deformity:
- Pseudohypertrophic osteoarthropathy
- Psoriatic arthritis
- Flexion contracture of the joints
- Mucopolysaccharidoses
- Neurogenic arthropathies
- Calcium pyrophosphate dihydrate crystal-deposition disease
- Genu varum and valgum

Misinterpretation of x-ray films:
- Arthritis with previous OA changes
- Initial stage of osteoarthritis; radiograph may be normal
- Flexion contracture; can cause a virtual loss of joint-space width
- Neurogenic and metabolic arthropathies

BOX 193-4 Nonpharmacologic Approaches to Pain in Osteoarthritis

- Acupuncture
- Psychological aids
- Exercise
- Physical therapy
- Ultrasound
- Transcutaneous nerve stimulation
- Laser therapy
- Diathermy
- Thermal baths
- Massage
- Weight loss

surprisingly, these researchers learned that the decline was greater for those with more extensive misalignments. This clearly documents the importance of considering musculoskeletal dynamics in evaluating any subject presenting with OA. Those with misalignments may have to consider manual manipulation therapies, orthotics, and extremity adjustments, along with techniques such as regular massage therapy, to relax hypertonic muscles. From a prevention standpoint, assessing and treating younger individuals may also decrease the risk of OA later in life.

In addition to addressing alignment issues, various physical therapy modalities (e.g., exercise, heat, cold, diathermy, ultrasound) are often beneficial in improving joint mobility and reducing pain in OA, especially when administered regularly (Box 193-4). Much of the benefit of physical therapy is thought to be due to achieving proper hydration within the joint capsule.

Clinical and experimental studies seem to indicate that short-wave diathermy may be of the greatest benefit.[15-17] Combining short-wave diathermy therapy with periodic ice massage, rest, and appropriate exercises appears to be the most effective approach. Ultrasound and laser therapy have also been shown to be helpful.[18,19]

The best exercises are isometrics and swimming. These types of exercises increase circulation to the joint and strengthen surrounding muscles without placing excess strain on joints. Increasing quadriceps strength has been shown to improve the clinical features and reduce pain in OA of the knee.[20] Walking programs help to improve functional status and also relieve pain in patients with OA of the knee.[21]Patient-specific physical therapies may be useful as well. For example, four older adults with hand OA benefited from keyboard playing for 20 minutes a day, 4 days a week.[22]

Dietary and Exercise Considerations

Dietary therapy primarily involves the achievement of normal body weight and improved insulin sensitivity, since excess weight means increased stress on weight-bearing joints affected with OA. Obesity is a major risk factor for OA of the knee, and there is also considerable evidence linking OA to the metabolic syndrome owing to the negative effects that insulin resistance, inflammatory adipokines, and other features of this syndrome have on inflammation and joint structures.[23] Insulin stimulates chondrocytes to increase the synthesis and assembly of proteoglycans. Because the most prominent early change seen in the articular cartilage in OA is a decrease in both proteoglycan content and state of aggregation, insulin insensitivity or deficiency predisposes to OA.

Weight reduction, possibly due to a combination of mechanical and physiologic factors, reduces the risk for OA and has also been shown to reduce pain and improve cartilage function in existing OA, especially when combined with exercise.[3,24-26,27] Lack of exercise decreases the hydration of the joint cartilages and retards diffusion of nutrients into the affected area. When OA pain develops, sufferers often tend to reduce activity, which in turn decreases muscle strength. Greater muscle weakness increases joint wear, and the inactivity can lead to weight gain, which can exacerbate OA, causing this cycle to repeat itself. In addition, patients with diabetes and cardiovascular concerns may also increase their risks for these illnesses as exercise diminishes. Weight loss and exercise have independently been effectively used to decrease the causative factors of OA and produce clinical improvement, but best results are achieved by a combined approach. One study involved 252 obese elderly patients with a body-mass index of greater than 28 and radiographically confirmed OA who were randomized into healthy-lifestyle (control), diet-only, exercise-only, and diet-plus-exercise groups.[26] The exercise program involved hour-long sessions focusing on aerobics and resistance training three times a week. The goal of the dietary interventions was an average weight loss of 5% during the 18-month period. The most benefit was demonstrated in the diet-plus-exercise group. Compared with control patients and the diet-only group, subjects in the diet-plus-exercise group experienced a significant improvement in self-reported physical function, 6-minute walking distance, stair-climb times, and knee pain scores. Improvements in the exercise-only group were limited to the 6-minute walk distance.

GENERAL DIETARY GUIDELINES

In general, the principles detailed in Chapter 44 are appropriate for OA. Otherwise, the "Mediterranean diet" seems prudent. Typically this diet comprises abundant plant foods (including fruits, vegetables, whole-grain cereals, beans, nuts, and seeds); minimally processed seasonally fresh and locally grown foods; fish and poultry; olive oil as the main source of lipid; with dairy products, red meat, and wine in low to moderate amounts. Thus, the diet is rich in long-chain omega-3 polyunsaturated fatty acids and oleic acid (omega-9 monounsaturated), antioxidant nutrients, and unrefined carbohydrates. The Mediterranean diet has show significant effects in rheumatoid arthritis in two recent studies and may show similar benefit in OA.[28,29]

One popular dietary practice in the treatment of OA, conceived by Childers, a horticulturist, is the elimination of foods from the family Solanaceae (nightshade family). Childers arrived at this method after finding that this simple dietary elimination cured his own OA.[30] Childers developed a theory that genetically susceptible individuals might develop arthritis and other complaints from long-term low-level consumption of the *Solanum* alkaloids found in tomatoes, potatoes, eggplant, peppers, and tobacco. Presumably these alkaloids inhibit normal collagen repair or promote inflammatory degeneration of the joints. Although as yet unproved, this diet has been of benefit to some individuals.

Nutritional Supplements

Because Americans spend more on natural remedies for OA than for any other medical condition,[31] both the practitioner and the OA sufferer should be well informed about the clinical indications for these supplements.[32] Many botanical and nutritional supplements are not evaluated for quality control, so it is imperative that only reputable and independently verified products be used in order to gain the desired therapeutic effect.

Glucosamine Sulfate

Glucosamine sulfate has emerged as the most popular nutritional approach to OA. It is a simple molecule composed of glucose and an amine. Its main physiologic effect on joints is to stimulate the manufacture of glycosaminoglycans (GAGs). Glucosamine also promotes the incorporation of sulfur into cartilage. It appears that as some people age, they lose the ability to manufacture sufficient levels of glucosamine. The result is that cartilage loses its gel-like nature and ability to act as a shock absorber. The inability to manufacture glucosamine may be the major factor leading to OA. Extensive preclinical and clinical research, including long-term double-blind studies, support a rationale and role for glucosamine as a major consideration in the treatment of OA. This research and the clinical benefits of glucosamine sulfate in the treatment of OA are fully described in Chapter 94.

Chondroitin Sulfate

Chondroitin sulfate, as well as shark cartilage, bovine cartilage extracts, and sea cucumber, contains a mixture of intact or partially hydrolyzed GAGs of molecular weights ranging from 14,000 to more than 30,000. Chondroitin sulfate is composed of repeating units of derivatives of glucosamine sulfate with attached sugar molecules. Although the absorption rate of glucosamine sulfate is 90% to 98%, the absorption of intact chondroitin sulfate is estimated to be anywhere from 0% to 13%.[33,34] The difference in absorption is largely due to the difference in size. Chondroitin sulfate is at least 50 to 300 times larger than glucosamine sulfate, too large to pass the normal intact intestinal barrier. If chondroitin sulfate molecules were absorbed intact or partially digested, they would still be unlikely to produce any significant benefit, as the chondroitin sulfate molecules are too large to be delivered to cartilage cells. Furthermore, in patients with OA, levels of chondroitin sulfate in the synovial tissues are typically elevated.[35] These absorption problems suggest that any direct effect of these compounds in OA is highly unlikely. However, conflicting evidence supports the notion that exogenous chondroitin sulfate is indeed absorbed as a high-molecular-weight polysaccharide together with derivatives originating from a partial depolymerization, desulfatation, or both.[36-38]

Most likely any clinical benefit from chondroitin sulfate is due to the absorption of sulfur or smaller GAG molecules broken down by the digestive tract. However, even this is controversial, because in one human study, 1 g of chondroitin sulfate failed to increase serum GAG concentration at all, based on a highly sensitive measure of intact or depolymerized GAG absorption. These results prompted the researchers to conclude: "We suggest that chondroprotection by orally administered chondroitin sulfate is a biologically and pharmacologically unfounded theory."[33]

Pooled literature on the biochemistry of chondroitin sulfate offers enough information to assert that neither intact nor polymerized chondroitin sulfate is absorbed by the mammalian gastrointestinal tract. Therefore, no direct action of orally administered chondroitin sulfate on cartilage or chondrocytes is possible.

Despite the unlikeliness of any direct action, two published meta-analyses indicate that chondroitin may be superior to placebo in reducing the pain of OA.[32] One of these analyses may have been exaggerated by publication bias related to the manufacturer's sponsorship. The second meta-analysis did find chondroitin to be superior to placebo in reducing the painful symptoms of OA, although these authors also called for trials of longer duration. Finally, one study using 800 mg of chondroitin sulfate for two separate periods of 3 months over 1 year did show decreased pain and improved knee function as well as a decrease in joint-space narrowing over placebo.[39] This study reveals that even intermittent use of chondroitin may be effective.

The clinical studies that have been done with orally administered chondroitin sulfate demonstrate that it is less effective than glucosamine sulfate.[40-45] Furthermore, there is no evidence that using both glucosamine and chondroitin together is more effective than either alone.[46] In general, the more impressive results have been achieved with glucosamine sulfate. Nevertheless, given the safety record of chondroitin and the evidence of modifying joint-space pathology, chondroitin is a reasonable addition to an ostoarthritis patient's glucosamine regimen. In addition, chondroitin sulfate may be acting in some indirect way in improving joint health.

Hyaluronic Acid

Hyaluronic acid (HA) is an important GAG in joints, providing a structural framework and supporting the ability of cartilage to hold water. A type of connective tissue, it is the actual "glue" that holds our bodies together. By the time most people reach the age of 70, the HA content in their body has dropped by 80% from when they were 40, predisposing them to the loss of connective tissue integrity, particularly of the skin and joints. Weekly injections of HA (Synvisc, Hyalgan, Supartz, etc.) into joints affected by OA (viscosupplementation) has been shown to be an effective treatment for OA, with beneficial effects on pain, function, and patient global assessment. Such results have been seen at different postinjection periods but especially at the 5- to 13-week postinjection period.

Oral supplementation with HA has been shown to be a viable method of increasing body HA stores. HA supplements feature

HA derived from rooster combs, cow eyes, or from bacterial fermentation.

Two double-blind placebo-controlled studies have been done in OA with HA. In the first, 20 patients with knee OA were given either HA (80 mg/day) or placebo for 8 weeks.[47] Compared with the placebo group, pain scores were significantly improved in the HA group. In the second study, 60 patients with OA were randomized equally to receive either HA 200 mg, HA 100 mg, or placebo for 8 weeks.[48] After conducting a stratification analysis on the subjects with more severe pain (i.e., those with a Western Ontario and McMaster Universities Arthritis Index [WOMAC] pain score >10), significant reductions in pain scores and total symptom scores were seen with the 200- but not with the 100-mg dose.

Niacinamide

In the 1940s and 1950s, William Kaufman, and later Abram Hoffer, reported good clinical results in the treatment of hundreds of patients with rheumatoid arthritis and OA using high-dose niacinamide (i.e., 900 to 4000 mg/day in divided doses).[49,50] Kaufman documented improvements in joint function, range of motion, and increased muscle strength and endurance as well as a reduction in the sedimentation rate. Most patients achieved noticeable benefits within 1 to 3 months, with peak benefits noted between 1 and 3 years of continuous use.

These clinical results were more recently evaluated in a well-designed double-blind placebo-controlled trial.[51] Seventy-two patients with OA were randomized for treatment with niacinamide (3000 mg daily in six divided doses) or placebo for 12 weeks. Outcome measures included global arthritis impact and pain, joint range of motion and flexibility, erythrocyte sedimentation rate (ESR), complete blood count, liver function tests, serum cholesterol, serum uric acid, and fasting blood sugar. The researchers found that niacinamide produced a 29% improvement in global arthritis impact compared with a 10% worsening in the placebo group. Pain levels did not change, but those on niacinamide reduced their NSAID use. Niacinamide supplementation reduced the ESR by 22% and increased joint mobility by 4.5 degrees over controls (8 degrees vs. 3.5 degrees); otherwise there were no other changes in blood chemistry. Side effects, primarily mild gastrointestinal complaints, were more common in the niacinamide group but could be effectively managed by recommending that the pills be taken with food or fluids.

Niacinamide at this high dose can result in significant side effects (e.g., glucose intolerance, liver damage) and therefore requires strict supervision.

S-Adenosylmethionine (SAMe)

S-Adenosylmethionine (SAMe) is an important physiologic agent formed in the body by combining the essential amino acid methionine with adenosine triphosphate (ATP). A deficiency of SAMe in the joint tissue, just like a deficiency of glucosamine, leads to loss of the gel-like nature and shock-absorbing qualities of cartilage. A meta-analysis of 11 studies reports the benefits of SAMe in the treatment of OA by reducing pain and improving functional limitations.[52]

SAMe has been shown to be important in the manufacture of cartilage components.[53] In one double-blind study, supplemental SAMe increased cartilage formation as determined by magnetic resonance imaging in 14 patients with OA of the hands.[54] In addition to this effect, SAMe has also demonstrated some mild pain-relieving and antiinflammatory effects in animal studies.

A total of 21,524 patients with OA have been treated with SAMe in published clinical trials. In double-blind trials, SAMe has demonstrated similar reductions in pain scores and clinical symptoms to NSAIDs like ibuprofen, indomethacin, naproxen, and piroxicam. All of these studies indicate that SAMe offers significant advantages over NSAIDs. Although the drugs are associated with a significant risk of toxicity, side effects, and actual promotion of the disease process in OA, SAMe offers similar benefits with minimal risk or side effects. Side effects include occasional gastrointestinal disturbances, mainly diarrhea.[32] For more information, see Chapter 120.

Vitamin C

Results from the Framingham Osteoarthritis Cohort Study indicate that a high intake of antioxidant nutrients, especially vitamin C, may reduce the risk of cartilage loss and disease progression in people with OA.[31] A threefold reduction in the risk of OA progression was found in the middle and highest tertiles of vitamin C intake. These results highlight the importance of a diet rich in plant-based antioxidant nutrients protecting against chronic degenerative diseases, including OA.

Deficient intake of vitamin C is common in the elderly, resulting in altered collagen synthesis and compromised connective tissue repair.[55] Several in vitro studies have demonstrated that vitamin C has an anabolic effect on cartilage.[56,57] Research has confirmed the importance, indeed necessity, for an excess of ascorbic acid in human chondrocyte protein synthesis.[58] One in vivo study of experimental OA in guinea pigs found that cartilage erosion was much less and the overall histologic and biochemical changes in and around the OA joint much milder in animals kept on high doses of vitamin C.[55] A human study showed that a history of self-reported vitamin C supplementation indicated an effect in halting the progression of OA.[59]

Vitamins C and E appear to possess synergistic effects.[55] The researchers concluded as follows: "Thus, both vitamins E and C appear to enhance the stability of sulfated proteoglycans in the complex structure comprising articular cartilage. Judicious use of these vitamins in the treatment of OA, either alone or in combination with other therapeutic means, may thus be of great benefit to the patient population by retarding the erosion of cartilage."

Vitamin D

Several studies have shown low serum levels of vitamin D appear to be associated with an increased risk for progression of OA, especially in people under 60 years of age.[60-62] In one study, patients with vitamin D deficiency had lower preoperative Harris hip scores and were significantly less likely to attain excellent outcomes from total hip replacement.[62] Low serum levels of vitamin D also predict loss of cartilage, as assessed by loss of joint-space and osteophyte growth. It seems reasonable to consider that exposure to adequate amounts of sunlight as well as sufficient intake in childhood and young adulthood may help to decrease the risk of OA. Although vitamin D may help to prevent OA, it is unknown whether increasing vitamin D intake will help decrease or reverse already established OA pathology.

Pantothenic Acid

Acute deficiency of pantothenic acid in the rat causes a pronounced failure of cartilage growth and eventually produces lesions similar to OA. Clinical improvement in OA symptomatology with the administration of 12.5 mg of pantothenic acid has been reported.[63,64] Results often did not appear for 7 to 14 days. However, a larger double-blind study in patients with primarily rheumatoid arthritis displayed no significant benefit from administration of 500 mg of pantothenic acid.[65]

Vitamins A and E, Pyridoxine, Zinc, Copper, and Boron

These nutrients are required for the synthesis of collagen and maintenance of normal cartilage structures. A deficiency of any one of these would allow accelerated joint degeneration. In addition, supplementation at appropriate levels may promote cartilage repair and synthesis. For example, boron supplementation has been used in the treatment of OA in Germany since the mid-1970s. This use was recently evaluated in a small double-blind clinical study and an open trial. In the double-blind study, of the patients given 6 mg of boron (as sodium tetraborate decahydrate), 71% improved, compared with only 10% in the placebo group.[66] In the open trial, boron supplementation (6 to 9 mg daily) produced effective relief in 90% of arthritis patients including patients with OA, juvenile arthritis, and rheumatoid arthritis.[67] The preliminary indication is that boron supplements are of value in arthritis, with many OA patients experiencing complete resolution.

Vitamin K

Studies have shown that low vitamin K status is associated with OA.[68,69] In one study looking at dietary factors in OA, only vitamin K intake was shown to be inversely associated with the prevalence of radiographic knee OA.[68] The presence of joint-space narrowing of the knee was also inversely associated with vitamin K intake. The prevalence of radiographic knee OA for each dietary vitamin K intake quartile decreased with the increased intake.[68] Vitamin K may have a protective role against knee OA and might lead to a disease-modifying treatment. In an ancillary study to a randomized controlled trial assessing the effects of phylloquinone supplementation (vitamin K arm) versus placebo on bone loss and vascular calcification among older adults regardless of their vitamin K status. The parent study was a 3-year double-blind controlled trial. Participants were randomized and stratified by gender to either the treatment group (which received 500 mcg of phylloquinone as part of a single daily effervescent multivitamin formulation) or the comparator group (which received an identical multivitamin formulation without phylloquinone) (Hermes Arzeneimittel GMBH, Munich, Germany), hereafter referred to as the placebo group. All study participants also received elemental calcium (600 mg/day) and vitamin D (400 IU/day) as separate tablets. Although there were no effects of vitamin K for radiographic OA outcomes, those with insufficient vitamin K at baseline who attained sufficient concentrations at follow-up had 47% less joint-space narrowing.[69] Foods rich in vitamin K include green tea, kale, turnip greens, spinach, and other green leafy vegetables.

Botanical Medicines

Historically, many herbs have been used in the treatment of OA. When inflammation is present, those botanicals and nutritional factors possessing antiinflammatory activity are indicated. Examples include bromelain, curcumin, and ginger.

Boswellia serrata

Boswellia serrata, a large branching tree native to India, yields an exudative gum resin known as salai guggul, which has been used for centuries, including use in arthritic conditions. Newer preparations concentrated for the active components (boswellic acids) are showing significant clinical results. Initially, boswellic acid extracts demonstrated antiarthritic effects in various animal models. Among several mechanisms of action are inhibition of inflammatory mediators, prevention of decreased GAG synthesis, and improved blood supply to joint tissues.[70] Clinical studies using herbal formulas with *Boswellia* have yielded good results in OA of the knee, with patients experiencing decreased knee pain and swelling and increased knee flexion and walking distance.[72-75] Corroborating the improvements in pain scores and joint function with *Boswellia* were significant reductions in synovial fluid matrix metalloproteinase-3, indicating improved stability of the collagen matrix.[73,74] The standard dosage for boswellic acids in arthritis is 400 mg three times daily. No side effects due to boswellic acids have been reported.

Procyanidolic Oligomers

Two double-blind studies have been conducted with Pycnogenol in OA. In the first study, Pycnogenol (100 mg) or placebo were given daily for 3 months to 156 patients with OA.[76] The global WOMAC questionnaire for OA score decreased by 56% in the treatment group versus 9.6% in the placebo group. Walking distance in the treadmill test was prolonged from 68 m at the start to 198 m in the Pycnogenol group compared with from 65 to 88 m in the placebo group. The use of drugs decreased by 58% in the Pycnogenol group versus 1% under placebo. Foot edema decreased in 79% of Pycnogenol patients vs 1% in controls. Similar results were seen in a second study when Pycnogenol was given at a dose of 100 mg daily.[77]

Limbrel (Flavocoxid)

Limbrel (Flavocoxid) is a proprietary mixture of the two flavonoid molecules baicalin and catechin. It is being promoted as possessing balanced inhibition ofcyclooxygenases 1 and 2, and 5-lipoxygenase without the associated cardiovascular, renal, or gastrointestinal side effects of standard NSAIDs. Double-blind studies have shown results comparable with those with naproxen in relieving pain scores due to OA, with both medications being given at a dose of 500 mg twice daily.[78-80] Flavocoxid does not increase bleeding time, inhibit platelet aggregation, or inhibit or potentiate the anticoagulant effect of warfarin.[81]

Zingiber officialinalis (Ginger)

A 6-week multicenter randomized controlled trial of 261 patients with knee OA given ginger extract or placebo found a moderate effect on symptoms, where 63% of the ginger subjects found relief versus 50% of the placebo users.[82] Those in the ginger group resorted to acetaminophen less frequently and had a reduction in knee pain on standing and after walking. Patients receiving ginger extract experienced more gastrointestinal adverse events, albeit mild, than did the placebo group (59 vs. 21 patients). One double-blind crossover trial found efficacy of 170 mg of ginger three times daily before the crossover, but by the end of the study, there was no benefit of ginger over placebo.[83] Clearly, more studies are necessary to assess ginger's effectiveness for OA.

Harpagophytum procumbens (Devil's Claw)

H. procumbens is a South African plant that grows in regions bordering the Kalahari. Secondary tuberous roots are used to prepare powders or extracts usually standardized for harpagoside, the principal active compound. A systematic review of the clinical efficacy of harpagophytum for OA concluded that products providing less than 30 mg of harpagoside per day in the treatment of knee and hip OA were of little use, whereas dosages providing 60 mg of harpagoside daily showed moderate evidence of efficacy in the treatment of spine, hip, and knee OA.[84] Some of the individual studies showed significant benefit. For example, in a 2-month double-blind study on spine and knee OA, 670 mg of powder three times a day was more efficient than placebo in reducing pain

scores.[85] In a 4-month double-blind study on hip and knee OA, 2.6 g of powder/day was equal in efficacy to 200 mg of diacerhein per day in improving pain scores, but was better tolerated.[86] In a review of 28 clinical trials of devil's claw extracts, adverse events occurred at a rate of about 3% and did not exceed the rate of those experienced with placebo.[146] Long-term use appears to be safe and without toxicity.

Yucca

A double-blind clinical trial found that a saponin extract of yucca demonstrated a positive therapeutic effect.[88] Results were of gradual onset, and no direct joint effects of the yucca saponin were noted. The researchers suggested that the clinical improvement was due to indirect effects on the gastrointestinal flora. This is an interesting suggestion, because bacterial lipopolysaccharides (endotoxins) have been shown to depress the biosynthesis of proteoglycans.[89] It is entirely possible that yucca decreases the absorption of bacterial endotoxins and thus reduces this inhibition of proteoglycan synthesis. If this is the mechanism of action, then other saponin-containing herbs and other ways of reducing the endotoxin load may be useful.

Additional Therapeutic Considerations

Topical Analgesics

The mainstay of natural topical preparations for OA are those containing either menthol-related compounds (e.g., one popular combination contains camphor 4% , menthol 10%, and methyl salicylate 30%) and/or capsaicin (typically creams containing 0.075%). These time-tested topical analgesics can often provide significant relief in OA, although each has compliance issues. Alternatives are products containing Celadrin—a mixture of cetylated fatty acids (Celadrin) with cetyl myristoleate, cetyl myristate, cetyl palmitoleate, cetyl laureate, cetyl palmitate, and cetyl oleate. Celadrin has been shown to impact several key factors that contribute to inflammation. Its main action appears to be its ability to enhance the health and integrity of cell membranes. It therefore halts the production of inflammatory compounds known as prostaglandins. It also reduces the production of the negative immune factors like IL-6, which play a central role in inflammation. Studies have assessed both the oral and topical use of Celadrin. In a study with oral Celadrin, 64 patients with chronic OA of the knee were evaluated at baseline and at 30 and 68 days after consuming either placebo or Celadrin. Results indicated that compared with placebo, Celadrin improves knee range of motion (patients treated with Celadrin exhibited a significant 10.1 degree increase in knee flexion and overall joint function compared with patients given placebo.[90]

The effect of the Celadrin cream was studied in OA of the knees. Forty patients were randomly assigned to receive either the Celadrin cream or a placebo. Patients were tested on three occasions: (1) at baseline, (2) 30 minutes after initial treatment, and (3) after 30-day treatment of cream application twice a day. Assessments included knee range of motion, timed "up-and-go" from a chair and stair climbing, and two other functional tests. For stair-climbing ability and the up-and-go test, significant decreases in time were observed 30 minutes after the first administration and after 1 month of use only in the Celadrin group. Likewise, range of motion of the knees increased with Celadrin both 30 minutes after the initial application and after 1 month's use. In contrast, no difference was observed in the placebo group. The other functional tests also clearly demonstrated improvements with Celadrin, whereas the placebo failed to produce results.[91]

In another study with topical Celadrin in patients with knee OA, patients were assessed by having them stand on a special platform for 20 and 40 seconds to measure static postural stability (the ability to stand comfortably in one place for a period of time). Again, only those subjects using the Celadrin cream demonstrated improvements.[92]

One of the key points regarding Celadrin is that unlike many other natural approaches, it produces almost immediate results.

Proteolytic Enzymes

Preparations of proteolytic enzymes (e.g., pancreatic proteases chymotrypsin and trypsin, bromelain, and fungal proteases) have been found useful in OA as well as a wide range of other inflammatory conditions (see Chapters 106 and 111 for more information). Several recent studies have used tablets containing a combination of bromelain 90 mg, trypsin 48 mg, and rutin 100 mg (Phlogenzym) at a dosage of 2 tablets three times daily or 3 tablets twice daily on an empty stomach. Two of these studies, both double-blinded, showed that this combination at the recommended dosage level produced clinical results in reducing pain scores due to OA on par with the drug diclofenac (100 mg daily).[93,94] However, another double-blind study with bromelain alone (800 mg daily) produced no significant effects in OA.[95]

Acupuncture

Traditional Chinese medicine typically views OA as a "bi" or pain syndrome, with pathogenic etiologies stemming from coldness, dampness, heat, and wind. Each one of these types typically has a separate clinical picture and requires the use of specific acupuncture points. Standard Western medical systems have been slow to adopt acupuncture practice as standard adjunctive care despite mounting research evidence supporting the safety and efficacy of acupuncture in reducing pain from OA.[96-97]

For example, a number of studies have focused on knee OA. One observational study of 563 patients (88% female) with chronic knee OA found that 75% of the participants achieved a reduction in pain of 45% or more with acupuncture.[98] An open randomized controlled trial evaluated the effect of acupuncture with and without adjunctive conventional medications.[99] In this study, 30 patients with symptomatic knee OA were randomized to one of three treatment groups. Those patients given acupuncture only or acupuncture combined with conventional medications achieved a highly significant improvement in pain. The acupuncture-free group experienced no change until after a course of acupuncture later in the study, when their improvement became significant. Similarly, significant positive changes were seen with pain and stiffness scores. These benefits were maintained during the month following the acupuncture course.

Traditional Chinese medicine considers an etiology of pain as "stuck qi." In this case, the addition of electrical energy to the area can reestablish qi flow, thus alleviating pain. One single-blinded randomized controlled study examined the effectiveness of electroacupuncture and transcutaneous electrical nerve stimulation (TENS) to alleviate OA-induced knee pain.[100] In this research, 24 subjects (23 women and 1 man) with a mean age of 85 years were given electroacupuncture, TENS, or no treatment. Subjects in the electroacupuncture group received low-frequency (2 Hz) treatment at two local acupuncture points (ST-35, Dubi and Neixiyan) of the painful knee for 20 minutes. Subjects in the TENS group received low-frequency TENS treatment of 2 Hz and pulse width of 200 ms at the same acupuncture points for 20 minutes. In both treatment groups, electrical treatment was carried out for a total of eight sessions in 2 weeks. The other control subjects received OA

knee care and education only. After eight sessions, there was a significant reduction of knee pain in both the electroacupuncture and TENS groups with prolonged analgesic effect at a 2-week follow-up evaluation. Electroacupuncture also gained an advantage by lowering scores for the timed up-and-go test, which TENS did not achieve.

Electroacupuncture has also been tested in a head-to-head 186-patient randomized single-blind placebo-controlled trial against the NSAID diclofenac.[102] For these knee patients, improvement of OA symptoms in most outcome parameters was greatest in the electroacupuncture group. Unlike the diclofenac and placebo groups, most of the patients rated their results with electroacupuncture as "much better," and substantially better pain management and functionality were obtained in the electroacupuncture group as well.

In considering an acupuncture regimen, researchers of one randomized controlled trial for patients with OA of the knee concluded that acupuncture is most effective when it is employed early in the treatment plan. Additionally, on the basis of patient evaluations, it seems that, in order to avoid a rebound effect, treatments should be administered with a tapering, methodical decrease in frequency once the acute treatment period is completed.[103] Because it has been reported that the density of peripheral nerve endings in the skin or muscles is much greater in the acupuncture points compared with areas beyond these points,[103] it is possible that an abrupt lack of stimulation in these areas may untowardly affect neurotransmitter release, thus contributing to a rebound effect.

Magnetic Therapies

Magnetic therapy has been used in the treatment of a wide variety of chronic pain syndromes.[104] Magnetic fields may have the ability to stimulate chondrocyte proliferation and increase the synthesis of proteoglycans.[32] A number of studies clearly support magnetic therapy when used for knee OA.[105-108] One is a multicenter double-blind randomized placebo-controlled trial that enrolled 75 patients with OA of the knee who had previously been unable to obtain acceptable results using conventional treatments.[105] Using low-frequency pulsed fields, improvements in the level of pain, functionality, and physician global evaluation of patients' condition were notable. Mean morning stiffness also decreased by 20 minutes in the group using magnetic therapy while increasing by 2 minutes in the placebo group. A second placebo-controlled randomized double-blind clinical study of 176 patients with osteoarthritic knees also showed significant results using low-amplitude and low-frequency fields.[107] Reduction in pain after a treatment session was significantly greater in the magnet-on group (46%) compared with the magnet-off group (8%). A smaller 29-subject study of knee OA used either high-strength magnetic or placebo knee-sleeve treatment for 4 hours in a monitored setting and self-treatment 6 hours daily for 6 weeks.[106] This study demonstrated a significant decrease in pain scores in the active group and only a minimal improvement in the placebo group at 4 hours of treatment but no significant differences at 6 weeks. Magnetic therapies may be a useful treatment for OA.

Relaxation Techniques

Relaxation techniques such as meditation, deep breathing, and guided imagery have been used for many types of pain conditions. A study of 66 elderly people suffering from chronic OA pain evaluated the effect of daily music listening on pain levels from OA.[109] Differences in perceptions of pain were measured over 14 days in an experimental group who listened to Mozart selections for 20 minutes daily and a control group who sat quietly for 20 minutes daily. Those who listened to music had less pain when compared with those who sat quietly and did not listen to music. The amount of pain perceived by the Mozart group also decreased incrementally over the 14-day study period.

THERAPEUTIC APPROACH

Although there appear to be several worthwhile approaches used to control OA through natural therapies, a direct clinical study of a comprehensive, integrated program has yet to be conducted. The therapeutic approach recommended here is based on reducing joint stress and trauma, promoting collagen repair mechanisms, and eliminating foods and other factors that may inhibit normal collagen repair. All diseases or predisposing factors (see Table 193-1) should, of course, be controlled. NSAIDs such as aspirin should be avoided as much as possible. If NSAIDs must be used, deglycyrrhizinated *G. glabra* should be used to help protect the gastrointestinal tract from their damaging effects, and the use of NSAIDs should be discontinued as soon as possible (see Chapter 96 for more information).

Diet

The achievement of ideal body weight is the primary dietary goal. All simple, processed, concentrated carbohydrates must be avoided; complex-carbohydrate high-fiber foods should be emphasized; and fats should be kept to a minimum. Plants of the Solanaceae family should be eliminated (tomatoes, potatoes, eggplant, peppers, and tobacco). Liberal consumption of flavonoid-rich berries or extracts is also important.

Supplements

- Glucosamine sulfate: 1500 mg/day
- Niacinamide: 500 mg six times/day (under strict supervision—liver enzymes must be regularly assayed)
- Vitamin A: 5000 IU/day
- Vitamin C: 1000 to 3000 mg/day
- Vitamin B_6: 50 mg/day
- Vitamin K: 0.5 mg/day
- Pantothenic acid: 12.5 mg/day
- SAMe: 400 mg three times a day
- Zinc: 45 mg/day
- Copper: 1 mg/day
- Boron: 6 mg/day

Botanical Medicines

- *Boswellia serrata*: equivalent to 400 mg boswellic acids three times a day
- Procyanidolic oligomers from either pine bark (Pycnogenol) or grape seed extract: 100 to 300 mg a day
- Limbrel (Flavocoxid): 500 mg twice a day
- *Harpagophytum procumbens*: Dosage should provide a minimum of 60 mg harpagoside a day
- Dried root powder (tablet or capsule): 2000 mg three times a day
- Fluid extract (1:1): 2 mL three times a day
- Dry powdered extract (standardized to contain 2.5% harpagoside): 750 to 1000 mg three times a day
- Yucca leaves: 2 to 4 g three times a day

Topical Application

Choose one of the following:
- Cetylated fatty acid cream (Celadrin) can be applied to the affected area twice a day.
- Menthol preparations can be applied to affected areas twice a day.
- Capsaicin preparations can be applied to affected areas twice a day.

Physical Therapy and Exercise

Physical activity that induces physiologic or traumatic strain such as occupational or recreational overuse of a joint must be avoided. Normalization of posture and orthopedic correction of structural abnormalities should be used to limit joint strain. Daily nontraumatic exercise (isometrics, walking, and swimming) is important but should be carefully monitored. Short-wave diathermy, hydrotherapy, and other physical therapy modalities that improve joint perfusion are indicated.

Acupuncture

Acupuncture can be administered two to four times weekly until acute symptoms resolve. Then the frequency of treatments should be gradually decreased. Maintenance treatments once every 2 weeks to once a month may help to prevent recurrence.

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CHAPTER 194

Osteoporosis

Tori Hudson, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- Usually asymptomatic until fracture and/or severe backache occurs
- Most common in postmenopausal white women
- Spontaneous fractures of the hip and vertebra
- Excess decrease in height
- Defined as a T-score at or below a bone mineral density of -2.5 standard deviations below that of a young normal adult

GENERAL CONSIDERATIONS

Osteoporosis is the most common bone disease in humans and poses a serious health threat for postmenopausal women. It is characterized by diminished bone strength, which leads to an increased risk of fracture. Bone mineral density (BMD) is a major determinant of bone strength and is the most commonly measured quality of bone. Osteoporosis is determined by bone densitometry and, according to the World Health Organization (WHO), is defined by a a BMD T-score less than or equal to -2.5 at the total hip, femoral neck, or lumbar spine (with at least two vertebral levels in the posteroanterior position) in a postmenopausal woman or a man over age 50.[1,2] Most other organizations support this description. The presence of a fragility fracture also justifies a clinical diagnosis of osteoporosis.

Osteoporosis most commonly occurs in postmenopausal women, and the risk increases with age. Although the prevalence is 4% in women between 50 and 59 years of age, it rises to 52% in women age 80 and above.[3] Osteoporosis of the hip occurs in 13% to 18% of white American women and another 37% to 50% have low bone mass (often called osteopenia) of the hip.[4]

Osteoporosis is responsible for approximately 90% of all hip and spine fractures in white American women ages 65 to 84.[5]

However, most postmenopausal women who have fractures at any site do not actually have a diagnosis of osteoporosis.[6]

Hip fractures occur at age 82 on average and cause up to a 25% increase in mortality within 1 year of the fracture; an additional 25% of such patients require long-term care after a hip fracture and 50% will have some long-term loss of mobility.

The hip is not the only site where fractures result in serious morbidity. Vertebral fractures occur in a woman's mid-70s and cause significant pain as well as loss of height and an exaggerated kyphosis or deformity of the thoracic spine. In addition to pain, restricted range of motion, changes in posture, restricted lung function, and digestive problems can all be caused by vertebral fractures of the thoracic or lumbar region or both. Other tolls can accumulate because of osteoporosis. Depression, anxiety, low self-esteem, changed body image, and loss of independence are other burdens of this disease. Once a vertebral fracture has occurred, there is at least a five- to sevenfold increase in the risk of subsequent vertebral fractures.[7,8]

Economically, osteoporosis imposes enormous costs—estimated at $14 billion annually—on the health care system. Hip fractures are the most costly owing to the expense of initial hospital care, first-year postfracture care, and long-term treatment.

Although not commonly recognized, men are also at risk of osteoporosis as they age. Hip fractures in men account for one third of all hip fractures and have a higher mortality than those in women.[9]

PATHOPHYSIOLOGY

The process of bone resorption (breakdown) and bone formation is called bone remodeling. Osteoclasts stimulate the production of acids and enzymes that dissolve minerals and protein in bone and thus promote bone resorption. Osteoblasts create a protein matrix primarily of collagen, resulting in the remineralization of the bone and thereby promoting bone formation. Bone remodeling is normally a balance of bone resorption and bone formation. An imbalance between bone removal and bone replacement results in bone loss and an increase in the risk of bone fracture.

In childhood, bone mass rapidly increases and then slows in the late teens, but it continues to increase during the 20s. In women, the bone-building process is nearly complete by age 17. After achieving a peak bone mass, around age 28, women slowly lose an average of 0.4% of bone mass in the femoral neck each year. After menopause, the rate of loss is faster, with an average 2% loss annually during the first 5 to 10 years. Bone loss continues in older women past age 70 but at a much slower rate.

RISK FACTORS

Risk factors for osteoporosis are distinguished from risk factors for osteoporotic fracture. Major risk factors for osteoporosis in postmenopausal women are advanced age, genetics, lifestyle issues (low calcium, low vitamin D intake, and smoking), thinness, and menopausal status. The most common risk factors are as follows:

- Age (50-90 years)
- Female
- Thinness—weight below 127 pounds
- Height
- Low BMD of the femoral neck
- Prior fragility fracture
- Parental history of hip fracture
- Current smoker (tobacco)
- Long-term use of glucocorticoids
- Rheumatoid arthritis
- Other causes of secondary osteoporosis (e.g., primary hyperparathyroidism, renal calcium leak)
- Alcohol intake above two units daily
- Low level of vitamin D

Genetic Factors

The level of peak bone mass is greatly influenced by genetic factors. Earlier studies suggest that up to 80% of the determination of peak bone mass might be due to genetic factors.[10-12] Young daughters of women with osteoporotic fractures have lower bone mass compared with other children their age, and first-degree relatives of women with osteoporosis tend to have lower bone mass when compared with other women who do not have such a family history.[13] A history of fracture in a first-degree relative also increases fracture risk. A family history of fracture was found to be associated with a significant increase in osteoporotic fractures at any site.[14] In this same meta-analysis, hip fractures were almost 50% higher if a family had a history of fractures and 127% higher if a hip fracture had occurred in a parent. The greater bone mass of black women compared with white women also suggests a genetic influence.

One key genetic factor now being recognized is polymorphisms of the vitamin D receptor site. Some of these polymorphisms significantly increase the need for vitamin D.

Vitamin D Deficiency

The importance of vitamin D sufficiency in bone health has been underappreciated in the past. Emerging research is showing a direct correlation between both bone density and serum 25(OH)D3, with a corresponding inverse correlation with fractures of virtually all types.[15]

Lifestyle

Calcium and vitamin D intake, exercise, age at menarche, menstrual regularity, and alcohol and tobacco use also affect peak bone mass. All women lose bone mass in menopause, but several lifestyle factors affect the risk of developing osteoporosis, including physical activity, animal protein intake, acid-base homeostasis, calcium and vitamin D intake, smoking, and alcohol consumption. In order for a woman to achieve her genetically determined peak bone mass, she requires a balanced diet including adequate calories, protein, and calcium.[16] Good nutrition throughout life is necessary to maintain bone mass and strength. Adequate calcium and vitamin D have crucial roles in maintaining bone mass in older women. Calcium requirements change with age; during and after menopause, the need for calcium increases. After age 65, women absorb 50% less calcium than younger women. The renal enzymatic activity that produces vitamin D metabolites and thus controls calcium absorption also decreases.

Dietary Protein

Not all studies have been consistent regarding whether or not excess dietary protein contributes to osteoporosis. The Nurses' Health Study showed that a high intake of animal protein but not plant protein was associated with an increased risk of forearm fracture.[17] Diets high in red meat are acid producing, and salts from bone may be mobilized to balance the acid and maintain the acid-base homeostasis the body requires. Diets high in fruits, vegetables, and plant proteins are alkaline forming.

Smoking

Female smokers tend to lose bone more rapidly and have a lower bone mass than those who do not smoke.[18,19] Some studies show that smokers also have a higher fracture rate.[20,21] In addition, female smokers reach menopause up to 2 years earlier than nonsmokers. It may be that smoking interferes with estrogen metabolism, although the mechanism is not clearly known.

Alcohol

Alcohol consumption of 7 ounces or more daily, which is considered heavy, has been shown to increase the risk of falls and hip fractures. However, moderate alcohol consumption seems to lower the risk of hip fractures in older women.[11] It is thought that moderate amounts of alcohol inhibit bone resorption by increasing estradiol concentrations and calcitonin excretion.[22,23]

Physical Activity

The effect of physical activity on the risk of osteoporosis cannot be overlooked. Highly active individuals have higher bone mass,[24] and those who have undergone prolonged bed rest or are confined to a wheelchair experience a rapid and dramatic loss of bone. Exercise functions primarily to reduce osteoporosis risk by stimulating osteoblasts.

Hormonal Factors

A woman's hormonal status clearly influences bone mass and the rate of bone resorption. At menopause, all women lose bone, and

this loss is especially accelerated in the first 5 years. The drop in estrogen production that comes with menopause, no matter the age, increases the rate of bone resorption. The earlier that occurs before the average age of menopause (51 years), the sooner the bones lose the protective effect of endogenous estrogen.

Women who have premature menopause (before age 40), late onset of menarche in adolescence, surgical menopause, or experienced periods of amenorrhea due to low estrogen levels in their reproductive years (ex/hypothalamic amenorrhea), are at greater risk of osteoporosis if they have not taken longer term estrogen replacement therapy. Women who had missed up to half of their expected menstrual periods had 12% less vertebral bone mass than did those with normal menstrual cycles; those who missed more than half had 31% less bone mass than healthy controls.[25]

The concentration of calcium in the blood is strictly maintained within narrow limits. If levels start to decrease, there is an increase in the secretion of parathyroid hormone by the parathyroid glands and a decrease in the secretion of calcitonin by the thyroid and parathyroids. If calcium levels in the blood start to increase, there is a decrease in the secretion of parathyroid hormone and an increase in the secretion of calcitonin. An understanding of how these hormones increase (parathyroid hormone) and decrease (calcitonin) serum calcium levels is necessary in order to understand osteoporosis.

Parathyroid hormone increases serum calcium levels primarily by increasing the activity of the osteoclast catabolism of bone, although it also decreases the excretion of calcium by the kidneys and increases the absorption of calcium in the intestines. In the kidneys, parathyroid hormone increases the conversion of 25-(OH) D_3 to 1,25-$(OH)_2D_3$.

Additional Factors

No one risk factor or combination of risk factors will accurately predict which patients will or will not experience osteoporosis or osteoporotic fractures. The more risk factors present, the greater the potential for lower bone mass and the higher the risk of fracture. Risk factors alone do not provide adequate assessment of low bone mass but rather are important guides in the clinical assessment of osteoporosis and fracture risks, and these contribute to optimal preventive strategies. Ultimately, an individual woman's risk of fracture is the most relevant parameter for her future with regard to osteoporosis. Various medical conditions and medications can interrupt normal bone physiology and lead to osteoporosis. Endocrine disorders, malignancies, and collagen metabolism disorders can have a direct effect on the ability of bones to remodel.

Secondary Causes of Bone Loss

Secondary causes of bone loss include certain disease states, genetic disorders, and many medications.

Medications:
- Aromatase inhibitors
- Cytotoxic agents
- Excessive thyroid dosing
- Gonadotropin-releasing hormone agonists or analogs
- Some long-term anticonvulsants (e.g., phenytoin)
- Glucocorticoid use for more than 3 months

Genetic disorders:
- Hemochromatosis
- Hypophosphatasia
- Osteogenesis imperfecta
- Thalassemia

Calcium balance disorders:
- Urinary calcium excretion

Endocrinopathies:
- Cortisol excess
- Cushing's syndrome
- Gonadal insufficiency
- Hyperthyroidism
- Primary hyperparathyroidism
- Type 1 diabetes mellitus
- Hypothalamic amenorrhea
- Premature ovarian failure

Gastrointestinal diseases:
- Primary biliary cirrhosis
- Celiac disease
- Crohn's disease
- Total gastrectomy
- Gastric bypass

Other conditions:
- Ankylosing spondylitis
- Chronic renal disease
- Lymphoma and leukemia
- Multiple myeloma
- Anorexia nervosa; bulimia
- Rheumatoid arthritis

DIAGNOSTIC CONSIDERATIONS

All postmenopausal women should be assessed for risk factors associated with osteoporosis. This assessment requires a history, physical examination, and diagnostic tests. The more recent World Health Organizations (WHO) FRAX risk factors (personal history of fracture after age 40, history of hip fracture in a parent, current cigarette smoking, excess alcohol consumption, glucocorticoid use, rheumatoid arthritis or other secondary causes of osteoporosis), bone density testing and the FRAX risk calculator are tools used to establish risk of fracture. The FRAX risk calculator is used for postmenopausal women who have low bone density but not osteoporosis. It determines the 10-year probability of any osteoporotic fracture and 10-year probability of a hip fracture. The FRAX risk calculator is available online. The goals of evaluation should be to identify those women at risk for osteoporosis or fracture; establish a diagnosis of osteoporosis, determine the severity of the diagnosis, or both; rule out secondary causes of bone loss in patients with osteoporosis; and identifying risk factors for falls and injuries.

The history and physical examination should focus on identifying the woman's risk factors. There can be physical signs of osteoporosis. Loss of height greater than 1.5 inches may be associated with compression of vertebrae due to fractures on the anterior vertebral body. Measurement of height annually is the simplest of procedures that can be used to identify the risk of osteoporosis. Excessive kyphosis of the thoracic spine, dowager's hump, dental caries, tooth loss, receding gums, and back pain should raise suspicion of osteoporosis. Weight should also be recorded to identify women with low BMI and thus increased risk for low bone density. Other aspects of evaluation should including the solicitation of acute or chronic back pain, signs of percussion tenderness on exam, and bone density testing. The risk of falls should be assessed and is increased by the following: medications that affect balance and coordination, muscle weakness, impaired vision, a history of falls/fainting or loss of consciousness, difficulty standing or walking, arthritis of the lower extremities, and neuropathy of the lower extremities.

TABLE 194-1 **Comparison of Tests Measuring Bone Density**

METHOD	SITE AND ACCURACY
DEXA	Hip, spine, total body: 90%-99%
PDXA	Forearm, finger, heel: 90%-99%
SXA	Heel: 98%-99%
QUS	Heel, shin: not available
QCT	Spine: 95%-97%
PQTC	Forearm: 92%-98%

DEXA, Dual-energy x-ray absorptiometry; PDXA, peripheral dual-energy x-ray absorptiometry; PQTC, peripheral quantitative computed tomography; QCT, quantitated computed tomography; QUS, quantitative ultrasound; SXA, single-energy x-ray absorptiometry.
Data from Jergas M, Genant HK. Current methods and recent advances in the diagnosis of osteoporosis. Arthritis Rheum 1993;36:1649-1662.

Bone Mineral Density Testing

BMD testing is the optimal method to establish a diagnosis of osteoporosis. There are several techniques to measure BMD, but the gold standard is dual energy x-ray absorptiometry (DEXA).[26] Other methods of assessing bone mass include computed tomography (CT), ultrasounds of the heel, and radiographs, none of which is as useful for diagnosis and follow-up as the DEXA scan. The tests that measure BMD and their relative accuracy are shown in Table 194-1.

In addition to providing the most reliable measurement of BMD, the DEXA scan requires less radiation exposure than a conventional radiograph or CT scan. Usually the DEXA scan is used to measure the density of both the hip and the lumbar spine. The hip is the preferred site for BMD testing, especially in women above age 60, because—owing to extraosseous ossification—the spinal measurements can be unreliable. The spine is useful in early postmenopausal women because the rates of bone loss then are greater because of lower estrogen levels. Although peripheral DEXA sites are accurate, they may be less useful because they may not correlate as well with fracture risk and BMD at the hip and spine. The use of DEXA testing in a postmenopausal woman should be based on her risk profile. Testing is not indicated unless the test results will influence management. The North American Menopause Society has established the following guidelines to determine for indications for BMD testing:

- All women 65 years of age and older
- Postmenopausal women with secondary causes of bone loss (e.g., steroid use, hyperparathyroidism)
- Postmenopausal women age 50 and above with additional risk factors (fracture after menopause, thinness or weight below 127 pounds, history of hip fracture in a parent, current smoker, rheumatoid arthritis, alcohol intake of more than two units per day [one unit being equal to 12 ounces of beer, 4 ounces of wine, or 1 ounce of liquor])
- Postmenopausal women regardless of age with postmenopausal fragility fractures, low body weight, or a family history of spine or hip fracture

Results of BMD tests are reported as standard deviations—either a Z-score or a T-score. A Z-score is based on the standard deviation from the mean BMD of women in the same age group. A T-score is based on the mean peak BMD of a normal young woman. The WHO criteria for the diagnosis of osteoporosis are based on T-scores, as shown in Table 194-2.

TABLE 194-2 **Interpretation of Bone Mineral Density Score**

STATUS	T-SCORE	INTERPRETATION
Normal	Above -1	BMD within 1 SD of a young normal adult's T-score
Osteopenia	Between -1 and -2.5	BMD between 1 and 2.5 SD below a young normal adult's T-score
Osteoporosis	Below -2.5	BMD 2.5 SD or more below a young normal adult's T-score

BMD, Bone mineral density; SD, standard deviation.

Laboratory Tests of Bone Metabolism

Biochemical markers of bone turnover appeal to some practitioners. A urine test measures the breakdown products of bone, such as cross-linked N-telopeptide of type I collagen or deoxypyridium. These tests measure bone turnover and can be correlated with the rate of bone loss, but they are not intended to be used for the diagnosis of osteoporosis or monitoring of bone loss. Such tests may be used to monitor the success (or failure) of therapy. They provide quicker feedback compared with DEXA, with which it can take up to 2 years to detect a therapeutic response. The DEXA test is best used to measure bone density, whereas urinary bone resorption assessments can be used to measure the rate of bone turnover. The reduction of urinary levels of these markers of bone breakdown over a 2-year period has produced increases in bone density measurements,[27] but the value of these markers in clinical practice has yet to be definitively confirmed.

Additional tests may be used to determine secondary causes of bone loss. These include serum calcium, 24-hour urinary calcium, parathyroid hormone, thyroid-stimulating hormone, free thyroxine level, serum albumin, serum alkaline phosphatase, erythrocyte sedimentation rate, complete blood cell count, and 25(OH)D3 levels.

Management Approaches Based on Testing

A therapeutic and management strategy focusing on lifestyle and supplementation may be all that is necessary for postmenopausal women who have been determined to be at low risk for osteoporotic fractures. The North American Menopause Society recommends adding proven osteoporosis drug therapy for the following patients:

1. All postmenopausal women who have had an osteoporotic vertebral or hip fracture
2. All postmenopausal women who have BMD values equal to or less than -2.5 at the lumbar spine, femoral neck, or total hip region.
3. All postmenopausal women who have T-scores from -1.0 to -2.5 and a 10 year risk, based on the FRAX calculator of major osteoporotic fracture (spine, hip, shoulder or wrist) of at least 20% or a hip fracture of at least 3% are at high risk, and drug therapy is recommended.

THERAPEUTIC CONSIDERATIONS

Osteoporosis is a complex condition involving medical, genetic, hormonal, lifestyle, nutritional, and environmental factors. A comprehensive plan that addresses these factors offers the greatest protection.

The primary goals in the treatment and prevention of osteoporosis are as follows:

- Preserve adequate bone mass
- Preserve bone strength

- Prevent skeletal fragility
- Prevent deterioration of the microarchitecture
- Prevent or reduce the risk of fractures

The primary role of alternative therapies is to prevent osteoporosis and, fortunately, osteoporosis is largely a preventable disease. Pharmacologic therapy reduces the risk of vertebral and hip fractures by about 50%. According to the North American Menopause Society and their 2010 position statement on osteoporosis, the following guidelines are indications for pharmacologic therapy[28]:

- All postmenopausal women who have had an osteoporotic vertebral or hip fracture
- All postmenopausal women who have BMD values consistent with osteoporosis (i.e., BMD T-score values equal to or less than -2.5) at the lumbar spine, femoral neck, or total hip region
- All postmenopausal women who have T-scores from -1.0 to -2.5 and a 10-year risk based on the FRAX calculator of major osteoporotic fracture (spine, hip, shoulder, or wrist) of at least 20% or of hip fracture of at least 3%

Individuals with secondary causes of bone loss require individualized management. Older postmenopausal women with a history of a previous nontraumatic nonpathologic vertebral fracture are at high risk of having another spine or hip fracture. These women in particular are candidates for treatment with proved conventional pharmacologic treatments regardless of their bone density.

Many pharmacologic therapies are available for osteoporosis treatment, including bisphosphonates, the selective estrogen receptor modulator (SERM), raloxifene, parathyroid hormone, estrogens, and calcitonin. There are currently no prospective studies comparing these therapies for anti fracture efficacy. All of the therapies mentioned above except estrogen have been studied for their effect on fracture only in patients with either a clinical or BMD diagnosis of osteoporosis. With all of these therapies, the absolute reduction in fracture risk is greatest in women who are at high risk for a fracture.

Pharmacologic Therapy

Hormone Replacement Therapy

As estrogen levels decline, bone remodeling increases and bone resorption outpaces bone formation. Both estrogen replacement therapy (ERT) with estrogen only and hormone replacement therapy (HRT), with estrogen and progestogen, reduce the rate of bone turnover and resorption.[29]

ERT can return the high resorption rates in postmenopausal women to those of the rates in premenopausal women. Long-term data on the effects of ERT and HRT on bone density and fracture risk come mainly from observational and epidemiologic studies. Epidemiologic research found a 54% reduction in risk of fractures in current users of ERT/HRT compared with those who never used it.[30] Researchers also found that ERT/HRT is more effective in reducing the fracture risk if it is begun within 5 years of menopause. If it was used more than 10 years earlier, it produced an even greater risk reduction—75% for wrist fractures and 73% for hip fractures.

A 2002 meta-analysis of 57 randomized clinical trials of systemic oral or transdermal estrogen and estrogen/progestogen at standard doses found BMD increases at all sites in postmenopausal women.[31] In trials of 2 years in length, the average difference in BMD after estrogen or estrogen/progestogen was 6.8% at the lumbar spine and 4.1% at the femoral neck.

The two largest and best-controlled trials are the Postmenopausal Estrogen/Progestin Interventions (PEPI) trials and the Women's Health Initiative (WHI). In the PEPI trials, 0.625-mg daily doses of conjugated equine estrogens with or without a progestogen (either medroxyprogesterone acetate or oral micronized progesterone) for 3 years significantly increased spinal BMD by 3.5% to 5.0%; there was also a 1.7% increase in hip BMD.[32] In the 5-year randomized controlled trial, the WHI HRT significantly increased spine BMD by 4.5% and total hip BMD by 3.7% in comparison with placebo; it also reduced the risk of hip fractures (34%), vertebral fractures (34%), and total body fractures (24%).[33]

Doses even lower than the standard dosages of estrogen have produced significant increased in spine and hip BMD in the range of 1% to 3%,[34-38] as has systemic estrogen via a vaginal ring (the Femring).[39]

In addition to increases in BMD, randomized trials and observational studies have indicated that standard doses of estrogen or estrogen/progestogen reduce fracture risk in postmenopausal women. Two meta-analyses found up to a 27% reduction in fracture risk.[40,41] Two large observational studies, the National Osteoporosis Risk Assessment study[42] of over 200,000 women and the Million Women Study[43] of over 138,000 women both reported significantly reduced risks for fractures. Despite these studies and more, estrogen-only or estrogen-plus-progestogen products are approved for prevention but not treatment of postmenopausal osteoporosis.

Now more than ever, it is important to individualize treatment options and more clearly identify the risk:benefit ratio. Generally, ERT/HRT is believed to work best during the first 5 to 10 years after menopause. The optimal duration and maximal duration have not yet been clearly determined and for this reason, in the face of the studies that show slight increases in risk of breast cancer and other potential issues, ERT/HRT will not be seen as a primary long-term treatment for osteoporosis except in those who do not tolerate bisphosphonates or who have menopausal symptoms that are not responding to other therapies.

Bisphosphonates

This class of drugs is thought to work by inhibiting osteoclast activity, thereby reducing bone resorption. Clinical trials demonstrate that bisphosphonates can significantly increase BMD at the spine and hip in postmenopausal women no matter their age. Bisphosphonates have been shown to reduce the risk of vertebral fractures in women with osteoporosis, by 40% to 70% and to reduce the incidence of hip fracture and other nonvertebral fractures by about half of this.[44,45] Most of the bisphosphonates available in the United States (alendronate, ibandronate, and risedronate) are intended for use in daily or intermittent oral doses. Zoledronic acid is available as an intravenous injection. Clinical trials that have demonstrated BMD responses show similar results for weekly oral dosing regimens of alendronate and risedronate, monthly oral dosing of ibandronate and risedronate, and intravenous dosing every 3 months of ibandronate.[46-49]

Bisphosphonates are not without problems and they should only be used with careful consideration—both for their potential benefit in women who have osteoporosis and are at higher risk for fracture (especially as they get older) and for their potential for serious risk. Some questions have arisen regarding the quality of the bone and possibly increased fractures with bisphosphonates in longer-term use in some individuals.[50] There may be the potential for over suppression of bone turnover with long-term therapy, resulting in a more brittle bone. Individual cases and small case series with unusual, poorly healing fractures have been reported recently, as well as atypical fractures of the femur. Research is under way to determine what is unique to these rare individuals.

Many clinicians are responding to these concerns by "drug holidays." Understanding the frequency and duration of these drug holidays is under investigation in ongoing studies.

Osteonecrosis of the jaw (ONJ) has been observed with bisphosphonate use.[51] This has occurred mainly in individuals on high-dose intravenous bisphosphonates and in those being treated with radiation for head and neck cancers. ONJ is characterized by a delay in healing of an oral lesion after surgery or extraction for more than 6 to 8 weeks. The incidence of ONJ with intravenous bisphosphonates in those without neck radiation has been reported to be as high as 12%. Oral incidence is much lower, at 0.03% to 0.06%. However, oral surgery increases the incidence sevenfold.[52] Currently, there is controversy in the research on whether to discontinue bisphosphonate therapy before dental extraction. Many practitioners are recommending suspending bisphosphonate therapy until the oral lesion has healed.

Although not common, long-term bisphosphonate use is also associated with insufficiency fractures of the femoral shaft, which commonly presents with prodromal thigh pain and may be bilateral.[53] This is one reason why the use bisphosphonates is now being recommended for a maximum of 5 years, which then allows bone remodeling.[54] Bone density should be monitored closely to ensure stable or minimal bone loss after discontinuation. It appears that 5 years of use may provide long-term fracture protection just as effectively as the drug taken for more than 5 years.

Oral bisphosphonates may cause other problems such as upper gastrointestinal disorders, including dysphagia, esophagitis, and esophageal and gastric ulcers. All bisphosphonates carry precautions regarding hypocalcemia and renal impairment. There can also be a transient flulike illness, although infrequently, with large doses of oral or intravenous bisphosphonates. How and when to take these drugs requires careful following of the directions.

In total, this class of drugs is an important option for selected individuals—it can be life-altering in terms of relieving pain and suffering and saving lives (especially in the case of hip fractures). Clinicians should become familiar with the FRAX tool for determining fracture risk in those that have low bone density but not osteoporosis; they should also informed themselves of the full scope of benefits and risks so as to be able to advise their patients. With proper care and monitoring for potential adverse events and loss of bone remodeling, bisphosphonates can be used when truly indicated and without adequate or appropriate alternative options in the context of a holistic/integrative approach to bone health and fracture protection.

(The editors recommend using the bisphosphonates only if the natural interventions described in this chapter have not produced satisfactory results.)

Selective Estrogen-Receptor Modulators

Selective estrogen-receptor modulators (SERMs) are nonsteroidal estrogen agonists and/or antagonists. Raloxifene, at a dose of 60 mg/day, is approved for the prevention and treatment of osteoporosis. Currently, this is the only SERM approved for the treatment of osteoporosis. In a 20-year study, raloxifene at 60 mg/day significantly improved BMD at the lumbar spine by 1.6% and at the femoral neck by 1.2%.[55] In the Multiple Outcomes of Raloxifene Evaluation trial, 3 years of raloxifene therapy at 60 mg/day in postmenopausal women increased BMD by 2.6% at the spine and 2.1% at the femoral neck.[56]

Parathyroid Hormone

Parathyroid hormone is given by subcutaneous injection once daily. This anabolic agent stimulates osteoblastic bone formation and increases trabecular bone density in women with osteoporosis.[57-59] One medication in particular, teriparatide (Forteo) is approved for the treatment of osteoporosis in postmenopausal women. Nineteen months of teriparatide treatment (20 mcg/injection per day) increased bone density in the spine by 8.6% and in the femoral neck by 3.5% compared with placebo.[59] In addition, the incidence of new vertebral fractures was reduced by 65% and nonvertebral fractures by 53%.

Calcitonin

Calcitonin is approved for postmenopausal osteoporosis treatment but not prevention. It is available as a nasal spray and a subcutaneous injection. The randomized controlled trial Prevent Recurrence of Osteoporotic Fractures (PROOF),[60] an intranasal spray containing calcitonin (delivering 200 IU/day) was used for 5 years by postmenopausal women with osteoporosis; this was found to reduce the risk of new vertebral fractures by 33% compared with placebo. No effect was seen on hip or nonvertebral fractures. Calcitonin spray may also be helpful in women with osteoporosis in that it can reduce bone pain from vertebral compression fractures.

New Therapies Being Researched

New drugs and treatments are being developed all the time, although some of them are not currently available in the United States, such as tibolone and oral strontium ranelate (Protelos). Denosumab (Prolia), a human monoclonal antibody to receptor activator of the nuclear factor-kB ligand, has recently been approved and is indicated for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture, have a history of an osteoporotic fracture, or have failed or are intolerant of other osteoporosis therapies. Other drugs are in development, including SERMs and full-length parathyroid hormone.

LIFESTYLE FACTORS

Certain lifestyle factors significantly affect bone health, but lifestyle approaches alone are not sufficient to prevent bone loss or fractures. Whether adequate alone or not, they do provide the foundation for nonpharmacologic and pharmacologic approaches to the prevention and management of osteoporosis.

Smoking tends to cause more rapid bone loss and lower bone mass. Smokers also tend to experience menopause 2 years earlier than nonsmokers.[61-63]

Postmenopausal smokers have higher fracture rates,[64] and meta-analyses have suggested that hip fracture risk may be increased in current smokers.[65] Such fractures may be a particular risk for women over the age of 60. The WHO reports that a history of smoking causes a substantial risk for future fracture independently of BMD.[66]

Moderate alcohol consumption is associated with an increased BMD in postmenopausal women,[67,68] but alcohol consumption greater than seven units a week is associated with an increase risk of falls.[69] It appears that consuming more than two units a day of alcohol is associated with an increased risk of osteoporotic fracture (one unit is the equivalent of 12 ounces of beer, 4 ounces of wine, or 1 ounce of liquor).[70]

Exercise

Numerous studies have demonstrated that physical fitness is the major determinant of bone density. Physical exercise consisting of

1 hour of moderate activity three times a week has been shown to prevent bone loss and actually increase bone mass in postmenopausal women.[71-76] Both weight-bearing and strength-training exercises are beneficial to the development of bone and maintenance of bone health and function.[77-79] Strength training has small but meaningful benefits to bone mass. In a meta-analysis of postmenopausal women, those who exercised increased their spine BMD by approximately 2%.[80]

In surgically menopausal women who have used estrogen therapy, the addition of strength training provides further benefits to BMD compared with estrogen alone.[81] If a particular exercise does not increase BMD, it can at least reduce the risk of falling and subsequent fractures. Muscle-strengthening and balancing exercises have been shown to reduce the risk of falls and fall-related injuries by 75% in women 75 years of age and older.[82] In contrast to exercise, immobilization doubles the rate of urinary and fecal calcium excretion, resulting in a significant negative calcium balance.[83] Although nutritional factors are important, an effective regimen for strengthening bones and reducing fractures would fall short if it did not emphasize physical activity. Weight-bearing exercises can be simple, such as walking or Tai Chi. Strength-training exercises can also be simple, with home barbells or resistance bands. Women with osteoporosis should consult resources that give guidance about effective exercises, safe activities, and exercises to be avoided.

General Dietary Factors

Many dietary factors have been suggested as causes of osteoporosis, including the following[84-86]:

- Low-calcium, high-phosphorus intake
- High-protein diet
- Low-protein diet
- A diet high in acid ash
- High-salt intake
- Trace mineral deficiencies

A vegetarian diet (both lacto-ovo and vegan) is associated with a lower risk of osteoporosis.[87,88] Although bone mass in vegetarians does not differ significantly from that in omnivores in the third, fourth, and fifth decades, there are significant differences in the later decades. These findings indicate that the decreased incidence of osteoporosis in vegetarians is not due to increased initial bone mass but rather to decreased bone loss.

Several factors are probably responsible for the decrease in bone loss observed in vegetarians. The most important of these is probably a lowered intake of protein. One point of view holds that a high-protein diet or a diet high in phosphates is associated with increased excretion of calcium in the urine. Raising daily protein from 47 to 142 g doubles the excretion of calcium in the urine.[89] A diet this high in protein is common in the United States and may be a significant factor in the increasing number of people suffering from osteoporosis in this country. The opposing point of view is that high-protein diets resulting in increased urinary calcium excretion and increased acid production—in essence, a negative calcium balance—may result only if the daily calcium intake is inadequate. Rather than reduce protein intake, it would be advisable to increase calcium intake and increase the dietary intake of fruits and vegetables for their alkalinizing effect.[90] A reasonable guide and compromise might be to assure a minimum of 20 g/day of protein, especially in elderly patients over age 80, and limit the upper end to 60 g or so.

The issue here is not protein per se but rather the pH effects of the diet. When the diet induces acidosis—which is typical of a diet high in protein and salt—the body maintains pH by buffering with calcium, which is taken from the bones. Although calcium supplementation can prevent bone loss, for those at risk and in excess doses, it poses an increase in calcium kidney stones. A possible strategy to reduce this risk of kidney stones is to supplement with calcium citrate.[91]

Gastric Acid

It has long been believed that the absorption of calcium depends on it becoming ionized in the intestines, largely on the basis of the secretion of gastric acid. Furthermore, it has been believed that the poor ionization of calcium is a major problem with calcium carbonate—the most widely used form of calcium for nutritional supplementation, as it has been thought that in order for calcium carbonate to be absorbed it must first be solubilized and ionized by stomach acid.

Although decreased gastric acidity may be seen in as many as 40% of postmenopausal women,[91a] a critical review of available human studies indicates that the effects of increased gastric pH are apparent only when poorly soluble calcium salts (like calcium carbonate) are taken after an overnight fast.[92] In a fasting state, patients with insufficient stomach acid output can absorb only about 4% of an oral dose of calcium as calcium carbonate, whereas a person with normal stomach acid can typically absorb about 22%.[93] Patients with low stomach acid secretion need a form of calcium that is already in a soluble and ionized state, such as calcium citrate, calcium lactate, or calcium gluconate. About 45% of the calcium is absorbed from calcium citrate in patients with reduced stomach acid, compared with an absorption of only 4% for calcium carbonate.[92] However, when any form of calcium is taken with meals, there is little difference in its absorption even in elderly subjects with atrophic gastritis or those taking H_2-receptor antagonists.

Sugar

Another dietary factor that increases the loss of calcium from the body is refined sugar. Following sugar intake, there is an increase in the urinary excretion of calcium.[94] Considering that the average American consumes, in 1 day, 125 g of sucrose, 50 g of corn syrup, plus other refined simple sugars, and a glass of a carbonated beverage loaded with phosphates, along with the high amount of protein, it is little wonder that so many suffer from osteoporosis.

Soft Drinks

Soft drinks may be a major contributor to osteoporosis, as they are high in phosphates but contain virtually no calcium. This leads to lower calcium levels and higher phosphate levels in the blood. The United States ranks first among countries for soft drink consumption, with a per capita consumption of approximately 15 ounces a day.

The link between soft drink consumption and bone loss is going to be even more significant as children practically weaned on soft drinks reach adulthood. Soft drink consumption among children poses a significant risk factor for impaired calcification of growing bones. Because there is such a strong correlation between maximum BMD and the risk of osteoporosis, the rate of osteoporosis may eventually reach even greater epidemic proportions.

The severely negative effect that soft drinks have on bone formation in children was clearly demonstrated in a study that compared 57 children with low blood calcium, aged 18 months to 14 years, with 171 matched controls with normal calcium levels.[95] The goal of the study was to assess whether the intake of at least 1.5 quarts per week of soft drinks containing phosphates is a risk

for the development of low blood calcium levels. Of the 57 children with low blood calcium levels, 38 (66.7%) drank more than four bottles (12 to 16 ounces) per week, but only 48 (28%) of the 171 children with normal serum calcium levels drank as many soft drinks. For all 228 children, a significant inverse correlation between serum calcium level and the amount of soft drinks consumed each week was found.[96]

Green Leafy Vegetables

Consumption of green leafy vegetables (e.g., kale, collard greens, parsley, lettuce) offers significant protection against osteoporosis. These foods are a rich source of a broad range of vitamins and minerals that are important to maintaining healthy bones, including calcium, vitamin K_1, and boron.

Soy Isoflavones

The potential for soy protein or soy isoflavones to alter bone metabolism and bone resorption is currently contradictory and inconclusive.[97] The lack of agreement in the literature is thought to be related to variations in study design. These variations include differences in the dose and form of soy products studied (i.e., soy protein isolate, whole soy foods, or extracted soy isoflavones), differences in the menopausal status of the women studied (i.e., perimenopausal, early menopausal, or late postmenopausal), differences in the duration of the various trials, and differences in the tests used to assess bone density and bone metabolism. All of these different approaches and study designs make it very difficult to determine the effectiveness of soy for bone health and make the decision to include soy in a protocol for supporting bone health more difficult for the practitioner.

Soybeans contain a class of compounds called phytoestrogens, comprising mostly genistein, daidzein and glycitein, all of which have a biochemical structure similar to that of 17 beta-estradiol. The binding of isoflavones to estrogen receptors is preferential for the estrogen receptor beta and thus indicates that soy isoflavones act as selective estrogen modulators.[98] Daidzein is similar in shape to a drug called ipriflavone, which is used in Europe to treat osteoporosis. In the United States, ipriflavone is available as a nutritional supplement.

BMD is the gold standard for determining fracture risk due to nontraumatic events. Bone turnover is an independent predictor of fracture risk.[99]

Although the research on the effects of soy on bone metabolism has been inconsistent, many positive studies exist that suggest a role for soy in slowing bone turnover and increasing bone density in women. According to some experimental evaluations, soy appears to have an estrogenic effect on bone. The bone density of ovariectomized rats was evaluated in a study in which soy replaced casein in the diet; these rats were then compared with another group that received estrogen. The addition of soy inhibited bone loss, although not to the same extent as achieved with the estrogen treatment.[100] Another study of ovariectomized rats also reported a positive effect of the soy phytoestrogen genistein in maintaining bone.[101]

These authors also reported that genistein suppresses osteoclasts, the cells responsible for bone resorption, both in the test tube and in vivo. Arjmandi also did a double-blind randomized, controlled trial using 40 g of soy protein containing isoflavones over 3 months in postmenopausal women.[102] Bone resorption was decreased with soy protein as compared with milk protein.

Several human studies have provided further insight and comfort in the possible role of soy in our bone health. A study conducted at the University of Illinois found that menopausal women had an increase in mineral levels and density in their lumbar spines after taking 55 to 90 mg of soy isoflavones for 6 months.[103]

The placebo group showed the lowest bone density and the greatest bone loss, whereas the estrogen group showed the highest bone density and the slowest bone loss. The isoflavone diet was effective in preventing bone loss in the fourth lumbar vertebra and, although less so, in the right hip. Soy isoflavones seem to have more of an effect on trabecular bone (more predominant in the spine) than on cortical bone (more predominant in the hip). The soy did not show as great an ability to prevent bone loss as the estrogen group, but the positive effect it showed is encouraging.

An analysis of the relationship of soy isoflavone intake and BMD was conducted from the Study of Women's Health Across the Nation, a U.S. cohort study of women aged 42 to 52 years.[104]

For African American and white women, median intakes of genistein were too low to be analyzed. For Chinese women, no association between genistein and BMD was found. Premenopausal, but not perimenopausal Japanese women whose intakes were greater had a higher bone density of the spine and femoral neck. The mean spinal bone density of those women in the highest group was 7.7% greater than that of women in the lowest group. Bone density of the femoral neck was 12% greater in the group with the highest intake versus that with the lowest.

Other positive studies on soy and bone density also give some credence to the role of soy and bone health. In a study estimating the daily intakes of soy isoflavones in the diets of 478 postmenopausal Japanese women who reported soy consumption, high consumption of soy products was associated with increased bone mass.[105]

A recent meta-analysis further increases our optimism about using soy to inhibit bone resorption. Nine studies comprising a total of 432 menopausal women were evaluated in this meta-analysis.[106]

The amount of soy intake varied among the nine studies from 37 to 118 mg of isoflavones per day. Testing for urinary peptides (deoxypyridinoline), a marker of bone turnover, demonstrated that those who consumed isoflavones had a decrease in these biomarkers of 2.08 nmol/mmol compared with those who did not consume isoflavones. In five of the studies where isolated soy protein was used, there was no significant effect on urinary deoxypyridinoline. In the current analysis, a significant reduction in urinary deoxypyridinoline was not observed in those studies with isoflavones of less than 90 mg/day. In a review of the research in 2003, the author concluded that 90 mg/day of isoflavones day would be required to achieve benefits on bone health.[107]

In contrast to the positive studies, several clinical trials using a variety of soy protein isolate formulations found no clinically important effects of soy on bone metabolism or markers of bone turnover.[108-110]

Further inconsistent research can be seen with several clinical trials using soy protein or isoflavones that demonstrated a positive effect on BMD,[111-115] whereas others had no positive findings.[116,117]

Variations in dosing, duration, soy formulation used, and different study populations are possible reasons for inconsistent results on the effects of soy isoflavones on bone turnover and bone density. But another significant consideration may be how the isoflavones are metabolized in the gut. In the meta-analysis mentioned above, which included nine studies,[106] the significant effects on urinary peptides occurred in Asian women but not white women. This may be due to the conversion of daidzein into its active metabolite equol by intestinal flora and to the fact that only one third of white women can metabolize isoflavones into equol, whereas more than half of Asian women possess this ability.

TABLE 194-3 **Calcium Content of Select Soy Foods**

SOY PRODUCT	SERVING SIZE	MG OF CALCIUM
Tofu, firm	¼ block	553
Tofu, regular	¼ block	406
Soy milk, calcium-fortified	1 cup	80-300
Soy milk	1 cup	7
Soybeans, roasted	¼ cup	119
Soybeans, boiled	¼ cup	88
Tempeh	¼ cup	77

Soy isoflavones may also have more of an effect in postmenopausal women than in pre- or perimenopausal women. In one study, 53.3 mg/day of isoflavones was associated with an increase in bone density in postmenopausal women but not in premenopausal women.[118]

A nutritional influence of soy foods that may be overlooked is the amount of calcium in some of these foods or in diets that contain soy foods. A diet that includes greater amounts of soy products can account for a meaningful amount of calcium, and some soy foods can offer as much or more calcium as a serving of dairy products (Table 194-3).

With the inconsistent research, it is difficult to draw confident conclusions about the role of soy in bone health. Prudent clinical advice might be to increase soy foods as part of a regular diet in prevention strategies for all premenopausal, perimenopausal, and postmenopausal women. For all women who have significant risk factors for osteoporosis, soy supplementation could be added so that their total daily soy isoflavone intake would amount to approximately 90 mg/day. For treatment of perimenopausal and postmenopausal women who already have osteoporosis, this alone would not be considered adequate treatment.

Nutritional Supplementation

Calcium

Adequate calcium intake has an established role in maintaining bone health, primarily in very young women and the elderly. However, calcium is only modestly effective for slowing the loss of BMD in perimenopausal and early postmenopausal women. Calcium supplementation also appears to have an important role in improving the efficacy of pharmaceutical agents used to treat bone loss and osteoporosis.

Prior to the Women's Health Initiative study, there was no clear evidence that higher calcium intake decreased fracture risk.[119] A meta-analysis of prospective cohort studies and clinical trials found that higher calcium intake and calcium supplementation were not associated with a lower incidence of hip fractures.[120] In a 2004 meta-analysis of randomized controlled trials, supplementation with 500 to 2000 mg a day of calcium had only a modest benefit on bone density in postmenopausal women: the difference in the amount of bone loss between calcium and placebo was 2.05% for the total body, 1.66% for the lumbar spine, and 1.64% for the hip.[121] Two trials within this meta-analysis suggested a modest and nonsignificant benefit with calcium supplementation and the risk of nonvertebral fractures. In the Women's Health Initiative, which enrolled more than 36,000 postmenopausal women, supplementation with 1000 mg/day of calcium and 400 IU/day of vitamin D decreased the risk of hip fractures nonsignificantly by 12% when compared with placebo. However, when the analysis was restricted to women who took the tablets at least 80% of the time, calcium plus vitamin D significantly decreased hip fractures by 29% compared with placebo.[122]

Other calcium studies also showed a beneficial effect on bone loss. In postmenopausal women, calcium supplementation has been shown to decrease bone loss by as much as 50% at nonvertebral sites. The effects were greatest in women whose baseline calcium intake was low, in older women, and in women with established osteoporosis.[123] In a study by Elders et al,[124] a significant decrease in vertebral bone loss was observed with supplementation of 1000 to 2000 mg/day of calcium for 1 year. Bone loss was also less in the calcium group than in the control group after 2 years, but the difference was no longer statistically significant.

Dietary calcium is essential throughout a woman's life, and requirements increase with advancing age in part owing to reduced calcium absorption and decreased renal calcium conservation. However, calcium supplementation by itself is not effective in preventing the accelerated bone loss that occurs in the first few years after menopause. Ten years postmenopausal, calcium supplementation again becomes effective in reducing age-related bone loss.[125] Although consuming an adequate amount of calcium is important, it is too often overemphasized and supplemented at excessive doses, because calcium is only one of many nutritional and lifestyle factors that play a role in promoting bone health.

Vitamin D

Vitamin D enhances intestinal calcium absorption, thereby contributing to a favorable calcium balance. Increased calcium absorption also reduces parathyroid-hormone–mediated bone resorption. In the United States, most infants and young children receive adequate vitamin D from fortified milk. During adolescence, however, the consumption of dairy products drops off and inadequate vitamin D intake is more likely to affect calcium absorption adversely.

Several large randomized controlled trials have found that the combination of calcium and vitamin D had no significant effect on fracture risk.[119,123,126] However, virtually all of these use vitamin D doses that were inadequate to raise serum 25(OH)D3 levels into the effective range.

Nonetheless, a meta-analysis of randomized controlled trials in elderly postmenopausal women found that a still inadequate dose of 700 to 800 IU/day of vitamin D was associated with significant reductions in the risk of hip and nonvertebral fractures.[127] Especially in older women, vitamin D in combination with calcium supplementation reduced the rate of postmenopausal bone loss.[128] Vitamin D has also been shown to improve muscle strength[129] and balance,[130] thereby reducing the risk of falling.[131]

Magnesium

Magnesium is a cofactor for alkaline phosphatase, which plays a role in bone mineralization. Low magnesium status is common in women with osteoporosis, and magnesium deficiency is associated with abnormal bone mineral crystals.[132] Some women with reduced BMD do not have an increased fracture rate, possibly because their bone mineral crystals are of high quality owing in part to high levels of magnesium. In a group of postmenopausal women, supplementation with 250 to 750 mg/day of magnesium for 6 months followed by 250 mg/day for 6 to 18 months resulted in an increase in bone density in 71% of the women. This increase was noteworthy because it occurred without calcium supplementation.[133]

Strontium

Strontium is a nonradioactive earth element physically and chemically similar to calcium. Strontium ranelate is the specific strontium

salt used in clinical trials for osteoporosis, but this form of strontium is not available in the United States. Strontium in large doses stimulates bone formation and reduces bone resorption. In a phase 2 clinical trial, 2 g/day of oral strontium ranelate (containing 680 mg per day of elemental strontium) for 3 years was shown to reduce the risk of vertebral fractures and to increase BMD in 1649 postmenopausal women with osteoporosis.[134]

In the first year, there was a 49% reduction in the incidence of vertebral fractures in the strontium ranelate group and a 41% reduction at the end of 3 years. After adjusting for artifact effect on imaging, a 6.8% increase in BMD was seen at the lumbar spine after 3 years of strontium supplementation. There was also an 8.3% increase at the femoral neck, but there was insufficient data to adjust it for an artifact effect; therefore, it is not clear how accurate this is.

In a two year trial, 353 postmenopausal women with osteoporosis and a history of at least one vertebral fracture received a placebo or one of three different doses of strontium: 170 mg per day, 340 mg per day, or 680 mg per day.[135] A small increase in lumbar BMD was seen with each dose of strontium, but the difference compared with placebo was statistically significant only for the highest dose. The incidence of new vertebral deformities was lowest (38.8%) with the lowest dose of strontium, versus 54.7%, 56.7%, and 42.0% in the placebo, 340 mg/day, and 680 mg per day groups, respectively.

Strontium chloride is the most common form of strontium used in U.S. supplements. This form of strontium has not been the subject of published research. Owing to potential adverse effects of higher doses of strontium, including rickets, bone mineralization defects, and interference with vitamin D metabolism—it may be prudent to use low doses until more research has been conducted.

Zinc

Zinc is essential for the formation of osteoblasts and osteoclasts, and it enhances the biochemical action of vitamin D. Zinc is also necessary for the synthesis of various proteins found in bone. Low zinc levels have been found in the serum and bone of elderly people with osteoporosis.[136]

Copper

A deficiency of copper is known to produce abnormal bone development in growing children and may be a contributing cause of osteoporosis. In vitro studies have shown that copper supplementation inhibits bone resorption.[137,138] In a double-blind trial, supplementation with 3 mg/day of copper for 2 years significantly decreased bone loss in postmenopausal women.[139]

Manganese

A deficiency of manganese may be one of the lesser known but more important nutritional factors related to osteoporosis. Manganese deficiency causes a reduction in calcium deposition in bone. Manganese also stimulates mucopolysaccharide production, which provides a framework for the calcification process.[140]

Zinc, Copper, and Manganese

In a double-blind study of postmenopausal women, the combination of zinc, copper, manganese, and calcium appeared to be more effective than calcium alone for preventing bone loss in postmenopausal women.[141]

Boron

Boron supplementation reduces urinary excretion of calcium and magnesium and increases serum levels of 17 beta-estradiol and testosterone in postmenopausal women.[142] These observations suggest that boron supplementation could help to prevent bone loss.

Silicon

During bone growth and the early phases of bone calcification, silicon has an essential role in the formation of cross-links between collagen and proteoglycans. In animals, silicon-deficient diets have produced abnormal skull development and growth retardation,[143] and supplemental silicon partially prevented trabecular bone loss in ovariectomized rats.[144]

Folic Acid and Vitamin B_{12}

Accelerated bone loss in menopausal women may in part be due to increased levels of homocysteine, a breakdown product of methionine. Homocysteine has the potential to promote osteoporosis if it is not eliminated adequately. In a prospective study, women with high homocysteine levels had almost twice the risk of nonvertebral osteoporotic fractures as did women with low homocysteine levels. There was no association in that study between homocysteine levels and BMD at either the femoral neck or the lumbar spine, which suggests that the increase in fracture risk was due to poorer bone quality.[145] Folic acid promotes the remethylation of homocysteine to methionine, and supplementing postmenopausal women with this nutrient results in significant reductions in homocysteine levels.[146] Vitamin B_{12} has also been shown to reduce homocysteine levels. In a double-blind study of stroke victims with elevated homocysteine levels, daily supplementation with 5 mg of folic acid plus 1500 mcg of vitamin B_{12} for 2 years reduced hip fracture incidence by 78% compared with placebo.[147]

Vitamin B_6

Vitamin B_6 also plays a role in homocysteine metabolism. In people with the genetic disorder homocystinuria, vitamin B_6 supplementation reverses the elevated levels of homocysteine.[148] Animal studies have shown that vitamin B_6 deficiency can prolong fracture healing time,[149] impair cartilage growth, cause defective bone formation,[150] and promote osteoporosis.[151] Vitamin B_6 may also influence progesterone production and exert a synergistic effect on estrogen-sensitive tissue. Laboratory evidence of low vitamin B_6 status appears to be common, even among healthy individuals.[152]

Vitamin C

Vitamin C promotes the formation and cross-linking of some of the structural proteins in bone. Animal studies have shown that vitamin C deficiency can cause osteoporosis,[153] and it has been known for decades that scurvy, a disease caused by vitamin C deficiency, is also associated with abnormalities of bone.

Vitamin K

Vitamin K is required for the production of the bone protein osteocalcin. Osteocalcin draws calcium to bone tissue, enabling calcium crystal formation. Osteocalcin provides the protein matrix for mineralization and is thought to act as a regulator of bone mineralization.[154] Vitamin K plays a key role in the formation, remodeling, and repair of bone by attracting calcium to the site of this protein matrix.[155] A low dietary intake of vitamin K seems to increase the risk of osteoporotic hip fractures in women, according to data from the Nurses' Health Study.[156]

There are various forms of vitamin K, but the human trials have been done on vitamin K_1 (phylloquinone), MK-4, (MK-4, a form of vitamin K_2) and menaquinone-7 (longer-chain MK-7).

In a double-blind study, 452 men and women (ages 60-80 years) received a multiple vitamin/multimineral supplement providing 600 mg/day of calcium and 400 IU/day of vitamin D, plus either 500 mcg/day of vitamin K_1 or no vitamin K_1.[157] BMD (determined by DEXA) and bone turnover were measured at 6, 12, 24, and 36 months. There were no differences in BMD at the femoral neck, lumbar spine, or total body between the two treatment groups, indicating that vitamin K_1 did not enhance the effects of calcium, vitamin D, or other nutrients in this patient population. In the double-blind ECKO trial,[158] a daily 5-mg supplement of vitamin K_1 for 2 to 4 years did not protect against an age-related decline in BMD in postmenopausal women with osteopenia, but significantly fewer women in the vitamin K_1 group than in the placebo group had fractures.

Epidemiologic evidence has shown associations between low dietary intake of vitamin K and increased bone loss in elderly men and women. A 2006 meta-analysis of 13 randomized controlled trials[159] that gave vitamin K_1 or MK-4 (a form of vitamin K_2) supplements for longer than 6 months reported data on bone loss and fracture rates. All but one study showed a reduction in bone loss with supplemental vitamin K. All 7 of the 13 studies that reported fracture data were in Japanese individuals and used MK-4. Most of these trials used a high dose, 45 mg/day.

Although the recommended dietary intake of vitamin K is 90 to 120 mcg/day, the optimal dose and form of vitamin K supplementation to achieve a protective effect on bone loss and fracture reduction is not known. The majority of studies used MK-4 at doses approximately 400-fold higher than dietary recommendations for vitamin K_1. An additional issue is that these studies have been conducted almost exclusively in Japanese postmenopausal women. This population group may be influenced by unique dietary, environmental, and/or genetic factors, so it is not clear whether the findings from these studies can be generalized to other populations. In contrast to the seven positive Japanese studies, in a double-blind trial, 381 postmenopausal women received either phylloquinone 1 mg/day, MK-4 45 mg/day, or placebo for 12 months.[160] No effect of phylloquinone or MK-4 on the bone density of the lumbar spine or proximal femur was observed.

Two long-term trials have previously been done evaluating the effect of vitamin K_1 supplementation on bone loss. In one study using 1 mg/day of vitamin K_1 plus calcium and vitamin D for 3 years in postmenopausal women aged 50 to 60 years,[161] bone loss was reduced at the femoral neck, but there was no beneficial effect on spinal bone density. In a second study,[162] 200 mcg/day of vitamin K_1 plus calcium and vitamin D given for 2 years to non-osteoporotic women aged 60 years or above resulted in a modest increase in BMD of the radius but not the femoral neck.

Menaquinone-7, or MK-7 (a longer-chain form of vitamin K_2), is found in natto (highest concentration in fermented soybeans) and cheese and in lower concentrations in meat and other dairy products; a very small amount is produced by gut bacteria from dietary vitamin K_1.[163] MK-7 has been found in animal studies to be more potent and more bioavailable as well as to have a longer half-life than MK-4. When taken as a daily supplement (0.22 µmol/day), MK-7 is more effective than K_1 in carboxylating osteocalcin. This is thought to be due to MK-7's much longer residence time and the higher serum concentrations of MK-7 achieved during its prolonged intake.[164] The longer-chain menaquinones such as MK-7 are much more hydrophobic, which contributes to their much longer half-lives (8 hours for K_1 and MK-4 vs 96 hours for MK-7).[165] In a study of Japanese postmenopausal women, a significant inverse association was found between natto consumption and the incidence of hip fractures.[166] In a study of osteoporosis after organ transplantation, 1 year of MK-7 supplementation (180 mcg/day) resulted in increased bone mineralization compared with placebo.[167] However, a study of early menopausal women given 1 year of supplementation of 360 mcg/day of MK-7 in the form of natto capsules did not show a significant improvement in bone density despite a reduction in uncarboxylated osteocalcin.[168] A likely reason for these inconsistent results is the confounding effect of vitamin D status. The study in post-transplant patients noted a high incidence of vitamin D deficiency, which was found to affect the results.

Botanical Medicine

Camellia sinensis (Green Tea)

Population-based studies, as well as experimental studies, have demonstrated that green tea consumption may offer significant protection against osteoporosis.[169] Green tea is rich not only in health promoting polyphenols, but is also a major source of vitamin K_1. In order to take advantage of this protection it requires 3 to 5 cups per day, providing a minimum of 250 mg per day of polyphenols (also referred to as catechins), or alternatively a green tea extract providing the same level of polyphenols. In the experimental studies, the basic mechanism of green tea polyphenols was to impair bone resorption while at the same time stimulating osteoblast activity.[170-172] This effect would have tremendous significance if confirmed in human clinical trials.

THERAPEUTIC APPROACH

The most effective approach to osteoporosis is prevention. The risk of developing osteoporosis may be reduced by optimizing peak bone mass in the younger years and minimizing subsequent bone loss in elderly women. In order to maximize peak bone mass (even in the context of hereditary and other nonmodifiable risk factors), lifestyle, proper nutrition with a whole-foods diet, and moderate exercise should begin during childhood and adolescence; thereafter the avoidance of smoking and excessive alcohol consumption should be added to this regimen and continue throughout life. The physician is encouraged to maintain a key interest in dietary habits that promote optimal bone health and include nutritional supplementation that may lower patients' risk and provide optimal bone strength, bone architecture, and bone density, thus reducing the risk of fractures later in life.

Numerous modifiable and non-modifiable factors influence the risk of developing osteoporosis. For the majority of women, osteoporosis is a preventable illness if dietary and lifestyle measures are implemented. Lifestyle modifications and nutrient supplementation may reduce the risk of osteoporosis and the associated debilitating fractures in many women but not all. For women who have already been diagnosed with osteoporosis, these nutritional and lifestyle factors can serve as an adjunct to conventional therapies to slow bone loss and, more importantly, decrease the risk of fractures.

The primary goals are the prevention of excessive bone loss and reduction of risk for fractures. In cases of actual osteoporosis (vs osteopenia), the recommendations given in this chapter should be used in conjunction with appropriate medical care, which may include the use of various prescription drugs.

Exercise

Weight-bearing exercise four times a week plus strength training/weight training two or more times a week is recommended.

Habits

- Intake of less than seven units of alcohol per week
- Avoidance of smoking and secondhand smoke
- Implementation of measures to prevent falls

Diet

A balanced diet with a particular focus on adequate protein, daily soy isoflavones, green leafy vegetables, adequate calcium and vitamin D, vitamin K, and magnesium. A holistic approach also recommends that patients avoid dietary factors that promote calcium excretion, such as salt, sugar, excessive protein, and soft drinks.

Supplements

- High-potency multiple-vitamin-and-mineral formula
- Key individual nutrients:
 - Calcium: 1000 mg/day
 - Magnesium: 350 to 500 mg/day.
 - Vitamin D_3: 2000 to 5000 IU a day (ideally measure blood levels and adjust dose accordingly)
 - Vitamin B_6: 25 to 50 mg/day
 - Folic acid: 800 mcg/day
 - Vitamin B_{12}: 800 mcg/day
 - Vitamin K_2 (MK-7): 100 mcg/day
- Fish oils: 1000 mg EPA+DHA a day
- Soy isoflavonoids: 90 mg/day; or Ipriflavone: 600 mg/day
- Strontium: 170 to 680 mg/day (please read discussion above)

Botanical Medicine

- Green tea: Either 3 to 5 cups per day or a take a green tea extract that provides 250 to 300 mg polyphenols (also referred to as catechins) a day.

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CHAPTER 195

Otitis Media

Pina LoGiudice, ND, LAc

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

Acute otitis media is characterized by the following:
- Earache or irritability
- History of recent upper respiratory infection or allergy
- Red, opaque, bulging eardrum with loss of the normal features
- Fever and chills

Chronic or serous otitis media is characterized by the following:
- Painless hearing loss
- Dull, immobile tympanic membrane

GENERAL CONSIDERATIONS

Otitis media occurs as a result of inflammation, swelling, or infection of the middle ear. Otitis media is of two types: chronic and acute.

Acute otitis media is usually preceded by an upper respiratory infection or allergy. The organisms most commonly cultured from middle ear fluid during acute otitis media include *Streptococcus pneumoniae* (40%-50%), *Haemophilus influenzae* (30%-40%), and *Moraxella catarrhalis* (10%-15%). Chronic otitis media—also known as serous, secretory, or nonsuppurative otitis media; chronic otitis media with effusion; and "glue ear"—involves a constant swelling of the middle ear.

Acute otitis media affects two thirds of American children by 2 years of age, and chronic otitis media affects two thirds of children younger than the age of 6.[1] Otitis media is the most common diagnosis in children and is the leading cause of all visits to pediatricians. It is the main reason for antibiotic and surgical interventions in kids. Children diagnosed with otitis media during infancy are also at greater risk for developing late-onset atopy, such as allergic eczema and asthma during the school-age years. The more frequent the otitis, the stronger these associations.[2] A conservative estimate is that approximately $4 billion to $8 billion is spent annually on the medical and surgical treatment of earache in the United States.

Standard Medical Treatment

The standard medical approach to otitis media in children is to administer antibiotics, analgesics (e.g., acetaminophen), or antihistamines. If the ear infection is long standing and unresponsive to the drugs, surgery is performed. The surgery involves the placement of a tiny plastic myringotomy tube through the eardrum to facilitate the normal drainage of fluid into the throat via the eustachian tube. It is not a curative procedure, since children with myringotomy tubes in their ears are in fact more likely to have further problems with otitis media.

Myringotomies are currently being performed in nearly 1 million American children each year. It appears that the unnecessary surgery of the past, the tonsillectomy, has been replaced by this new procedure. In fact, there is a direct correlation between the decline of the tonsillectomy and the rise of the myringotomy. More than 2 million myringotomy tubes are inserted into children's ears each year in addition, there are also 600,000 tonsillectomies and adenoidectomies. These surgeries are unnecessary for most children.

A 1994 evaluation of the appropriateness of myringotomy tubes in children younger than 16 years of age in the United States found that only 42% were judged to have been appropriate.[3] These results mean that several hundred thousand

children are subjected to a procedure that will do them little good and possibly significant harm.

A number of well-designed studies have demonstrated that there were no significant differences in the clinical course of acute otitis media when conventional treatments were compared with placebo. Specifically, no differences were found between nonantibiotic treatment, ear tubes, ear tubes with antibiotics, and antibiotics alone.[4-8] Interestingly, in some studies children not receiving antibiotics did have fewer recurrences than those receiving antibiotics. This reduced recurrence rate is undoubtedly a reflection of the suppressive effects antibiotics have on the immune system while also disturbing the normal flora of the upper respiratory tract.[9]

Because most children with acute otitis media (70%-90%) have spontaneous resolution within 7 to 14 days, antibiotics should not initially be routinely prescribed for all children.[8,10] Extensive reviews of the scientific literature on the value of antibiotics in the treatment of otitis media over the past 30 years have led to the following conclusions:

- The benefit of routine antimicrobial use for otitis media, judged by either short- or long-term outcomes, is unproved.
- Existing research offers no compelling evidence that children with acute otitis media routinely given antimicrobials have a shorter duration of symptoms, fewer recurrences, or better long-term outcomes than those who do not receive them.
- Although the prevention of mastoiditis and meningitis is a rationale for antimicrobial treatment, little evidence exists that routine treatment is effective for this purpose.
- Antimicrobials did not improve outcome at 2 months, and no differences in rates of recovery were found for either antimicrobial type or duration.

Whereas these results have been accepted by some U.S. pediatricians, others still rely heavily on antibiotics to treat otitis media. Instead of antibiotics, the recommendation from this group of experts was to use analgesics (e.g., acetaminophen) and for the caregiver to keep a close watch. Results of clinical trials have shown that more than 80% of children with acute otitis media respond to a placebo within 48 hours. Although analgesics may be of use to limit the child's pain, they have their own toxicity profile. We therefore recommend other proved pain-relieving options like botanical eardrops as a replacement analgesic (see later).

Apart from the fact that antibiotics are not very effective in otitis media, their widespread use and abuse is becoming increasingly alarming. Risks of antibiotics include allergic reactions, gastric upset, accelerated bacterial resistance, and unfavorable changes in nasopharyngeal bacterial flora. Antibiotics not only fail to eradicate the organisms but can induce middle-ear superinfection. Moreover, antibiotic prescribing can increase the rate of return office visits and the likelihood of seeking medical care for future illness.[11] Additionally, studies on concomitant antibiotic and steroid treatment have revealed poor results on long-term efficacy for chronic otitis media.[12]

Antibiotics are encouraging the near-epidemic proportion of chronic candidiasis sufferers as well as the development of "superbugs" that are resistant to currently available antibiotics. The position of the American Academy of Otolaryngology–Head and Neck Surgery states that there is no evidence indicating that systemic antibiotics alone can improve treatment outcome and that these agents should not be used save the situation of an underlying systemic infection.[13] According to many experts as well as the World Health Organization, we are coming dangerously close to arriving at a "postantibiotic era" in which many infectious diseases will once again become almost impossible to treat because of an overreliance on antibiotics (see Chapter 56 for further information).[14]

The bottom line is that otitis media is normally a self-limited disease. It normally remits on its own regardless of treatment. High rates of spontaneous resolution have been well documented in the medical literature. Three meta-analyses independently found that approximately 80% of children with acute otitis media had spontaneous clinical relief within 2 to 14 days. Some studies of children younger than 2 years of age do suggest a lower spontaneous resolution of about 30% after a few days.[11]

The risks and failure with antibiotics, when coupled with the high rate of spontaneous resolution and the high recurrence rate of otitis media following the insertion of ear tubes, suggest that conservative (nonantibiotic, nonsurgical) treatment alone would reduce the incidence of otitis media and decrease the associated yearly financial costs. To examine this concept, the authors of one clever study gave the caregivers of children with nonsevere acute otitis media a "safety prescription" of antibiotics to be filled only if there was no improvement within 2 days. This method of "wait and see" reduced median antibiotic prescriptions by 31%, compared with 12% in a control practice.[15]

Although standard antibiotic and surgical procedures may not be statistically effective, each child must be evaluated individually and appropriate follow-up including physician-family communication should be devised and assured before a decision not to use these procedures is made. Special circumstances in the interest of preventing hearing loss–induced developmental delays would suggest a more appropriate use of ear tubes.

Finally, pneumococcal and viral vaccines have been designed but have also shown little benefit, probably due to the multifactorial nature of this condition.[11] Given the inherent risks and complications, vaccinations do not appear to be warranted at this time.

Causes

The primary risk factors for otitis media are as follows[1]:

- Day care attendance
- Wood-burning stoves
- Parental smoking or exposure to other secondhand smoke
- Food allergies
- Not being breastfed
- Pacifier use[11]
- Previous antibiotic use
- Winter season
- Underlying rhinitis, cleft palate, and Down syndrome

All of these factors share a common mechanism—abnormal eustachian tube function, the underlying cause in virtually all cases of otitis media. The eustachian tube regulates gas pressure in the middle ear, protects the middle ear from nose and throat secretions and bacteria, and clears fluids from the middle ear. Swallowing causes active opening of the eustachian tube owing to the action of the surrounding muscles. Infants and small children are particularly susceptible to eustachian tube problems because in them the tube is smaller in diameter and more horizontal.

Obstruction of the eustachian tube leads first to fluid buildup and then, if the bacteria present are pathogenic and the immune system is impaired, to bacterial infection. Obstruction results from collapse of the tube (due to weak tissues holding the tube in place, an abnormal opening mechanism, or both), blockage with mucus in response to allergy or irritation, swelling of the mucous membrane, or infection.

Otitis media may also have a genetic component; in twin studies, monozygotic twins tend to have a higher concordance rate in

otitis media histories than dizygotic twins.[11] Although immunoglobulin markers[16] and human leukocyte antigen (HLA)[17] have also been a focus of research, no specific genetic associations have been elucidated thus far. Research has also shown that children with blood type A have about a 50% higher rate of infection and are susceptible to more severe and repeated bouts of ear infection. Children whose mothers are blood type A who have ear infections before 1 year of age have a relatively greater risk of having recurrent ear infections of an astounding 2677%.[18]

THERAPEUTIC CONSIDERATIONS

The primary treatment goals are to ensure patency of the eustachian tubes and to promote drainage by identifying and addressing causative factors. Supporting the immune system is also important. The recommendations that follow should be used along with recommendations for immune support given in Chapter 56.

Bottle-Feeding

Recurrent ear infection is strongly associated with early bottle-feeding, whereas breast-feeding (for a minimum of 3 months) has a protective effect.[19,20] Whether this is due to cow's milk allergy or to the protective effect of human milk against infection has not yet been conclusively determined. It is probably a combination.

In addition, bottle-feeding while a child is lying on his or her back (bottle-propping) leads to regurgitation of the bottle's contents into the middle ear and should be avoided.

Whatever the "causative" organism in otitis media—viral (respiratory syncytial virus, rhinovirus, or influenza A) or bacterial *(S. pneumoniae, M. catarrhalis,* or *H. influenzae)*—human milk offers protection owing to its high antibody content, which helps to inhibit infectious agents.[21] A breast-fed infant's thymus gland (the major organ of the immune system) is also roughly 20 times larger than that of a formula-fed infant.[22]

Food Allergy

The role of allergy as the major cause of chronic otitis media has been firmly established in the research literature.[23-28] Since the previous publication of this textbook, eight clinical studies have shown similar results. Most studies show that 85% to 93% of these children have allergies: 16% to inhalants only, 14% to food only, and 70% to both.

One way in which prolonged breast-feeding prevents otitis media may be by the avoidance of food allergies, particularly if the mother avoids sensitizing foods (i.e., those to which she is allergic) during pregnancy and lactation. In addition to breast-feeding, also of value is the exclusion or limited consumption of the foods to which children are most commonly allergic—wheat, egg, peanuts, corn, citrus, chocolate, and dairy—particularly during the first 9 months.

Because a child's digestive tract is quite permeable to food antigens, especially during the first 3 months, careful control of eating patterns (no frequent repetitions of any food, avoidance of the common allergenic foods, and the introduction of new foods in a controlled manner—that is, by introducing one new food at a time and carefully watching for a reaction) will reduce and prevent the development of food allergies.

An allergic reaction causes blockage of the eustachian tube by two mechanisms: inflammatory swelling of the mucous membranes lining the tube and inflammatory swelling of the nose, causing the "Toynbee phenomenon" (swallowing when both mouth and nose are closed, forcing air and secretions into the middle ear). The middle and inner ear are immunologically responsive, and this includes responsiveness to food hypersensitivities.[29] In chronic earaches, an allergic cause should always be considered and the offending allergens determined and avoided.

One illustrative study of 153 children with earaches demonstrated that 93.3% of the children (using the radioallergosorbent test for diagnosis—see Chapters 15 further discussion) were allergic to foods, inhalants, or both. When 119 of these children were treated with serial dilution titration therapy for inhalant sensitivities and an elimination diet for food allergens, 92% had improved after 12 months. This outcome compares favorably with that of the surgically treated control group (ear tubes and, as indicated, removal of the tonsils and adenoids), which showed only a 52% response.[23]

In another study, a total of 104 children ranging in age from 1.5 to 9 years with recurrent otitis media were evaluated for food allergy by means of skin-prick testing, specific IgE tests, and food challenges.[28] Results indicated a statistically significant association between food allergy and recurrent otitis media in 81 of the 104 patients, or 78%. The elimination diet led to a significant amelioration of chronic otitis media in 70 of 81 patients, or 86%, as assessed by detailed clinical evaluation. The challenge diet with the suspected offending foods provoked a recurrence of serous otitis media in 66 of 70 patients, or 94%.

The frequency distribution of allergies to individual foods is listed in Table 195-1, and the frequency distribution according to number of food allergens is listed in Table 195-2.

Reflux

Preliminary studies strongly suggest a link between gastroesophageal reflux disease in infants and young children with otitis media. Studies suggest significant improvements in disease burden from otitis media and hearing loss with acid-blocking drug

TABLE 195-1 **Food Allergy in Children With Chronic Otitis Media**

FOOD	NO. OF PATIENTS	PERCENTAGE OF PATIENTS
Cow's milk	31	38
Wheat	27	33
Egg white	20	25
Peanuts	16	20
Soy	14	17
Corn	12	15
Tomatoes	4	5
Chicken	4	5
Apple	3	4

TABLE 195-2 **The Frequency Distribution According to Number of Food Allergens**

NO. OF FOOD ALLERGENS	PATIENTS/TOTAL	PERCENTAGE
1	11/81	13.6
2-4	66/81	81.5
5-7	3/81	3.7
8-10	1/81	1.3

therapy. In one study, 47 patients 6 months to 7 years of age, average age 18.5 months, were prescribed a 15-mg dose of lansoprazole in the morning and, depending on age, ranitidine (4 mg/kg per day) or nizatidine (5 mg/kg per day) at bedtime. The Pediatric Reflux Finding Score, which is used to assess the severity of extraesophageal reflux via fiberoptic laryngoscopy, showed significant improvements at visits two and three. Of note, although there were improvements, there was also a high dropout rate in this study, possibly owing to medication side effects.[30]

From a naturopathic standpoint, the idea that digestive function plays a role in otitis media is important. Although the use of the medications mentioned above is not recommended, the use of treatments such as food allergy avoidance, a focus on healthful foods, and measures to support digestive health are likely to produce similar positive effects.

Thymus Gland Extract

The thymus gland secretes a family of hormones that act on white cells to ensure their proper development and function. Studies with calf thymus extracts given orally have demonstrated impressive clinical results in various clinical conditions in children.[31-33] Specifically, thymus extracts have been shown to improve immune function, decrease children's food allergies, and improve a child's resistance to chronic respiratory infections. Thymus extracts may be of particular benefit in chronic otitis media. For more information, see Chapter 56.

Naturopathic Ear Drops

Even though most cases of otitis media resolve spontaneously, often otalgia (ear pain) can persist during the period of improvement, sometimes motivating anxious parents to request unnecessary antibiotic therapy. Naturopathic botanical ear drops have been shown to be as effective as either antibiotic and anesthetic drops[34,35] and offer a much less toxic approach to pain management.

In a double-blind outpatient trial,[34] one group from Israel studied 171 children ages 5 to 18 who were randomly assigned to receive treatment with naturopathic herbal extract ear drops (NHEDs) or anesthetic ear drops (amethocaine and phenazone) with or without amoxicillin (80 mg/kg/day). The plant medicine was a combination of *Calendula officinalis* flowers (marigold, 28%), *Hypericum perforatum* complete herb (St. John's wort, 30%), and *Verbascum thapsus* flowers (mullein, 25%) in olive oil with the essential oils *Allium sativum* (garlic, 0.05%) in olive oil (10%), *Lavendula officinalis* (lavender, 5%), and tocopherol acetate oil (vitamin E, 2%); it was dosed at 5 drops three times daily. All groups had a statistically significant improvement in ear pain over the course of the 3 days, with a 95.9% reduction in the NHED-alone group. The NHED plus antibiotics produced a 90.9% diminution in pain. The anesthetic alone and anesthetic with antibiotics produced 84.7% and 77.8% reductions, respectively.

Although this was a notable study, we would like to see future studies designed with a control as well, because this study does not confirm whether the improvements are superior to the passage of time alone. Furthermore, this study does not address the sometimes more refractory management of children below 5 years of age. Nevertheless, given the positive outcomes in this study and significantly lower toxicity profile than those of conventional antibiotic or anesthetic medications, naturopathic eardrops are clearly the superior choice for children with ear pain–associated otalgia. As a side note, there are numerous other botanical anodynes not employed in this formula that would be worthy of study as well.

Echinacea

Echinachea is well known to treat upper respiratory infection, and in vitro studies of echinacea suggest a stimulatory effect of *Echinacea purpurea* preparations on various components of the cytokine cascade.[36] A few evaluations in adults see improvement in cold severity and duration,[37] whereas other studies do not show benefit.[38] One more recent analysis suggests that *Echinacea* shows no benefit and is associated with a borderline increased risk of infection compared with placebo. Despite randomization, this study did have notable disparities among treatment groups regarding frequency of confounding factors, including frequency of otitis media prior to study entry and day care attendance. The children on *Echinacea* in this study's sham manipulation group had double the incidence of upper respiratory infections in the previous year compared to the placebo arm and were 50% more likely to be in day care. These confounding factors are so significant that the study results are useless. As a monotherapy, *Echinacea's* efficacy is unclear. Given this botanical's long history of benefit, it is likely that it is a helpful ally in combination with other natural treatments.

Xylitol

Xylitol is a commonly used sweetener known mostly for its anticariogenic properties. It is a sugar alcohol derived mainly from birch and other hardwood trees and has demonstrated inhibition of *S. pneumoniae.* Two randomized trials illustrated xylitol's ability to reduce acute otitis media incidence by 40%. In one study[39] of 306 day care children with recurrent acute otitis media, 157 children were given xylitol (8.4 g/day) chewing gum and 149 children were given a sucrose control gum. During the 2 months of the trial, at least one event of acute otitis media was experienced by 20.8% of the children who received sucrose compared with only 12.1% of those receiving the chewing gum containing xylitol. Significantly fewer antimicrobials were prescribed among those receiving xylitol.

In a second randomized controlled blinded trial,[40] 857 healthy children were randomized to one of five treatment groups to receive control syrup, xylitol syrup, control chewing gum, xylitol gum, or xylitol lozenges. The daily dose of xylitol varied from 8.4 g (chewing gum) to 10 g (syrup). The design was for 3 months. Although at least one event of otitis was experienced by 41% of the 165 children who received control syrup, only 29% of the 159 children receiving xylitol syrup were affected. Likewise, compared with control subjects, the occurrence of otitis decreased by 40% in the children who received xylitol chewing gum and 20% in the lozenge group. Thus, the occurrence of acute otitis media during the follow-up period was significantly lower in those who received xylitol syrup or gum, and these children required antimicrobials less often than did controls.

As a note, xylitol has been criticized as a practical method because the studies suggest that dosing needs to be four to five times per day, which may decrease compliance and therefore overall effectiveness. Although two children in the xylitol group experienced diarrhea, no other untoward effects were reported for this safe and useful treatment.

Sinupret

Sinupret is an herbal combination originating in Germany that consists of sorrel (aerial) *(Rumex acetosa)* 36 mg, European elder (flower) *(Sambucus nigra)* 36 mg, Cowslip (flower with calyx) *(Primula veris)* 36 mg, European vervain (aerial) *(Verbena officinalis)* 36 mg, and (gentian (root) *(Gentiana lutea)* 12 mg.

One study of 64 children evaluated 32 children using amoxicillin alone and 32 using amoxicillin plus Sinupret. The Sinupret seemed to have more effective antibiotic properties and reduced the frequency of complications.[41] A second integrative study of 40 children with a mean age of 4.5 years found similar results.[42] This herbal combination may be a reasonable choice for children already started on antibiotic medication.

Vitamin A

Vitamin A plays a role in the prevention of oxidative tissue damage, immune system function, and mucous membrane integrity. Although it has not been studied in children, animal studies have shown that pretreatment with vitamin A before *S. pneumoniae* inoculation conferred protection by increasing antioxidant enzyme activity and reducing the formation of malondialdehyde and nitric oxide.[43]

Humidifiers

Humidifiers are popular treatments for otitis media and upper respiratory tract infections in children. According to a 1994 study that evaluated the role of low humidity in this disorder, this may be justified.[44] Using a rat model, the study examined the effect of low humidity on the middle ear. Twenty-three rats were housed for 5 days in a low-humidity environment (10%-12% relative humidity) and 23 control rats were housed at 50% to 55% relative humidity. Microscopic ear examinations were graded for otitis media before testing and on test days 3 and 5. The lining of the middle ears and eustachian tubes were examined by biopsy. Significantly more effusions (fluid in the rustachian tubes) were observed in the low-humidity group on both days 3 and 5, but biopsy results were similar in both groups.

This study indicates that low humidity may be a contributing factor in otitis media. Possible explanations are that low humidity may induce nasal swelling and reduce ventilation of the eustachian tube, or that it may dry the eustachian tube lining, which could lead to an inability to clear fluid as well as to increased secretions. The mast cells residing in the lining of the eustachian tubes may also come into play by releasing histamine and producing swelling.

Although preliminary, this research indicates that increasing humidity with the help of a humidifier may be an important goal in the treatment of otitis media with effusion.

Osteopathic Manipulation

One case study reports benefits of osteopathic manipulation to decrease the frequency of otitis media in children with recurrent disease,[45] whereas another randomized controlled trial using up to five osteopathic manipulative treatments over a 3-month period did not show benefit.[46] The osteopathic approach acknowledges abnormal structural dynamics, which can contribute to change in function. These dynamics may be modulated with cranial manipulative work.[47,48] In young patients with structural dysfunction, this may be a beneficial treatment in conjunction with other therapies suggested in this chapter.

Homeopathy

Homeopathy is an energetic medicine based on the law that "like cures like." Used extensively in Europe and India, homeopathy is gaining some acceptance as a viable, nontoxic, individualized option to treat various conditions. Research regarding its use is beginning to build up.

One randomized double-blind placebo-controlled pilot study was conducted in a private pediatric practice with 75 children aged 18 months to 6 years. All had had middle ear effusion and ear pain, fever, or both for no more than 36 hours. Each child received either an individualized homeopathic medicine or a placebo three times daily by mouth for 5 days or until symptoms subsided. Results demonstrated a statistically significant decrease in symptoms using homeopathy over placebo and nonstatistically significant fewer treatment failures in the group receiving homeopathy.[49]

Similarly, a second study found excellent results regarding the homeopathic pain reduction rate; that is, pain was reduced by almost 2½ times over placebo controls, with 39% of the patients improving after 6 hours and another 33% after 12 hours. A follow-up study using a different homeopathic agent was given if results were not seen in the first 6 hours.[50] A German prospective study has also found comparable results in evaluating homeopathic treatment versus conventional therapies.[51]

More clinical trials are necessary to elucidate the optimal uses of homeopathy. In the meantime, homeopathy is proving to be an effective and extremely safe option to consider in the treatment of otitis media.

THERAPEUTIC APPROACH

The key factor in the natural approach to chronic otitis media in children appears to be the recognition and elimination of allergies, particularly food allergies, as well as support for the immune system and digestive function.

Diet

Because it is usually not possible to determine the exact allergen during an acute attack, the most common allergic foods should be eliminated from the diet:

- Milk and other dairy products
- Eggs
- Wheat
- Corn
- Oranges
- Peanuts
- Chocolate

The diet should also eliminate concentrated simple carbohydrates (e.g., sugar, honey, dried fruit, concentrated fruit juice), because they inhibit the immune system. These simple dietary recommendations bring relief to most children in a matter of days.

Nutritional Supplements

- Children's multivitamin and mineral formula
- Vitamin A: 50,000 IU/day for up to 2 days in children below 6 years of age and 4 days in children above age 6
- Beta-carotene (natural mixed carotenoids): age in years × 20,000 IU/day (up to 200,000 IU/day)
- Vitamin C: age in years × 50 mg every 2 hours
- Bioflavonoids: age in years × 50 mg every 2 hours
- Zinc: age in years × 2.5 mg a day (up to 30 mg)
- Thymus extract: the equivalent of 120 mg pure polypeptides with molecular weights less than 10,000 or roughly 500 mg of the crude polypeptide fraction a day

Botanical Medicines

- *Echinacea* species: Onehalf the adult dosage is appropriate for children younger than 6 years of age; the full adult dosage (given later) is appropriate for children above age 6 (*Echinacea* is safe for children). The following doses can be given up to three times a day:
 - Dried root (or as tea): 0.5 to 1 g
 - Freeze-dried plant: 325 to 650 mg
 - Juice of aerial portion of *Echinacea purpurea* stabilized in 22% ethanol: 2 to 3 mL
 - Tincture (1:5): 2 to 4 mL
 - Fluid extract (1:1): 2 to 4 mL
 - Solid (dry powdered) extract (6.5:1 or 3.5% echinacoside): 150 to 300 mg
- Xylitol: approximately 8 g/day as either chewing gum chewed throughout the day or 10 g of the syrup per day in divided doses
- Naturopathic eardrop formula: five drops in the affected ear three times daily
- Sinupret: as adjunctive treatment when antibiotics are employed
- Consider cranial manipulative work

Physical Medicine

Local application of heat is often helpful in reducing discomfort. It can take the form of a hot pack, the application of warm oil (especially mullein oil), or by blowing hot air into the ear with the aid of a straw and a hair dryer. These treatments help to reduce pressure in the middle ear and promote fluid drainage.

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CHAPTER 196

Parkinson's Disease

Laurie K. Mischley, ND, Kelly Jennings, ND, MSOM, LAc, Peter B. Bongiorno, ND, LAc, and Pina LoGiudice, ND, LAc

DIAGNOSTIC SUMMARY

Motor symptoms are considered cardinal in Parkinson's disease (PD)[1]:

- Tremor—The most common parkinsonian feature is a resting tremor, maximal when the limb is at rest and diminishing with voluntary movement and sleep. The tremor affects to a greater extent the most distal part of the extremity; it is typically unilateral at onset, becoming bilateral as the disease progresses. Approximately 30% of PD sufferers do not have tremor at disease onset, yet most develop it as disease progresses.
- Joint stiffness and increased muscle tone—Combined with a resting tremor produces a ratchety "cogwheel rigidity" when the limb is passively moved.
- Slow movement (bradykinesia) or inability to move (akinesia)—Produces difficulties not only with the execution of a movement but also with the planning and initiation of movement. Performance of sequential and simultaneous movements is also hindered. For many, bradykinesia is the most disabling symptom in the early stages of PD.[2]

Other common motor symptoms[1]:

- Postural instability is typical in the late stages of PD, leading to impaired balance and frequent falls. It is often absent in the initial stages of disease, especially in younger patients.
- "Pill rolling" motion of the thumb and forefinger.
- Stooped posture, progressively shortened and accelerated steps that get progressively faster and may end up in a fall ("festinating gait").
- Reduced or fixed facial expressions ("masked face"); low-volume or monotone voice or both.
- Small handwriting (micrographia) that decreases in size toward the end of a writing sample.
- Gastrointestinal symptoms: Constipation is often one of the earliest symptoms, with difficulty swallowing (dysphagia) common later in the disease course.

Neuropsychiatry

- Cognitive disturbances are being increasingly recognized as symptoms of PD. Although they can occur early in PD, cognitive deficits progress with the course of disease, leading to dementia in about 80% of cases,[3,4] by the tenth year. Most common cognitive deficits include the ability to make decisions and adapt to new environments, poor problem solving, fluctuations in attention, slowed cognitive speed, and memory problems—specifically in recalling learned information, with an important improvement when cues are given.
- Alterations in behavior and mood, including depression, apathy, and anxiety. Poor impulse control can result in behaviors such as punding, binge eating, craving, hypersexuality, or pathologic gambling. These are likely related to a dopamine dysregulation syndrome often associated with the medications for PD.[1]
- Psychotic symptoms, such as hallucinations or delusions, can be common in later PD.[1]

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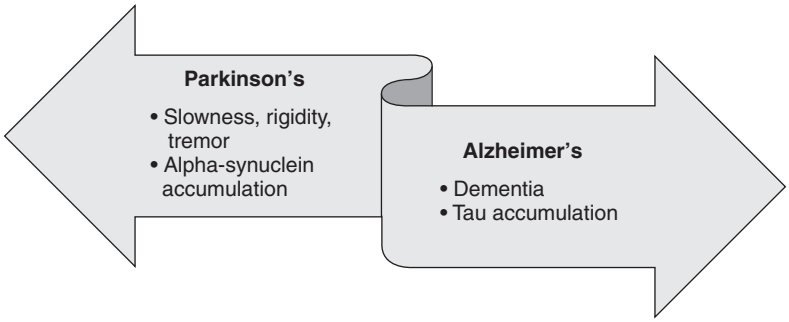


FIGURE 196-1 Characteristics of Parkinson's disease and Alzheimer's disease.

GENERAL CONSIDERATIONS

Epidemiology

First described by James Parkinson in 1817, PD occurs in approximately 0.3% of the general population and about 1% of the population older than 60 years of age in industrialized countries.[2,5]

This progressive neurologic disorder results from a deterioration of neurons in the substantia nigra. This creates a shortage of the neurotransmitter dopamine, causing the impairments that characterize the disease. People with PD often experience limb tremor, muscle rigidity, difficulty walking, and problems with balance and coordination. According to the Parkinson's Disease Foundation, PD affects more than 7 million people worldwide and at least 1 million in the United States.[5] About 50,000 new cases are reported annually in the United States. These figures are expected to increase as the average age of the population increases. The disorder appears to be slightly more common in men than women, with whites being 1.5% more likely to contract PD than African or Asian populations in industrialized countries.

The prevalence and incidence of PD rise with age, with the average age at onset being approximately 60 years. Because PD is a disease of the aged, disease rates are low in people below age 40. PD is found in many geographic regions of the world and rates vary from country to country.

Pathophysiology

As with most neurodegenerative diseases, oxidative and nitric oxide stress, inflammation, and mitochondrial dysfunction are the primary contributors to cell death. A decrease in glutathione concentrations, the brain's primary antioxidant, is the earliest reported biochemical event to occur in the parkinsonian substantia nigra. Mitochondrial dysfunction has been implicated ever since it was observed that an inhibitor of complex I of the electron transport chain can induce parkinsonism. Recent research indicates that several PD-associated genes interface with pathways regulating mitochondrial function, morphology, and dynamics. Sporadic and familial PD may converge at the level of mitochondrial integrity.[6]

The primary pathology of PD is the degeneration of brain cells, or neurons, in the substantia nigra pars compacta of the brain. These neurons produce dopmine, a critical signaling molecule. The loss of dopamine results in a profound and multifaceted disruption of normal information flow through the basal ganglia. Pathologically, Lewy bodies are considered the hallmark of classic PD. Found in the substantia nigra, Lewy bodies are abnormal accumulations of α-synuclein, a normal cellular protein that has been marked for degradation by the ubiquitin complex but appears to have escaped the normal degradation process. The presence of Lewy bodies cannot be used as a diagnostic criterion because they can be seen only at autopsy. Autopsies have uncovered Lewy bodies in a surprising number of older persons without a diagnosis of PD. Unfortunately, symptoms do not occur until the nervous system's "reserve" has been exhausted and significant nervous system damage has already occurred. It is estimated that more than 50% of the substantia nigra has been lost by the time the diagnosis of PD is made.

Several neurodegenerative disorders have excessive protein deposition as a common pathophysiologic mechanism; the primary differences being the location of deposition and/or the protein(s) that accumulate (Figure 196-1).

Substantia Nigra Cell Death

Apoptosis accounts for much of the pathology seen in PD as well as in diseases like Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis (Lou Gehrig's disease), which are marked by the loss of brain neurons. Elevated apoptosis in these neurologic diseases seems to be related to a lack of production of nerve growth factor and to free radical damage. A combination of such factors could likely cause many cells to destroy themselves. Manipulation of this process of apoptosis may help in treating these neurologic diseases. In fact, studies in animal models imply that long-term delivery of nerve growth factors could protect against programmed cell death in these conditions.[7-9] Until the mechanisms of apoptosis are elucidated, some natural therapeutics that may decrease programmed cell death, such as melatonin therapy, may be of benefit in PD (see further discussion of melatonin later).

Oxidative Stress and Glutathione Deficiency

Biochemical changes including increased levels of neurotoxic metals, the inhibition of mitochondrial complex I activity, and depleted glutathione levels occurring in the substantia nigra[10] all suggest that oxidative stress is present and pathologically involved in PD patients.[11] Using healthy patients as a control, studies in patients dying from PD have observed 40% reduced glutathione levels in these patients, whereas oxidized glutathione was insignificantly marginally elevated.[12] Depletion of glutathione levels in the brain may be an early component of the disease process, because these suboptimal levels have also been found to occur in presymptomatic PD, also known as incidental Lewy body disease.[13]

Some researchers are finding that this glutathione deficiency may be a common denominator in all parkinsonian conditions associated with nigral damage.[10] Although not completely elucidated, it is known that glutathione exhibits several functions in the brain by acting as an antioxidant and a redox regulator. Glutathione depletion has been shown to affect mitochondrial function probably via selective inhibition of mitochondrial complex I activity. Oxidative damage due to glutathione depletion may also

encourage the aggregation of defective proteins, leading to cell death of nigral-striatal dopaminergic neurons.[11]

Glutathione depletion may enhance the susceptibility of substantia nigra to destruction by endogenous or exogenous toxins. Restoring antioxidant levels within the brain may be a valuable therapeutic strategy for PD.[10]

Environmental Exposures

Epidemiologic studies and animal experimental models have identified an association between PD and the following environmental risk factors: rural residence, farming, well-water drinking, exposure to pesticides (including organochlorines, carbamates, paraquat, maneb, rotenone, and diethyldithiocarbamate), and long-term occupational exposure to copper, iron, lead, and manganese.[14] Additionally, it is possible that the pesticides and metals act synergistically with other exposures to increase the risk of PD.[15-18] Another example of environmental exposure is iatrogenic parkinsonism caused by exposure to central dopamine antagonists. The literature for these associations is provided below.

MPTP

The first hint that PD may be related to an environmental toxin came from a report based on a series of patients who developed parkinsonism after exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a contaminant found in synthetic heroin.[19] It was found that MPTP can freely cross the blood–brain barrier, is selectively taken up by dopaminergic cells, and inhibits mitochondrial complex 1 function in the respiratory chain, an established factor in the PD pathophysiology.[20] MPTP is the only environmental agent that has been directly linked to the development of levodopa-responsive parkinsonism, a form that is clinically indistinguishable from PD.[1]

Rotenone

Rats exposed to the organic pesticide rotenone develop parkinsonian symptoms as well as changes in the brain resembling those seen in PD in humans. Mimicking the effect of MPTP, rotenone works by inhibiting complex I of the mitochondrial respiratory chain. It was observed that chronic, systemic inhibition of mitochondrial complex I by the lipophilic pesticide rotenone can cause highly selective nigrostriatal dopaminergic degeneration that is associated behaviorally with hypokinesia and rigidity. Additionally, nigral neurons in rotenone-treated rats accumulate fibrillar cytoplasmic inclusions that contain ubiquitin and α-synuclein.[21] These inclusions are the major constituent of intracellular protein inclusions forming the Lewy bodies and Lewy neuritis in dopaminergic neurons of the substantia nigra. Other studies have also shown that chronic administration of rotenone over a long period can increase nitric oxide and lipid peroxidation products in the brain cortex and striatum in rats, which then clearly mimic parkinsonian behavioral symptoms such as akinesia and rigidity.[22] Interestingly, rotenone is a natural pesticide and until *very recently* was allowed to be used in organic produce.

A 2009 case-controlled multicenter study analyzed the effect that occupation had on PD risk. Occupational pesticide exposure emerged as the most consistent etiologic association with parkinsonism. In experimental settings, the three specific pesticides identified (2,4-dichlorophenoxyacetic acid, paraquat, and permethrin) all have effects on dopaminergic neurons. This convergence of epidemiologic and laboratory data from experimental models of PD lends credence to a causative role of certain pesticides in the neurodegenerative process.[23]

Maneb and paraquat, two widely used pesticides, have been associated with PD. Researchers studied pesticide exposure in California's Central Valley and found that when people were exposed to both maneb and paraquat within 500 meters of their homes, their likelihood of being diagnosed with PD was substantially increased as compared with those without exposure. The majority of the risk for being diagnosed with PD was attributed to exposure between 1974 and 1989—and all those so exposed were then children, teenagers, or young adults. This group of people, who had younger-onset PD (meaning that they were diagnosed before the age of 60), were four to six times more likely to develop PD if they were exposed to both pesticides.[24]

Another 2007 study done in five countries in Europe also explored this association; 959 prevalent cases of parkinsonism and 1989 controls were questioned regarding lifetime occupational and hobby exposure to solvents, pesticides, iron, copper and manganese. Pesticide exposure and increased prevalence of PD suggest a causative role. Repeated traumatic loss of consciousness was also associated with increased risk.

Solvents

Some case-control studies and case reports have shown an association between solvent exposure and parkinsonism.[25] Records from a major United Kingdom engineering company were culled in order to explore the relationship of metal and solvent exposure and PD. The results of this survey demonstrated a significant exposure-response relationship for solvents and almost a 400% increase in risk for employees exposed for 30 years or more. This study suggests that sustained cumulative exposure is probably significant because there was no evidence of overall increase in risk for those exposed for shorter durations. The authors noted that possibly the more heavily affected workers experienced exposure before the introduction of stricter industrial environmental controls later in the twentieth century or exposure to older solvents such as trichloroethylene, 1,1,1-trichloroethane, carbon tetrachloride, kerosene, white spirit, and acetone, which were more widely used three or more decades ago and may have played a greater etiologic role.[26]

Although the study mentioned previously showed no increased risk of PD in relation to metal exposure, occupational exposure to specific metals—especially manganese, copper, lead, iron, mercury, zinc, and aluminum—appears, based on epidemiologic studies, to be a risk factor for PD.[27] Elevated levels of several of these metals have also been reported in the substantia nigra of PD subjects. Like pesticides, several divalent and trivalent metal ions are also found to contribute to accelerations in the rate of α-synuclein fibril formation. In one study, aluminum contributed to fibril formation, along with the chloride salts of copper^{2+}, iron^{3+}, cobalt^{3+} and manganese^{2+}.[27] Chronic mercury inhalation has also been linked to cortical and cerebellar atrophy, dementia, Parkinson's disease, and ataxia of the lower limbs.[28]

Manganese

Manganese toxicity is different than PD, but the two present very similarly. With toxicity, manganese-induced damage is found in the substantia nigra, globus pallidus, and caudate nucleus with depletion of dopamine and serotonin levels and has been linked to psychiatric changes followed by impaired motor activity with muscle rigidity and tremors.[14]

Welders, who are commonly exposed to substantial amounts of manganese, do not have a higher incidence of PD, but they do appear to develop the disease approximately 11 years before most other PD patients do. Other sources of manganese include well water and industrial waste. Unfortunately, it is not routine to assess

manganese levels in patients presumed to have PD, and little research has been done on chronic, low-level exposure to ambient manganese (i.e., from industrial waste.) As imaging techniques improve and become more readily available, it will be easier to differentiate manganism from PD.

Iron

Iron accumulation has been related to neurologic disorders such as Alzheimer's disease, PD, type I neurodegeneration with brain iron accumulation, and others. Increased levels of iron as well as accompanying lipid peroxidation combined with a decreased level of glutathione and superoxide dismutase activity are present in the substantia nigra of patients with PD.[11,29] Although it is unclear whether the accumulation of iron in the brain is primary or secondary to the development of neurodegenerative disorders,[30] one animal study has shown that unilateral injection of $FeCl_3$ into the substantia nigra of adult rats results in a 95% decrease of striatal dopamine, which impaired dopamine-related behavioral responses. This supports the assumption that iron may trigger the dopaminergic neurodegeneration of PD.[31]

Detoxification Dysfunction

The role of xenobiotic metabolizing enzymes (XMEs) in the disease etiology of PD has been under investigation by numerous researchers for the last two decades. The association of a number of defects in both phase I and phase II reactions with PD and motor neuron disease has been extensively studied. It has been demonstrated by in vivo or in vitro methods and by the functional genomics of XMEs and neurodegenerative diseases that PD and motor neuron disease (MND) can be associated with problems in xenobiotic metabolism; moreover, it appears that 38% to 39% of patients with MND/PD have a defect in the S-oxidation of the mucoactive drug carbocysteine by an unknown cytosolic oxidase. This implies that in a significant number of PD patients there may be an underlying dysfunction in the body's ability to detoxify.[32]

This dysfunction theoretically could lead to an increased vulnerability to neurotoxins following exposure to sulfur-containing substances.[33] Connections with Alzheimer's disease and other motor neuron diseases have also been made.[34] Certainly genetic determination is but one factor and must be looked at in light of the strong support that has been found for the roles of nutritional and environmental factors, discussed elsewhere in this chapter.[35]

DIAGNOSTIC CONSIDERATIONS

No diagnostic test can clearly identify PD. It is usually diagnosed by a neurologist who can evaluate symptoms and their severity. Often a proper diagnosis will depend on a thorough neurologic exam. Brain imaging as well as blood and urine tests can help to determine whether a patient has PD or another similar disorder.

THERAPEUTIC CONSIDERATIONS

Naturopathic philosophy prioritizes prevention of disease as the primary therapeutic strategy. This is especially difficult in PD, where the degenerative process begins about a decade before the symptoms of the disease are diagnosed. The slow, insidious nature of PD makes prevention and even early detection especially difficult. Conventionally, few efforts have been made to identify susceptible individuals, most likely because there are no established conventional neuroprotective agents; an individual identified as having a high likelihood of developing PD would be left to wait until symptoms appeared. Naturopathically, there are dozens of lifestyle modifications and nutraceuticals with preliminary data supporting their role in neuroprotection. With tools in hand, identifying those at risk for developing PD becomes practical and pressing. Immediate family members of those with PD are at increased risk, and symptoms such as restless legs syndrome, loss of smell, and constipation often precede the onset of tremor by several years; individuals with these symptoms are encouraged to consider the therapeutic strategies below.

Conventional Medicine

Unfortunately, no conventional therapy has been shown to modify the progressive pathology of degeneration in PD.[36] However, PD symptoms are somewhat treatable. For decades, the drug levodopa, commonly known as L-dopa, has been the mainstay of PD treatment. It is synthesized by the enzyme tyrosine hydroxylase from the food-derived aromatic amino acid tyrosine. Modern treatment combines L-dopa with a peripheral decarboxylase enzyme inhibitor to minimize conversion of L-dopa to dopamine outside the nervous system.[29]

Although initially effective in the early stages of the disease, L-dopa provides only symptomatic relief without altering disease progression, and it loses efficacy with time.[2] The side effects of L-dopa can include motor complications, particularly fluctuations and dyskinesias, as well as nausea, vomiting, orthostatic hypotension, sedation, hallucinations, and delusions; moreover, L-dopa contributes to decreased slow-wave peristaltic activity,[37] which may contribute to inadequate digestive function. It may also contribute to subtle detrimental effects on cognitive function[38] and may have a wide array of other psychiatric manifestations, such as propensity to gamble.[39] Responses to the drug may become more erratic over time. For these reasons, newer drugs are now also used either alone or in combination with L-dopa. Proper concomitant naturopathic care can drastically reduce the side effects of L-dopa. It is important to emphasize that in spite of the side effects, this drug is excellent for controlling symptoms and must be considered as part of the overall treatment plan.

After being virtually abandoned for 20 years, another allopathic treatment that is gaining more prominence is deep brain stimulation (DBS). DBS involves implanting a brain stimulator, a device similar to a heart pacemaker, in a certain area of the brain. The desired effect is to decrease the overactivity of the excitatory glutamatergic subthalamus–internal pallidum pathway caused by the loss of dopaminergic neurons within the substantia nigra. How DBS works is not well known, but it has been hypothesized that the stimulatory effect may modulate the neuronal activity and thus avoid disease-related abnormal neuronal discharges. Potential candidates for DBS are selected according to strict criteria. For some people, DBS may control symptoms so well that medications can be greatly reduced.[40]

Diet

Healthy dietary habits might be useful to treat and prevent PD. One large case-control study[41,42] revealed that PD patients tended to consume fewer raw vegetables, less alcohol and coffee, and more meat than control subjects. Patients with PD also reported higher carbohydrate consumption and equivalent intakes of protein and fat. Other researchers have shown an increased consumption of animal-source fat in patients with PD.[43-45] Although researchers need to learn more about how food choices relate to PD, a higher intake of vegetables and a low intake of fat seem to be reasonable choices in helping to prevent and possibly treat neurodegeneration.

Food Sources of L-dopa

Interestingly, certain foods are a good source of natural L-dopa. Anecdotal reports have demonstrated that patients with PD show improved symptom control when they are consuming meals of broad beans. In some cases the response to *Vicia faba* (fava beans) may be even greater than to conventional L-dopa medication. Fava beans are a good source of L-dopa: a 100-g serving of *V. faba* pods contains about 250 mg of l L-dopa, equivalent to the L-dopa content of one of the standard pharmaceutical formulations.[29] Until more is known about how to use fava beans as an L-dopa source, unsupervised replacement or coadministration of L-dopa with fava beans is not recommended.

Calorie Restriction

Overeating is a major modifiable risk factor for several age-related diseases, including PD. Calorie restriction (CR) is usually defined as 10% to 25% less caloric intake than the average Western diet. Throughout history, the majority of the world's population has struggled to obtain food. The *ability* to overeat is a relatively new phenomenon and, accordingly, the amount of food one should eat has only recently become a subject of study. In a primate model of PD, a CR diet (30% reduced) decreased the progression of PD. Animals that had been fed the reduced-intake diet had more dopamine in their brains and more glial-cell-line–derived neurotrophic factor (GDNF), a small protein that promotes the survival of neurons. GDNF's most prominent feature is its ability to support the survival of dopaminergic and motoneurons. The results suggest that CR extends life span and increases resistance of the brain to insults that involve metabolic compromise and excitotoxicity.[46] As opposed to the attempts at augmenting antioxidant levels using exogenously supplied antioxidants, which have been largely unsuccessful, one of the proposed mechanisms of CR is enhanced production of antioxidants via intrinsic pathways.[47] Given what is known about PD and CR, this theory is highly plausible and warrants further investigation.

Low-Protein Diet

For those patients taking L-dopa, a low-protein diet may be useful. One double-blind study compared a low-protein intake of 50 g/day for men and 40 g/day for women with a high-protein intake of 80 g/day for men and 70 g/day for women. By the end of the trial, total performance scores were significantly improved in the treatment group given lower protein intakes. Additionally, tremor, hand agility, and mobility in the low-protein groups also improved.[48]

Absorption of L-dopa is delayed or diminished by amino acids in protein meals.[38] It has been shown that the modification of meal patterns so that most of the protein intake occurs in the evening also improved symptoms.[48] It is therefore recommended that patients on L-dopa take their medication with a high-carbohydrate meal and delay protein intake until the final meal of the day so as to optimize the therapeutic efficacy of the medication.[29]

Antioxidants

Given the abundance of data suggesting that an excessive free radical burden contributes to PD, it is logical to consider antioxidant augmentation as a therapeutic target. Unfortunately, the PD-antioxidant research has been disappointing. One large well-designed study attempted to use high-dose vitamin E as a treatment, with no apparent improvement in symptoms or disease progression.[48a] A prospective study evaluated 76,890 women for 14 years and 47,331 men for 12 years. All the participants were health care professionals, mostly doctors and nurses. Every 2 to 4 years they filled out detailed surveys about their diets, including their vitamin intake from both foods and pills. A total of 371 people developed PD during the study. The investigators found that neither vitamin C nor carotenoid intake lowered the risk. The results were the same for the use of vitamin E supplements. This study seems to support the idea that vitamin E supplementation does not help to protect against PD. However, those participants who ate vitamin E–rich foods as parts of their diets curiously developed the fewest cases of PD.[49]

Glutathione

Given the importance of glutathione as a powerful brain tissue antioxidant, effective repletion should be a therapeutic priority. Combined intravenous and oral liposomal glutathione replacement is safe, well tolerated, and may offer a therapeutic benefit.[48] *N*-acetylcysteine and α-lipoic acid are glutathione precursors that may also be of use. As a systemic antioxidant, glutathione's ongoing repletion may help ameliorate PD-related damage to the heart, liver, muscles, and other organs as well. It is also recommended to take other antioxidants for synergistic support. Especially noteworthy is high-dose vitamin C, which provides antioxidant-reducing equivalents known to conserve glutathione.[48]

Vitamin D

Vitamin D, a fat soluble prohormone, has been linked to maintaining physiologic function as well as preventing diseases such as bone, cardiovascular, autoimmune, and neurologic disorders. Endogenous synthesis occurs in the skin with exposure to ultraviolet-B radiation, primarily from sunlight. Diet, such as fortified foods and certain fish, can also provide minor amounts of vitamin D. Deficiency can result from inadequate sun exposure, metabolic or absorption disorders, and other genetically influenced factors.

Patients with chronic neurodegenerative disease are at increased risk for vitamin D insufficiency due to advanced age, obesity, and decreased sun exposure. One study demonstrated that patients with PD were more likely to exhibit vitamin D insufficiency than those with Alzheimer's disease, a related neurodegenerative disorder. Vitamin D regulates multiple cellular processes known to be abnormal in PD, including cellular differentiation, proliferation, and apoptosis. The researchers of this study suggest that PD patients should be checked more regularly for low 25-hydroxyvitamin D levels as a strategy for minimizing further complications of the disease.[50]

Coenzyme Q_{10}

Coenzyme Q10 (CoQ_{10}) is also known as ubiquinone; its primary biochemical action is as a cofactor in the electron transport chain, the series of redox reactions involved in the synthesis of adenosine triphosphate (ATP). CoQ_{10} is best known for its role in treating cardiovascular disease (CVD), and CVD is a well-established comorbidity in PD. Preliminary data suggest that CoQ_{10} is one of the most promising neuroprotective agents for PD.

A randomized placebo-controlled double-blind clinical pilot study suggested that high-dose CoQ_{10} may also help slow symptom progression in early PD. In this study, 80 unmedicated patients with early-stage disease were randomly given CoQ_{10} at dosages of 300, 600, or 1200 mg/day or a placebo. Using the Unified Parkinson's Disease Rating Scale (UPDRS), they were followed up for 16 months or until disability requiring treatment with L-dopa had developed. It was found that patients on CoQ_{10} fared significantly better than their placebo counterparts, with those taking 1200 mg showing the greatest results.[51] A second placebo-controlled double-blind experiment used 360 mg of

CoQ_{10} for 4 weeks in 28 treated and stable PD patients. CoQ_{10} supplementation provided a significant although mild symptomatic benefit in PD symptoms and a significantly better improvement in visual defects compared with placebo.[52]

High doses of CoQ_{10} have proved to be safe in the short term. In a 2-week open-label trial, 17 patients with PD received an increasing dosage of CoQ_{10} (1200, 1800, 2400, and 3000 mg/day, respectively) with an unvarying dosage of 1200 IU/day of the α-tocopherol form of vitamin E. The plasma level of CoQ_{10} was measured at each dosage. Thirteen of the subjects were increased to the 3000-mg dose, with no CoQ_{10}-related side effects. One patient became orthostatic and one was dyspeptic, but these conditions were unrelated to the CoQ_{10}. Looking at the blood, plasma levels of ubiquinone reached a plateau at the 2400-mg/day dosage. This study was not long enough to assess any clinical effect on the disease itself,[53] but a follow-up study is under way.

Melatonin

Melatonin is a hormone manufactured from serotonin and is secreted by the pineal gland. Known as a powerful antioxidant, melatonin is an established treatment option for jet lag and various sleep disorders. Although studies show that melatonin does not induce any increase in cerebrovascular blood flow,[54] evidence supports the role of melatonin as a protector of neuronal cells, most likely by supporting mitochondrial function and preventing apoptosis.

As an antioxidant, melatonin can directly scavenge oxidants produced during normal metabolism, and it indirectly promotes the activity of antioxidant enzymes such as superoxide dismutase and catalase. Second, melatonin increases the activity and the expression of electron transport chain complexes during physiologic and pathologic situations. As a result, melatonin increases ATP production and promotes glutathione homeostasis. It has also been postulated that melatonin may interact with the mitochondrial genome in order to enhance production of proteins.[55] Tissue culture models of PD using low doses of 6-hydroxydopamine to induce apoptosis of undifferentiated and neuronal rat adrenal pheochromocytoma cells have also shown melatonin to prevent apoptosis in these models.[56]

It is theoretically possible that melatonin exacerbates symptoms of PD because of its putative interference with dopamine release.[57] But the larger body of literature agrees that PD is probably due to multiple issues of compromised mitochondrial activity in the substantia nigra,[58] loss of glutathione,[59] oxidative damage, and increased apoptotic events. Reasonably, melatonin supplementation may yield a direct benefit. Clinical studies are necessary to evaluate the effectiveness of melatonin in PD.

Reduced Nicotinamide Adenine Dinucleotide

Found useful in treating animal models of PD,[60] the coenzyme nicotinamide adenine dinucleotide (NADH) is known to enhance endogenous dopamine production by supplying reducing equivalents to the rate-limiting, tyrosine hydroxylase–catalyzed step of dopamine synthesis in both tissue culture and human evaluations.[61] A positive effect has been found using NADH both intravenously and intramuscularly in 34 PD patients in an open-label trial. In this trial each patient experienced a beneficial clinical effect: 21 showed a "very good" (better than 30%) improvement of disability, and 13 patients showed a "moderate" (up to 30%) improvement. The effect of NADH was dependent on both the dose given and the severity of disease. The optimal therapeutic range for NADH was 25 to 50 mg per day. Intravenous administration seemed to work better than intramuscular injection. The presence of homovanillinic acid in the urine was significantly increased in all patients. The presence of this metabolite indicates stimulation of endogenous L-dopa biosynthesis.[62] A second study of 15 patients prospectively investigated the administration of one 10-mg treatment over 30 minutes a day for 7 days. These patients were also taking L-dopa medications. The patients' UPDRS scores improved, and significant increases in plasma L-dopa were observed.[63] Nevertheless, owing to lack of sufficient studies and theoretical considerations for underlying NADH disposal, many in the medical community do not currently recommend the widespread use of NADH for PD.[61] As with many newer therapies, more rigorous studies are necessary to confirm their benefit and elucidate any side-effect risk.

Creatine

Creatine is an important player in brain homeostasis and acts as a temporal and spatial buffer for cytosolic and mitochondrial pools of the cellular energy currency, adenosine triphosphate, and its precursor adenosine diphosphate.[64] Well known mostly as a bodybuilding supplement, oral creatine monohydrate has also been shown to enhance memory and is being studied for the treatment of neurologic, neuromuscular, and atherosclerotic disease.[60]

Adhihetty et al[65] have written an excellent review article on the neuroprotective potential of creatine to combat cellular energy impairment in neurodegenerative disease.

Botanical Medicines

Camellia sinensis (Green Tea)

Epidemiologic studies consistently demonstrate that the consumption of green and black tea offers protection against the development of PD. As a good source of polyphenols, green tea may play a role in preventing and treating the oxidative stress. The biological properties of green tea polyphenols reported in the literature include significant penetration of the blood-brain barrier, antioxidant actions, free radical scavenging, iron-chelating properties, inhibition of (3)H-dopamine and (3)H-methyl-4-phenylpyridine uptake, reduction of catechol-*O*-methyltransferase activity, activation of protein kinase C or the extracellular signal-regulated kinase signal pathway, and modulation of the cell survival/cell cycle gene.[66,67] Green tea polyphenols have demonstrated neuroprotective activity in cell cultures and animal models, including the prevention of neurotoxin-induced cell injury.[66,68] Green tea polyphenols, such as (-)-epigallocatechin-3-gallate, are now being considered as therapeutic agents aimed at altering brain-aging processes and serving as possible neuroprotective agents.[69]

Ginkgo biloba

Ginkgo biloba extract (GBE) exerts profound, widespread tissue effects including membrane-stabilizing, antioxidant, and free radical–scavenging effects. GBE also enhances the utilization of oxygen and glucose. GBE is an extremely effective inhibitor of lipid peroxidation of cellular membranes. Although there are no clinical studies in PD patients, GBE is well researched for its beneficial effects in Alzheimer's disease,[70,71] and has been shown useful in animal models of PD.[70,72] GBE possesses a protective effect on the PD models both in vivo and in vitro. Antioxidation and antiapoptosis are proposed to be involved in the mechanisms underlying the neuroprotective effect of GBE.[72]

Mucuna puriens (velvet bean)

The seed powder of the velvet bean has long been used in traditional Ayurvedic medicine for diseases including PD. It is a rich

natural source of L-dopa, but other components also contribute to its medicinal actions. An extract of velvet bean was studied in 60 patients with Parkinson's disease (before treatment 26 patients were given Sinemet with the extract and the remaining 34 were not given any medication).[73] Statistically significant reductions in symptom scores were seen from the beginning to the end of the 12-week study. The amount used in the study was 7.5 grams of the extract dissolved in water 3 to 6 times daily. In another study, 8 PD patients were challenged with single doses of 200/50 mg L-dopa/carbidopa (LD/CD), 15 and 30 g of velvet bean preparation in randomized order at weekly intervals.[73a] Compared with standard LD/CD, the 30 g velvet bean preparation led to a considerably faster onset of effect (34.6 vs 68.5 minutes), reflected in shorter times to peak L-dopa concentrations in the blood, and fewer side effects. The researchers felt that the velvet bean might possess advantages over conventional L-dopa preparations. This conclusion has been confirmed in various animal models.[73b,73c] Individuals taking medications like Sinemet and L-dopa should be aware that velvet bean consumption may increase L-dopa levels too high.

Piper methysticum (Kava-Kava)—Caution

Although no side effects have been reported using standardized kava extracts at recommended levels in clinical studies, there have been isolated reports of kava causing an onset of parkinsonian symptoms.[74] Additionally, several case reports have indicated that kava may interfere with dopamine and worsen PD.[75,76] Until this issue is resolved, kava extract should not be used in PD patients or those considered genetically susceptible.

Other Therapeutic Considerations

Smoking

A number of epidemiologic studies demonstrate that smoking is associated with a lower incidence[77] and delayed onset[78] of PD. Although it is unclear which mechanisms account for this effect, it is postulated that nicotine may enhance the striatal stimulation of dopaminergic neurons, which are selectively damaged in PD. Because the risk:benefit ratio of smoking is high, it is not advised that smoking be suggested as a reasonable preventive measure.

Estrogen

Increasing evidence suggests that estrogens may modulate the activity of dopamine,[79,80] may act as an antiapoptotic agent,[81] and could affect the neuronal pathways affected in PD.[82] Animal studies have demonstrated that estrogens influence the synthesis, release, and metabolism of dopamine and may actually modulate the expression and function of dopamine receptors. Some clinical studies have also suggested that parkinsonian symptoms may worsen after menopause and that hormone replacement therapy can be protective,[83,84] whereas others hypothesize that decreases in circulating estrogen may improve PD.[79]

The conflicting findings suggest that several variables including age, estrogen dose and formulation, as well as timing and length of dosing period may determine whether benefits are seen and what their nature might be.[82] At this time it may be best for clinicians to pay close attention to correlations between menstrual pattern and symptomatic disease in order to make the best patient-specific choices with regard to hormone replacement.

Homeopathy

No clinical studies are available to support the use of homeopathy in PD, although anecdotal success stories are known. Some of the remedies and the symptoms they are said to relieve may include the following:

- *Agaricus muscarius:* crawling sensations, vertigo with impulse to fall backward, symptoms worse in cold weather
- *Antimonium crudum:* Parkinsonian movements associated with gastric symptoms; desire for sour foods that do not sit well in the digestive tract; a thickly white-coated tongue; stubbornness; anxiousness; a general feeling of disgust with worse symptomatology caused by heat, wine, or moonlight
- *Argentum nitricum:* tremulousness

Acupuncture and Tui Na

In traditional Chinese medicine, pathogenic wind is considered the main agent responsible for the symptoms of PD. The treatment strategy is thus to calm this wind and tranquilize the mind. In more conventional terms, it is hypothesized that acupuncture may increase levels of dopamine in the brain and augment the excitability of the dopamine neurons.[85] Animal studies have shown neuroprotective effects of acupuncture on the nigrostriatal system.[86,87] Acupuncture and *tui na*, which is a Chinese therapeutic massage, have both improved clinical disease symptoms and signs and possibly delayed disease progression.[88,89] In one study, 20 patients with PD were treated twice a week with acupuncture. Standard scales including the UPDRS and Hoehn and Yahr staging were used. In addition, quantitative motor tests including timed evaluations of arm pronation supination movements, finger dexterity, finger movements between two fixed measured points, the stand-walk-sit test, and a patient questionnaire designed for the study were employed. Objective improvements were noted in the sleep and rest categories, with no other obvious improvements. However, on the patient questionnaire, 85% of patients reported subjective improvement of individual symptoms including tremor, walking, handwriting, slowness, pain, sleep, depression, and anxiety.[90] Another study of 26 patients found improvements in auditory-evoked brainstem potential examinations.[83]Acupuncture treatments are considered safe and well tolerated[90] and should be considered as a safe means to improve sleep and patient perception of parkinsonian symptoms. More studies are necessary to confirm objective improvements in clinical presentations.

THERAPEUTIC APPROACH

Diagnosis

Besides standard neurologic rating scales and imaging, serum iron, ferritin and total iron binding may be useful to look for iron overload. Blood levels of homocysteine may also uncover homocysteinuria, a potential facilitator of disease progression. A careful history and testing should evaluate for heavy metal and pesticide exposures.

Dietary Recommendations

- The diet should be low in animal fats and high in fiber, specifically legumes and vegetables.
- Antioxidant-rich foods are recommended, including nuts and seeds, green leafy vegetables (bok choy, chard, etc.), beans, spices (turmeric, clove, cinnamon), coffee, and chocolate.
- Pesticides should be avoided by eating organic when possible.
- To maintain bowel health and facilitate the detoxification processes of the liver, high sulfur-containing foods like garlic, onions, and eggs, as well as water-soluble fibers such as guar gum, oat bran, pectin, and psyllium seed are recommended.

- For patients taking levodopa, a lower protein intake is recommended (50 g/day for men and 40 g/day for women). In an effort to optimize the medication's therapeutic efficacy, such patients should take their medications 30 to 45 minutes before protein-containing meals.
- Owing to constant movement, weight loss may be an issue with some patients; therefore, caloric intake may need to be adjusted to specific patient needs.

Lifestyle Recommendations

Patients with PD should be advised to do the following:
- Avoid cooking in aluminum pots.
- Exercise regularly—tandem and recumbent bikes are especially well suited for individuals with PD.
- Hang onto banisters and sit in chairs with higher arms.

Nutritional Supplementation

- Iron and manganese supplements should be avoided.
- High potency multiple vitamin and mineral formula (without iron)
- Vitamin D3: 2000 to 4000 IU a day (ideally measure blood levels and adjust dose accordingly)
- Fish oils: 1000 to 3000 mg EPA+DHA a day
- Exogenous glutathione should be administered; however, the best delivery system has yet to be elucidated. Intranasal glutathione has been anecdotally reported to be effective. N-acetyl cysteine (500 mg twice a day) and ketogenic diets have been shown to boost brain glutathione levels.
- Vitamins B_6 and B_{12} as well as folic acid should be provided in doses sufficient to maintain homocysteine levels below 10. If homocysteine levels do not drop adequately, betaine may be added to the regimen.
- NADH (tradename: Enada): 10 to 20 mg a day
- CoQ10: Estimated daily dose to achieve target levels in PD based upon available forms for best results take in divided dosages:
 - Ubiquinone powder in hard gelatin capsule: 1200 to 2400 mg in divided doses
 - Ubiquinone suspended in oil in soft gelatin capsule w/rice bran oil: 600 to 1200 mg in divided doses
 - Ubiquinone solubilized (e.g., Q-gel) in soft gelatin capsule: 300 to 400 mg in divided doses
 - Ubiquinone nanonized in soft or hard gelatin capsule: 250 to 400 mg in divided dosages
 - Ubiquinone emulsified with soy peptide (BioQ10 SA) in soft or hard gelatin capsule: 200 to 400 mg in divided doses
 - Ubiquinol in soft gel capsule: 200 to 400 mg in divided doses

Botanical Medicines

- Green tea: Three cups a day may be taken, or about 3 g of soluble components providing roughly 240 to 320 mg of polyphenols. For a green tea extract standardized for 80% total polyphenol and 55% epigallocatechin gallate content, this would mean a daily dose of 300 to 400 mg.
- *Mucuna puriens*: Dose equivalent to 30 g dried powdered seed.

Acupuncture

Treatments involving needling and *tui na* massage according to traditional Chinese medicine are recommended.

CONCLUSION

Naturopathic medicine holds tremendous potential for the prevention and treatment of PD. Unlike conventional therapies that treat only symptoms and have notable side-effect profiles, naturopathic strategies attempt to optimize function as well as to reduce free radical production and exposure to neurotoxins. It is ideal for patients that the conventional and naturopathic strategies are not at odds with one another; rather, they complement each other well.

Randomized controlled trials are ill-suited study designs for diet and lifestyle interventions and even less optimal for diseases like PD, where the disease is not diagnosed until late in the course. In the meantime, dozens of epidemiologic studies suggest that the diet and lifestyle choices we make over the course of our lives offer some protection against the development of this disease. It is logical and prudent to incorporate foods, activities, and supplements that may have neuroprotective potential; this is especially true for those who are at high risk of developing PD, have symptoms associated with PD, or have been recently diagnosed. Whereas neuronal regeneration is considered virtually impossible, neuoroprotective strategies are likely to be elucidated in the near future. As with all therapies, individuals are advised to explore the risks and benefits with their providers and initiate the strategies that are most appropriate for each situation.

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CHAPTER 197

Pelvic Inflammatory Disease

Tori Hudson, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- Dyspareunia
- Mucopurulent cervical discharge
- Pelvic pain; bilateral adnexal tenderness
- Palpable adnexal mass
- Elevated temperature (above 101°F)
- Cervical motion tenderness
- White blood cell count (WBC) 20,000/μL, with marked leukocytosis, elevated sedimentation rate, or both
- *Neisseria gonorrhoeae* (GC) and *Chlamydia trachomatis* (CT) most common, followed by *Ureaplasma urealyticum, Mycoplasma hominis, Streptococcus* species, *Escherichia coli, Haemophilus influenzae, Peptostreptococcus,* and *Peptococcus**
- Transvaginal ultrasound shows thickened fluid-filled tubes or tubo-ovarian mass
- Acute and chronic endometritis on endometrial biopsy
- Laparoscopy—the gold standard

GENERAL CONSIDERATIONS

Pelvic inflammatory disease (PID) is a categorical name for a range of pelvic infections and inflammations. The CDC defines PID by the presence of abdominal and adnexal tenderness and cervical motion tenderness in the absence of another definable cause of the patient's symptoms. The diagnosis does not require the presence of elevated WBC, erythrocyte sedimentation rate (ESR), or of fever.

PID causes women to make an estimated 2.5 million outpatient visits to health care providers each year. One fourth of these women will suffer serious long-term sequelae and all are at risk for recurrence.[1]

The social and physical costs of PID are also significant: the risk of ectopic pregnancy increases sixfold after a single episode of PID, and there is an estimated 13% risk of infertility after one infection and a 70% risk after three infections.[2] For these reasons as well as costs, prevention and aggressive full-spectrum care of the acute phase are vital.

Etiology

Several organisms (listed in Table 197-1[3]) are known to be implicated in the etiology of PID, but GC and CT are the most common. Because of the complexities and inconsistencies involved in sampling and laboratory verification, it is difficult to make definitive statements about the causal agents in PID. Asymptomatic chlamydial infections are an important cause of PID. An estimated 1 million new

*Testing methods for GC and CT include cell culture (the gold standard), direct fluorescent antibody (DFA) testing, enzyme immunoassay (EIA) antigen detection technique, nucleic acid hybridization tests (DNA probes), nucleic acid amplification (polymerase chain reaction [PCR] or ligase chain reaction [LCR]), and the newer ThinPrep Pap Collection system. The new Centers for Disease Control and Prevention (CDC) recommendations are that all sexually active adolescents undergo routine screening for CT during annual pelvic examinations. The CDC also recommends that routine screening of asymptomatic women between 20 and 24 years of age should be considered, particularly if they have a new male sex partner, more than one male sex partner, or do not use barrier contraception.

TABLE 197-1 **Microorganisms Involved in Pelvic Inflammatory Disease**

ORGANISM	INCIDENCE (%)
Neisseria gonorrheae	40-60
Chlamydia trachomatis	30
Mycoplasma hominis	8
Ureaplasma urealyticum	4

Data from Karchmer AW. Sexually transmitted diseases. In Dale DC, Federman DD, eds. Scientific American medicine. New York: Scientific American, 1996:7:XXII-10-13.

infections with GC occur in the United States annually. More than 4 million infections occur annually due to CT. The true incidence of CT infection is probably higher because not all states require reporting. A higher proportion of PID has been ascribed to CT than to GC.[4]

Neisseria gonorrhea

The incidence of GC in the United States increased by a factor of 2.7 from 1960 to 1980.[5] The infection has reached pandemic proportions in the United States, where it is estimated that for each reported case, four cases go unreported.[6] Gonococci have been recovered from the urethra of 2.2% of sexually active servicemen who had minimal or no symptoms and from 40% of asymptomatic males who had contact with symptomatic women.[7] In addition, an estimated 80% of the men and women exposed to *Gonococcus* will develop infections.[8]

For a seemingly delicate and fastidious species, *Neisseria* has impressive infective abilities, preferring human columnar and transitional epithelia. In less than 1 hour after intercourse, *Gonococcus* can establish itself on the urethral mucosa, where it successfully resists the flow of urine.[9] Favored sites in the lower female genital tract are Bartholin's and Skene's glands, the urethra, and the endocervical canal.[6] Direct spreading can occur from the endocervix across the endometrial surface to the tubal mucosa, or migration can occur through subendothelial vascular and lymphatic channels.[2] Perhaps the most common method of spreading, however, is by vector: GC attached to spermatozoa are physically carried to the fallopian tubes.[6] Primary pathogens can also enter the upper tract from retrograde menstruation or uterine contractions during intercourse.[10]

In the acute state, the gonococci and polymorphonuclear lymphocytes accumulate in the subepithelial connective tissue, resulting in patchy destruction of the overlying mucosa.[9,11] The consequent thinning of the mucosal lining is thought to facilitate the penetration of GC into deeper tissue.[9] It is probably for this reason that gonococci are reported to survive only a short time in the fallopian tubes.[12] However, they may be not only surviving but thriving. The descent of the microbe beyond the surfaces being examined makes detection difficult.[12]

Concomitant infections are known to occur with GC.[13] Some researchers have even proposed that GC's primary role appears to be paving the way for secondary invaders from normal vaginal flora, allowing access to the upper tract.[14] The associated infection will frequently be CT, but a superinfection can also be present, in which case one will find that anaerobic bacteria have colonized as well.[13]

Chlamydia trachomatis

In the United States it is estimated that 20% to 30% of PID cases are caused by CT.[3,15] Further, one study found that acute chlamydial PID may be subclinical or silent in 66% to 75% of the cases.[16] Laboratory diagnosis of chlamydial infection is difficult, which, combined with CT's propensity to be asymptomatic, renders thorough assessment of the scope of these infections nearly impossible.

A 5-year study conducted in urban Sweden showed that, despite a decrease in the incidence of gonococcal PID, the total number of cases of acute PID were unchanged or even increased in the last year of the study.[17] Another European study, conducted in 1977, found that 62% of women with acute salpingitis had elevated (titer ≥ 1:64) chlamydial IgG antibodies.[18] However, most other studies completed to date show much lower percentages. These numbers will no doubt change as diagnostic technology improves and the clinical presentation of CT is more widely understood.

Anaerobic Infections

Anaerobes are the organisms most commonly isolated from the fallopian tubes or culs-de-sac of patients with PID.[19] Anaerobic bacteria are probably not the chief causative agents but rather opportunists, establishing themselves in unsuccessfully defended tissues.

Anaerobic infections are commonly found in immunocompromised hosts and are generally of endogenous origin.[20] The cervix and vagina of a normal healthy woman contain both anaerobic and aerobic bacteria.[21] Anaerobic infections establish themselves more often in older patients and in women with a history of prior PID.[5]

Other Organisms

Facultative aerobic organisms found in tuboperitoneal fluids from women with salpingitis have included coliforms, *H. influenzae*, *S.* species, and *M. hominis*.[22]

M. hominis has not been demonstrated as a sole etiologic agent but rather seems to be a common contributor to the polymicrobial milieu that is often discovered in PID. One study found *M. hominis* in cervical cultures from 81% of women patients with GC and 64% of those without GC.[23]

Complications

There are serious physical consequences for women who have had PID. It has been estimated that, in the postinfection state, one of four women suffers from one or more sequelae such as abdominal pain, infertility, or ectopic pregnancy.[5] Dyspareunia is a symptom that is often not investigated but which, when relevant questions are asked, is frequently found in the post-PID sufferer.

Death from salpingitis is rare and is generally due to rupture of the tubo-ovarian abscess with subsequent peritonitis. A mortality rate of 5.2% to 5.9% has been calculated for tubo-ovarian abscesses; before 1950, mortality was 80% to 100%.[24,25] Better diagnostic understanding of this complication, treatment with antibiotics, and prompt surgical intervention have phenomenally improved both morbidity and mortality statistics.

The Fitz-Hugh–Curtis syndrome is a perihepatitis complicating the primary condition of PID. Characteristic violin-string adhesions attach the liver to the abdominal wall.[20,26] These adhesions are due to local peritonitis involving the anterior liver surface and the adjacent abdominal wall.[27] Historically, GC was thought to be the main contributor to this syndrome, but CT is now found more frequently.[20,21]

Infertility is a serious concern. Once a woman has had PID, she is at risk for additional attacks. This is in part because, after the fallopian tubes have been damaged by the infectious process,

normal defense mechanisms are impaired. Reinfection has been found to be the most important cause of infertility after PID.[28] One study comparing the rate of nonsurgical infertility in 1973 with that of 1976 noted a 45% increase. This translates to 122,000 infertile couples per year.[29] This increased incidence is consistent with the concurrent epidemic of sexually transmitted disease (STD)–associated PID.

An alarming statistical analysis has shown that for each 1000 girls born in 1950, a total of 138 had one or more bouts of PID by age 30; 26 were infertile because of the PID; and 9 had surgery for ectopic pregnancy.[5] Further, it has been postulated that by the year 2000 there will be one episode of salpingitis for each two women reaching reproductive age in 1970.[21]

Ectopic pregnancy is a severe sequelae, and any woman with a history of PID faces a sevenfold to tenfold increased risk.[5] Ectopic pregnancies tripled in the United States from 1967 to 1977. In 1977 ruptured ectopic pregnancies accounted for 12% of maternal deaths and were the leading cause of maternal death in nonwhite women.[29] In another study that followed women with PID for 9.5 years, 12.8% were infertile after one infection, 35.5% after two, and 75% after three infections. The same study showed that 1 in 24 women with PID will have an ectopic pregnancy.[30]

Risk Factors

In addition to the obvious factor of sexual contact, the main risk factors are age, use or history of use of an intrauterine device (IUD), and previous history of PID. An earlier "sexual debut" puts a young woman in a high-risk group for PID, especially when there are multiple sex partners. The risk in sexually active 15-year-olds is 1 in 8, whereas in the average 24-year-old it is 1 in 80.[5] One interesting hypothesis for these data is that the cervical mucus in the younger woman may be estrogen-dominated, creating an environment that is more accessible to pathogens.[22] Women with multiple partners have a 4.6-fold greater risk than women in monogamous relationships.[21]

A woman faces an increased risk of PID if she uses an IUD. Oral contraceptive (OC) users are somewhat less likely to have GC; on the other hand, they are at increased risk for chlamydial invasion. Birth control remains a potent issue, with barrier methods being the techniques of choice because of their decreased PID risk. It should also be noted that one author included his own clinical observation that women in his practice who had vasectomized men as partners only seldom developed PID.[31]

The last risk factor to be considered is iatrogenic. This occurs when invasive procedures have introduced pathogens, or in some other way disturbed the tract flora and induced PID. Among these procedures are the following:

- Cervical dilation
- Abortion
- Curettage
- Tubal insufflation
- Hysterosalpingography
- Insertion of an IUD

A hospital in Lund, Sweden, reported that 15% of its PID cases were iatrogenic. This indicates that PID may not be strictly an STD.[20]

Pathogen Access to the Upper Female Tract

The route by which the pathogens gain access to the upper female tract has only recently been explored. Menstruation, sperm, and trichomonads have all been shown to be important in the transportation of pathogens into the salpinx.

Often the onset of menses corresponds with the onset of an episode of PID. Infections occurring around the menses tend to be GC rather than CT, a clinical curiosity that may ultimately shed light on the etiology. One hypothesis is that menstrual regurgitation assists the inflammatory response by carrying sloughed endometrial epithelium, which may have attached GC or intracellular CT. These organisms can then proliferate in the tubal epithelium or on peritoneal surfaces.[10,32]

Human sperm has proved to be an interesting and multifaceted variable in the precipitation of PID. Some of the research targets bacteriospermia as a cause of infertility in men, findings that are clearly relevant to PID. Increasingly, STD research is noting the incidence of asymptomatic male carriers.[6,7,31,33-36] A large population study discovered that 66% to 75% of the men who tested positive for GC were asymptomatic.[7]

Designed to travel during intercourse, sperm also serve as effective vectors. Researchers took a look at this most basic interaction between a man and a woman by means of a laboratory experiment. They introduced organisms into capillary tubes containing cervical mucus, either alone or with added spermatozoa, and observed microbial motility. Cervical mucus had already been considered an effective mechanical and immunologic barrier between the abundant flora of the vagina and the upper tract, and the test results confirmed this idea. However, they also demonstrated that organisms attached to sperm could easily traverse the length of the mucus column. This may be particularly important during menses, because sperm migration has been observed through menstrual plasma but not during the luteal phase or through the cervical mucus of pregnancy.

Electron microscopy has produced amazing photographic evidence of organisms attached to sperm.[6,37] The mechanism observed with piliated GC is that pili twist together with the tails of the spermatozoa in a rope-in-a-spider-web arrangement around the bacteria. Sperm have also been found intimately associated with cytomegalovirus, *Toxoplasma, Ureaplasma urealyticum,*[32] and CT.[38]

Motile trichomonads serve as another transporter of PID. They can ascend from the vagina to the fallopian tubes, carrying additional invaders. In fact, it has been observed that trichomonads are never isolated from humans when heavy bacterial contamination is absent.[32]

DIAGNOSIS

Pelvic or lower abdominal pain is the most dependable symptom of PID; unfortunately, however, it is not specific. Rebound tenderness is not reliably reported; cervical motion tenderness and adnexal tenderness are much more common. The clinical picture of the various types of PID can easily mislead. In a large study, the clinical diagnosis of PID was confirmed at laparoscopy in only 65% of the patients. Appendicitis, hemorrhagic corpus luteum, pelvic endometriosis, ectopic pregnancy, mesenteric adenitis, and ovarian tumors accounted for 12%, while 23% were found to be normal.[39] Many PID patients have atypical signs and symptoms and some have no signs or symptoms at all.[5] Table 197-2 lists those most commonly found.

The woman with GC may appear more toxic and febrile and manifest leukocytosis, while CT-caused PID may give her an elevated sedimentation rate (ESR). Most episodes of gonococcal PID occur at or shortly after menses.[40] Gonococcal PID has a generally more severe clinical picture, but tissue damage and long-term sequelae can be more severe in CT. This attempt to differentiate clinical pictures becomes meaningless, of course, in the presence of mixed infections.

TABLE 197-2 **Common Signs and Symptoms in Acute Pelvic Inflammatory Disease**

SYMPTOM	INCIDENCE (%)
Lower abdominal pain	90
Adnexal tenderness on palpation	90
Pain on movement of the cervix	90
Vaginal discharge	55
Adnexal mass or swelling	50
Fever or chills	40
Irregular vaginal bleeding	35
Anorexia, nausea, and vomiting	25

Data from Karchmer AW. Sexually transmitted diseases. In Dale DC, Federman DD, eds. Scientific American medicine. New York: Scientific American, 1996:7:XXII-10-13.

BOX 197-1 **Differential Diagnosis of Pelvic Inflammatory**

- Acute appendicitis
- Acute cholecystitis
- Acute pyelonephritis
- Ectopic pregnancy
- Endometriosis
- Hemorrhagic ovarian cysts
- Intrauterine pregnancy
- Mesenteric lymphadenitis
- Ovarian cyst with torsion
- Ovarian tumor
- Pelvic thrombophlebitis
- Septic abortion

Any mucopurulent discharge should yield oxygen-sensitive organisms because offensive odor is considered diagnostic of anaerobic infection. Any woman who has such a discharge probably has well-developed PID, with opportunistic anaerobes following the primary invaders.[28] Box 197-1 shows the differential diagnoses of PID. Potentially lethal conditions to consider include ectopic pregnancy, tubo-ovarian abscess, ovarian cyst rupture with hemorrhage, and appendicitis.

In light of the Fitz-Hugh–Curtis syndrome, symptoms from the upper right quadrant in a sexually active woman may be an indirect sign of genital infection. The pain usually has a sudden onset and can overshadow the signs and symptoms of the underlying PID.[27]

In the event of rupture of a tubo-ovarian abscess, a sudden severe exacerbation of the pain can be observed. The pain is referred to the side of the rupture and is typically followed by generalized peritonitis and collapse. Shoulder pain may be present. The pulse will likely be elevated out of proportion to the fever and is frequently as high as 170.[25] Surgery must be performed within 12 hours or mortality becomes probable.

A careful history is, as always, invaluable. The patient's risk factors and history should be assessed for likelihood of infection with a sexually transmitted organism. The patient should be questioned about any new sex partner, method of contraception, and recent medical procedures. The source, severity, and characteristics of the pelvic/abdominal pain should be evaluated. Mucopurulent cervicitis should be considered as well, and the cervix should be cultured for GC and CT.

Empiric treatment of PID should be initiated in sexually active young women and other women at risk for STDs if they are experiencing pelvic or lower abdominal pain, if no cause for the symptoms other than PID can be identified, and if one or more of the following minimal criteria are present on pelvic examination:

- Cervical motion tenderness *or* uterine tenderness *or* adnexal tenderness

The following additional criteria above and beyond the minimal criteria may enhance the diagnosis of PID:

- Oral temperature above 101°F or 38.3°C
- Abnormal cervical or vaginal mucopurulent discharge
- Presence of abundant numbers of WBCs on saline microscopy of vaginal secretions
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein
- Laboratory documentation of cervical infection with GC or CT

The following criteria for hospitalization are suggested:

- Surgical emergencies (e.g., appendicitis) cannot be excluded.
- The patient is pregnant.
- The patient does not respond clinically to oral antimicrobial therapy.
- The patient is unable to follow or tolerate an outpatient oral regimen.
- The patient has severe illness, nausea and vomiting, or high fever.
- The patient has a tubo-ovarian abscess.



THERAPEUTIC CONSIDERATIONS

Criteria for hospitalization include surgical emergency or septic-appearing patient, pregnancy, failure to respond to oral antibiotics, and suspicion of tubo-ovarian abscess. Referral is necessary if the diagnosis is uncertain or a surgical emergency threatens. Should the physician decide not to hospitalize, a regimen of antibiotic therapy combined with the supportive therapies discussed later, can be tried if the patient's clinical and laboratory status can be reassessed in 48 to 72 hours. Laboratory values and objective patient criteria should direct all acute-phase treatment. The CDC leaves it to the individual practitioner to decide on the severity of the disease and the optimal treatment. Its guidelines do say that "Most experts encourage hospitalization and treatment with intravenous antibiotics."

Antibiotics

PID is a complex syndrome, with inconsistent and variable presentations in different women and including a range of symptoms and etiologic microorganisms. Because of this, broad-spectrum antibiotic regimens are employed that allow for some flexibility on the part of the practitioner. Regimens are tailored on the basis of clinical severity and laboratory findings, patient compliance, cost of medications, and availability of medications. Because some antibiotics cover only one organism, the CDC outpatient recommendations take into account the limited anaerobic activity of any one regimen.

Oral Treatment

Oral therapy can be considered for women with mild to moderately severe acute PID, because the clinical outcomes among women treated with oral therapy are similar to those in women treated with parenteral therapy. Women who do not respond to oral therapy within 72 hours should be reevaluated to confirm the diagnosis and should be given parenteral therapy (see Box 197-2).

Fifteen percent of women with PID fail to respond to primary antimicrobial treatment, 20% have at least one recurrence, and 15% are rendered infertile.[19]

Given the polymicrobial nature of PID, the complexities of isolation, antibiotic-resistant strains of microorganisms, and the realities of recurrence rate with antibiotic use, an approach that combines immune system enhancement and nontoxic therapies concurrently with antibiotics seems sound. However, there are no evidence-based therapies using natural therapies exclusively for

BOX 197-2 **Recommended CDC Oral Regimen (last updated 2010)**

Recommended Regimen

Ceftriaxone 250 mg IM in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH or WITHOUT
Metronidazole 500 mg orally twice a day for 14 days
OR
Cefoxitin 2 g IM in a single dose and Probenecid, 1 g orally administered concurrently in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH or WITHOUT
Metronidazole 500 mg orally twice a day for 14 days
OR
Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime)
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH or WITHOUT
Metronidazole 500 mg orally twice a day for 14 days

Parenteral and oral therapy appear to have similar clinical efficacy treating women with PID of mild or moderate severity. Clinical experience should guide decisions regarding transition to oral therapy, which usually can be initiated within 24 hours of clinical improvement.

Recommended Parenteral Regimen A

Cefotetan 2 g IV every 12 hours
OR
Cefoxitin 2 g IV every 6 hours
PLUS
Doxycycline 100 mg orally or IV every 12 hours

Intravenous infusion of doxycycline is painful and should be administered orally when possible. Bioavailability of oral and IV is similar.

Parenteral therapy may be discontinued 24 hours after clinical improvement, but oral therapy with doxycycline (100 mg twice a day) should continue to complete 14 days of therapy. When tubo-ovarian abscess is present, clindamycin or metronidazole along with doxycycline can be used for continued therapy because it provides more effective anaerobic coverage than doxycycline alone.

Recommended Parenteral Regimen B

Clindamycin 900 mg IV every 8 hours
PLUS
Gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing (3-5 mg/kg) can be substituted.

Parenteral therapy may be discontinued 24 hours after clinical improvement; ongoing oral therapy should consist of doxycycline 100 mg orally twice a day, or clindamycin 450 mg orally four times a day to complete a total of 14 days of therapy. When tubo-ovarian abscess is present, clindamycin or metronidazole along with doxycycline can be used for continued therapy because it provides more effective anaerobic coverage than doxycycline alone.

Data from Centers for Disease Control and Prevention, "Sexually Transmitted Diseases: Treatment Guidelines, 2010: Pelvic Inflammatory Disease," http://www.cdc.gov/std/treatment/2010/pid.htm, accessed May 15, 2012.

the treatment of PID. Antibiotics can help with the first phase of treatment but may not offer sufficient intervention for the devastation that regularly occurs in the wake of the primary infection.

Physical Medicine

Diathermy

In the 1920s and 1930s, pulsed, high-frequency diathermy was first reported to be beneficial in the treatment of women with PID.[41-43]

Pulsing electric energy for a short duration (65 mcs every 1600 mcs) at high intensity achieves the desired therapeutic result without the hyperpyrexia typically associated with diathermy. Local recovery is enhanced, the reticuloendothelial system is stimulated, and gamma-globulin fractions are increased.[21] There is no modern research on using this therapy, and practitioners should be very cautious in using it as a substitute for antibiotic therapy.

Sitz Baths

Traditionally, sitz baths have been an important component of the naturopathic treatment of PID. The contrast sitz bath is primarily used to increase pelvic circulation, bring an influx of macrophages to the area, and provide decongestion of the pelvic inflammatory reaction (for further discussion, see Chapter 40).

Nutritional Supplements

Vitamin C

Vitamin C may be useful in the treatment of women with PID for the following reasons:

- Its antiinflammatory effects help to decrease tissue destruction.
- Its support of collagen tissue repair helps to prevent the spread of infection (especially important in GC infections, which can spread through the subepithelial connective tissue, resulting in disorganization of the collagen matrix[8]).
- Its fibrinolytic activity helps to prevent pelvic scarring.

Beta-carotene

The normal ovary has a high concentration of beta-carotene. As these structures are bombarded by inflammation and the unwelcome company of aggressive microbes, it is essential to maintain optimal levels of carotene to allow for an optimal defense. Beta-carotene potentiates the beneficial effects of interferon and enhances numerous other immune functions such as antibody levels and WBC activity.[44,45] Beta-carotene is also important as an antioxidant, helping to limit the cell damage induced by the inflammatory process (see Chapter 69 for a full discussion of this nutrient).

Bromelain

Bromelain should be considered an important component of the treatment regimen. Adnexal exudate in PID frequently suppurates to form abscesses. If tissue irritation is relieved or ameliorated during the acute stage, much of the exudate can be absorbed and fewer adhesions will be formed.[41] Adhesions will form as the exudate lingers, the structures being overwhelmed by the inflammation. Also, after resolution, agglutination of the villous fold in the lumen of the tube may occur, resulting in scarring and tubal occlusion.[6]

Bromelain activates fibrinolysis, which can greatly diminish the enduring sequelae of the inevitable exudate. Bromelain also demonstrates antimicrobial properties, and an Italian study has shown that it penetrates the salpinx[46] (see Chapter 71 for further discussion).

Probiotics

When individuals take antibiotics, the gastrointestinal, vaginal, and bladder microflora are disrupted. This can cause side effects

with antibiotic use or after such use, including diarrhea, candidal vulvovaginits, and acute cystitis. Probiotics are generally defined as live microorganisms whose function is dependent on the ability of a strain to benefit the host when it is administered orally.

There are many species and strains that have been proved to have adhesive properties and can proliferate in these organs and thus prevent opportunistic overgrowth, as well as the side effects from antibiotics, and also restore the normal microflora. No one species or strain can be recommended here, but combination products to be considered should include at least one or more of the following: *Lactobacillus rhamnosus, L. plantarum, L. rheuteri, L. acidophilus, Bifidobacterium bifidum, B. lactis, B. breve,* and *B. longum*.

Botanical Medicines

Many botanicals have been shown to have antimicrobial and immunostimulating effects. Allicin extracts from garlic, golden seal and Oregon grape root, and echinacea should all be considered at least as part of a treatment plan and as adjuncts to antiobiotic therapy.

Vaginal Depletion Packs

Use of the vaginal depletion pack has historically been a part of traditional PID treatment, because it promotes the drainage of exudate from the involved tissues. (This is discussed in more detail in Appendix 12.) It may also stimulate the immune cells within the vagina to provide a first line of defense.

Hydrastis canadensis

The immune-potentiating specific antimicrobial properties and the general antibacterial nature of goldenseal make it indispensable in the care of PID. Since *Hydrastis canadensis* is also a trophorestorative to mucous membranes, the herb should be used throughout the rehabilitation period. (*H. canadensis* is discussed in more detail in Chapter 97.)

Prevention

STD prevention is an extremely important issue for all heterosexually and bisexually active women. The woman with no history of PID should still be concerned about the significant population of asymptomatic male carriers of STDs. The choice of birth control is pivotal. Women who use barrier methods of contraception have a lower risk of PID.

Oral Contraceptives

A surprising number of articles laud the use of oral contraceptives (OCs) for their apparent inhibition of GC.[21] Burnham[19] has suggested OC use after a first episode of PID to prevent recurrence. Apparently, estrogens create a thicker cervical plug, which offers protection against gonococci.[8,10] OCs also decrease the length and volume of menstrual flow, thus decreasing the exposure of the GC to this handy culture medium.

On the other hand, OC users have a higher risk of chlamydial infections.[8,32,40,47] Progesterone can produce cervical eversion, exposing the endocervical columnar epithelium—the target tissue of CT.[40] Estradiol has been implicated in suppressing the endocervical antibodies necessary for resolution of CT.[40] Animal experimentation finds that estrogen-treated individuals have a higher number of infected cervical cells and a longer duration of infection.[48] Because women are probably not selectively exposed to GC versus CT, OCs are not recommended.

Intrauterine Devices

The IUD has a bad reputation in PID.* This reputation is a carryover from the former Dalkon Shield, which is no longer available. Current IUDs such as the Copper T and the Mirena are generally considered safe. However, the use of an IUD is associated with a slightly increased risk of PID, especially in the first 4 months of use. An IUD allows the colonization of bacteria on its surface while simultaneously reducing local immunologic capacity.[49] If a woman with suspected PID has an IUD, it must be removed 12 to 24 hours after initiation of antibiotic therapy in order to prevent the spread of the infection during its removal.

Barrier Methods

Barrier methods of contraception are excellent choices for the prevention of PID. The condom is preferred to cervical protectors, as with this method the sperm more rarely reach the vaginal vault.

Douching

Haphazard douching is to be avoided because it disturbs the vaginal flora. All forms of douching increase the risk of PID and can cause organisms to ascend into the upper genital tract.

One study compared 100 consecutive patients hospitalized for PID with 762 controls and 119 women suspected of having PID.[50] Current douching (defined as any douching during the previous 2 months) was more common among those with PID than among those in both control groups. Among current douchers, PID was related to the frequency of douching. Those who douched three or more times per month were 3.6 times more likely to develop PID than those who douched less than once per month.

A much larger study surveyed 6984 women older than 18 years of age and found that 32% said they had douched within the previous week; 13% reported regular douching more than once a week.[51]

Intercourse During Menses

Intercourse during menses is not recommended unless a condom is used. GC risk is increased by the loss of the protective cervical mucus plug and by the prevalence of blood, a medium of choice for *Gonococcus*. The endometrium is also thought to offer local protection against bacterial invasion, and it is this layer that is being sloughed off during menses.

Smoking

When 197 women hospitalized for their first PID infection were compared with 667 controls with nongynecologic conditions, it was found that cigarette smokers, compared with women who had never smoked, had an elevated risk of PID of 1.7, and former cigarette smokers had an elevated risk of 2.3. There was no dose-response relationship.[52]

A more rigorous study found similar results. This was a case-controlled population-based study of 131 women between 18 and 40 years of age who were treated for their first episode of PID compared with 294 randomly selected patients from the same health maintenance organization. Current smokers compared with those who had never smoked had an increased risk of PID. Women who smoked 10 or more cigarettes a day had a higher risk than those who smoked less.[53]

Education

A physician should review the signs and symptoms of PID with all sexually active women and encourage any woman to seek counsel if she appears to fit the clinical picture for PID. The diagnosis is

*References 5, 16, 19, 22, 27, 54, 55.

easier to make and the recovery more rapid when treatment is instituted early.

THERAPEUTIC APPROACH

Treatment consists of two phases, both of which are important. The first therapeutic goal is to eliminate all pathogens and normalize the microflora of the adnexa. The second is to rehabilitate the damaged tissues.

Women should avoid intercourse until all signs and symptoms are resolved and their male partners have been examined and treated. In addition, all partners from up to 2 months before the illness should be examined[19] and treated if a diagnosis of PID is made. Increased bed rest must also accompany all forms of treatment.

These therapies are recommended as adjuncts to appropriate antibiotic treatment and immune support, as discussed in Chapter 56.

Diet

All dietary inhibitors of immune function (sugar, alcohol, saturated fats, simple carbohydrates) should be limited during both phases of treatment.

Supplements

- Beta-carotene: 100,000 IU/day for 2 or more months
- Vitamin E: 400 IU/day for 3 months
- Vitamin C: 500 mg four times a day for the first week of treatment and then decreased over 3 days to 250 mg three times a day
- Chlorophyll: 10 mg of fat/oil-soluble four times a day for 1 month
- Bromelain: 250 mg (1800 milk clotting unites [MCU]) four times a day for the first week and three times a day for 6 weeks
- Probiotics supplement: minimum 1 billion CFU per day, consider up to 24 billion CFU per day during antibiotic treatment and for 2 months thereafter

Botanical Medicines

- *H. canadensis*: 500 mg of the solid extract (4:1 or 8% to 12% alkaloid content) three times a day during the acute phase; 250 mg three times a day during recovery
- Vaginal packs: daily during the acute phase until there is adequate clinical and laboratory response. After the acute phase, vaginal packs need to be used three times a week, alternating with chlorophyll douches, for 3 weeks.

Physical Medicine

- Diathermy: pulsed, high-intensity diathermy for 10 minutes over the suprapubic area, 10 minutes over the liver, and 10 minutes in the area of the left adrenal (the right being presumably stimulated with the liver).
- Sitz baths: one to two times/day throughout the acute phase. Contrast sitz baths are given in groups of three alterations of hot to cold. Two separate tubs are necessary during this process. The hot is at 105°F to 115°F, the cold at 55°F to 85°F, with the temperatures dependent on the patient's tolerance. The standard treatment is 3 minutes hot and 30 seconds cold, with this cycle being repeated three times in one sitting. The water level in the hot tub is set 1 inch higher than in the cold. Adequate draping is necessary to prevent chilling. As with all hydrotherapy treatments, one always finishes with the cold.

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CHAPTER 198

Peptic Ulcer—Duodenal and Gastric

Michael T. Murray, ND

DIAGNOSTIC SUMMARY

- Epigastric distress 45 to 60 minutes after meals or nocturnal pain; both relieved by food, antacids, or vomiting
- Epigastric tenderness and guarding
- Symptoms chronic and periodic
- Gastric analysis showing acid in all cases, with hypersecretion in about one half the patients with duodenal ulcers
- Ulcer crater or deformity usually occurring at the duodenal bulb (duodenal ulcer) or pylorus (gastric ulcer) on radiography or fiberoptic examination
- Positive test for occult blood in stool

GENERAL CONSIDERATIONS

Peptic ulcer formation occurs in the stomach (gastric ulcer) and the first portion of the small intestine (duodenal ulcer). Duodenal ulcers are more common, with an estimated prevalence of 6% to 12% in the United States. Approximately 10% of the U.S. population have clinical evidence of duodenal ulcer at some time in their life. It is four times more common in men than in women and four to five times more common than clinically evident benign gastric ulcer.

Although symptoms of a peptic ulcer may be absent or quite vague, most peptic ulcers are associated with abdominal discomfort noted 45 to 60 minutes after meals or during the night. In the typical case the pain is described as gnawing, burning, cramplike, aching, or "heartburn." Eating or using antacids usually results in great relief. In the elderly, the presentation of peptic ulcer disease may also be subtle and atypical when compared with that in younger patients, leading to a delay in diagnosis.

Even though duodenal and gastric ulcers occur at different locations, they appear to be the result of similar mechanisms. Specifically, the development of a duodenal or gastric ulcer is due to damage to the protective factors that line the stomach and duodenum.

In the past, the focus has primarily been on the acidic secretions of the stomach as the primary cause of both gastric and duodenal ulcers. However, more recently the focus has been on the bacterium *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs (NSAIDs).

Gastric acid is extremely corrosive, with a pH of 1 to 3. To protect against ulcers, the lining of the stomach and small intestine is protected by a layer of mucin. In addition, the constant renewal of intestinal cells and the secretion of factors that neutralize the acid when it comes in contact with the stomach and intestinal linings also protect against ulcer formation.

Excessive gastric acid output is rarely a factor in gastric ulcers, because in these patients gastric acid output is usually normal or reduced. In contrast, almost one half of patients with duodenal ulcers have increased gastric acid output. This increase may be due to an increase in the number of parietal cells. As a group, patients with duodenal ulcers have twice as many parietal cells as normal controls.

Even with an increase in gastric acid output, under normal circumstances there are enough protective factors to prevent ulcer formation. However, when the integrity of these protective factors is impaired, an ulcer can form. A loss of integrity can be due to *H. pylori,* NSAIDs, alcohol, nutrient deficiency, stress, and many other factors. Of these factors, *H. pylori* and NSAIDs are by far the most significant.

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Several chronic diseases have also been associated with an increased risk of developing peptic ulcers. These include Crohn's disease, chronic renal failure, liver cirrhosis, cystic fibrosis, chronic obstructive pulmonary disease, systemic mastocytosis (a condition in which there are too many immune mast cells in the body), and myeloproliferative disorders (polycythemia vera, chronic myelogenous leukemia, agnogenic myeloid metaplasia, and essential thrombocythemia).[1]

Helicobacter pylori

The role of *H. pylori* in peptic ulcer disease has been extensively investigated. It has been shown that 90% to 100% of patients with duodenal ulcers, 70% with gastric ulcers, and about 50% of those above age 50 test positive for *H. pylori*.[2] However, more than 80% of *H. pylori*–infected people never actually develop an ulcer.[3] Although it is has been discovered that certain genotypic strains of *H. pylori* may confer additional cytotoxic risk for gastric pathologies,[4] conflicting information warrants further research.[5,6] The presence of *H. pylori* is determined by testing the level of antibodies to *H. pylori* in the blood or saliva or by culturing material collected during an endoscopy as well as measuring the breath for urea.

Low gastric output as well as low antioxidant content in the gastrointestinal mucosa is thought to predispose to *H. pylori* colonization. This increases gastric pH, thereby setting up a positive feedback scenario and increasing the likelihood for the colonization of the stomach and duodenum with other organisms.[7]

Aspirin and Other Nonsteroidal Antiinflammatory Drugs

Aspirin and other NSAIDs are associated with a significant risk of peptic ulcer. In addition, the combination of NSAID use and smoking is particularly harmful to the ulcer patient.[8] Although most studies documenting the relative frequency of peptic ulcers as a consequence of NSAID use have focused on NSAIDs in the treatment of arthritis and headaches, the risk of gastrointestinal bleeding due to peptic ulcers was recently evaluated for aspirin at daily doses of 300, 150, and 75 mg—doses commonly recommended to prevent heart attacks and strokes.[9]

A study conducted at five test hospitals in England found an increased risk of gastrointestinal bleeding due to peptic ulcer at all dosage levels. However, the dosage of 75 mg/day was associated with 40% less bleeding than 300 mg/day and 30% less bleeding than 150 mg/day. The researchers concluded: "No conventionally used prophylactic aspirin regimen seems free of the risk of peptic ulcer complications."

Although there has been a reduction in ulcers induced by NSAIDs with the development of the selective cyclooxygenase-2 inhibitors (Rofecoxib, Celecoxib) for arthritic conditions, aspirin-induced ulcers continue to remain an ongoing issue owing to the increased use of aspirin for protection against cardiovascular events.[8]

THERAPEUTIC CONSIDERATIONS

Individuals experiencing any symptoms of a peptic ulcer need competent medical care. Peptic ulcer complications such as hemorrhage, perforation, and obstruction represent medical emergencies that require immediate hospitalization.

Obviously the best treatment of a peptic ulcer involves identification of the causative factor and its appropriate elimination.

Lifestyle Factors

Stress and Emotions

Stress is universally believed to be an important factor in the pathogenesis of peptic ulcers. However, this belief is based on uncontrolled observations. The medical literature is controversial, and every substantial attempt to examine this assumption has been fraught with methodologic errors.[10]

This problem is further complicated by the observation that men and women with peptic ulcers appear to have distinctly different psychological profiles. In addition, several studies have shown that the number of stressful life events is not significantly different in peptic ulcer patients as compared with carefully selected, ulcer-free controls. These data suggest that it is not simply the amount of stress but rather the patient's response to it that is the significant factor. A large prospective study of 4000 persons who had no history of peptic ulcer disease revealed that those who perceived more significant stress in their lives were at increased risk for developing peptic ulcers[11] (see Chapter 60 for a more complete discussion).

Psychological factors are probably important in some patients with peptic ulcer disease but not in others. As a group, ulcer patients have been characterized as tending to repress emotions, patients should be encouraged to discover enjoyable outlets of self-expression and emotion.

Smoking

Increased frequency, decreased response to peptic ulcer therapy, and an increased mortality due to peptic ulcers are all related to smoking. Three postulated mechanisms for this association are the following[11]:

- Decreased pancreatic bicarbonate secretion (an important neutralizer of gastric acid)
- Increased reflux of bile salts into the stomach
- Acceleration of gastric emptying into the duodenum

Bile salts are extremely irritating to the stomach and initial portions of the duodenum. Bile salt reflux induced by smoking appears to be the most likely factor responsible for the greater incidence of peptic ulcer among smokers. However, the psychological aspects of smoking are also important, because the chronic anxiety and psychological stress associated with smoking appear to worsen ulcer activity.

Nutritional Factors

Food Allergy

Clinical and experimental evidence points to food allergy as a prime etiologic factor.[12-15] The lesions of peptic ulcers and the Arthus reaction (a local inflammatory response due to deposition of immune complexes in tissues) show the same microanatomic changes.[2] In one study, 98% of patients with radiographic evidence of a peptic ulcer had coexisting lower and upper respiratory tract allergic disease.[14] In another study, 25 of 43 allergic children had x-ray–diagnosed peptic ulcers.[15] Clinically, an elimination diet has been used with great success in treating and preventing recurrent ulcers.[13,14] Food allergy is also consistent with the high recurrence rate of peptic ulcers.

Ironically, many people with peptic ulcers soothe themselves by consuming milk, a highly allergic food. Milk should be avoided on this basis alone. However, there is additional evidence suggesting that milk should be avoided by patients with peptic ulcers; for example, population studies show that the higher the milk consumption, the greater the likelihood of ulcer, and milk significantly increases the production of stomach acid.[16]

Fiber

A diet rich in fiber and low in refined sugar is associated with a reduced rate of duodenal ulcers as compared with a low-fiber diet.[3] The therapeutic use of a high-fiber diet in patients with recently healed duodenal ulcers reduces the recurrence rate by one half.[17] This is probably a result of fiber's ability to delay gastric emptying of the liquid phase, counteracting the rapid movement of this phase into the duodenum, which is normally seen in ulcer patients. Although several fibers often used to supplement the diet (e.g., pectin, guar gum, psyllium) have been shown to produce beneficial effects, a diet rich in plant foods is best.[18,19]

Cabbage

Raw cabbage juice has been well documented as having remarkable success in treating peptic ulcers.[20-22] One liter per day of the fresh juice, taken in divided doses, resulted in total ulcer healing in an average of only 10 days. Further research has shown that the high glutamine content of the juice is probably responsible for the efficacy of cabbage in treating these ulcers. In a double-blind clinical study of 57 patients, 24 using 1.6 g/day of glutamine and the rest using conventional therapy (antacids, antispasmodics, diet, milk, and a bland diet), glutamine proved to be the more effective treatment. One half of the glutamine patients showed complete healing (according to radiographic analysis) within 2 weeks, and 22 of the 24 showed complete relief and healing within 4 weeks.[23] Although the mechanism for these results is not known, it is postulated by the authors to be due to the role of glutamine in the biosynthesis of the hexosamine moiety in certain mucoproteins. This could stimulate mucin synthesis, which would benefit peptic ulcer patients.

In addition, cabbage-family isothiocyanates like sulforaphane (SF) have shown considerable activity against *H. pylori*. In one double-blind study, 48 *H. pylori*–infected patients were randomly assigned to feedings of broccoli sprouts (70 g/day; containing 420 µmol of SF precursor) for 8 weeks or to consumption of an equal weight of alfalfa sprouts (not containing SF) as placebo. Intervention with broccoli sprouts but not with placebo decreased the levels of urease measured by the urea breath test and *H. pylori* stool antigen (both biomarkers of *H. pylori* colonization) and serum pepsinogens I and II (biomarkers of gastric inflammation). Values recovered to their original levels 2 months after treatment was discontinued.[24]

Bismuth Subcitrate

Bismuth is a naturally occurring mineral that can act as an antacid; it also exerts activity against *H. pylori.* The best-known and most widely used bismuth preparation is bismuth subsalicylate (Pepto-Bismol). However, bismuth subcitrate has produced the best results against *H. pylori* and in the treatment of peptic ulcers.[23,25] In the United States, bismuth subcitrate preparations are available through compounding pharmacies (to find a compounding pharmacist in your area, call the International Academy of Compounding Pharmacists at 1-800-927-4227).

A key advantage of bismuth preparations over standard antibiotic approaches to eradicating *H. pylori* is that although the bacteria may develop resistance to various antibiotics, they are unlikely to develop resistance to bismuth. As concerns in the medical community grow regarding the failures of current regimens due to resistance, nonpharmacologic management options are becoming required.[26] In India for example, 80% of isolates from 259 peptic ulcer patients tested have shown resistance to metronidazole.[27]

Although resistance to ciprofloxacin and tetracycline was minimal (1% to 4%) in this study, it is evident from recent medical history that greater resistance to these antibiotics will continue to develop. This makes bismuth a rational treatment choice in order to prevent the further development of recalcitrant strains. The usual dosage for bismuth subcitrate is 240 mg twice daily before meals. For bismuth subsalicylate, the dosage is 500 mg four times daily. Bismuth preparations are extremely safe when taken at prescribed dosages. Bismuth subcitrate may cause a temporary and harmless darkening of the tongue, stool, or both. Bismuth subsalicylate should not be taken by children recovering from the flu, chickenpox, or other viral infections as it may mask the nausea and vomiting associated with Reye syndrome, a rare but serious illness.

Flavonoids

Flavonoids are known to counteract both the production and secretion of histamine, an important factor in ulcer formation. They are generally regarded as antiallergy compounds. The use of these compounds seems particularly indicated owing to the probable allergic etiology of peptic ulcers.

Catechin, via its ability to inhibit histidine decarboxylase, offers antiulcer activity. Experimental studies in guinea pigs and rats have demonstrated that catechin has significant antiulcer activity in various models.[28,29] In a human clinical study, oral administration (1000 mg five times daily) resulted in reduced histamine levels in the gastric tissue (determined by biopsy) of normal patients and those with gastric and duodenal ulcers and acute gastritis.[29] It was also demonstrated that the histamine levels, which significantly increase in patients with urticaria and food allergy after the local application of the antigen to the gastric mucosa, could be decreased by the prior administration of catechin.

In a recent study, several flavonoids were shown to inhibit *H. pylori* in a clear-cut concentration-dependent manner.[30] In addition, unlike antibiotics, the flavonoids were also shown to augment natural defense factors that prevent ulcer formation. The activity of flavone, the most potent flavonoid in the study, was shown to be similar to that of bismuth subcitrate.

Sofalcone—a synthetic derivative of sophoradin, a flavonoid found in *Sophora tonkinensis*, an herb used in traditional Chinese medicine—has shown good results in healing ulcers after the eradication of *H. pylori*.[31,32]

Miscellaneous

Vitamins A and E have been shown to inhibit the development of stress ulcers in rats and are important in maintaining the integrity of the mucosal barrier.[33,34] High-dose vitamin A therapy was shown to be useful in the treatment of chronic gastric ulcers in one clinical trial.[35]

Zinc increases mucin production in vitro and has been shown to have a protective effect on peptic ulcers in animals[36] and a curative effect in humans.[37]

Melatonin has been shown in experimental studies to be successful in mitigating breakdown of the gastric lining and resultant ulcer formation.[38] Because this research has focused more on hypersecretion situations, melatonin may be more applicable for duodenal ulcer conditions, where the acid secretion is generally increased.

Botanical Medicines

Glycyrrhiza Glabra. Licorice has historically been regarded as an excellent medicine for peptic ulcer. However, owing to the known aldosterone-like side effects of glycyrrhizinic acid (GA), a procedure was developed to remove GA from licorice and thus to form deglycyrrhizinated licorice (DGL). The result is a very successful antiulcer agent without any known side effects (see Chapter 96).[7,39-43]

The proposed mechanism of DGL is that it stimulates or accelerates the differentiation of glandular cells as well as mucus formation

and secretion.[39] Clinical studies have demonstrated no significant differences in recurrence rates between cimetidine and DGL drug regimens, and rat and human studies have shown the efficacy of DGL in preventing aspirin-induced ulceration and gastric bleeding.[41-43]

An obvious question related to DGL is: "Does DGL have any effect on *H. pylori*?" The answer appears to be yes, because DGL is composed of several flavonoids that have been shown to inhibit *H. pylori*.[30,44]

It appears that in order to be effective in healing peptic ulcers, DGL must mix with saliva. DGL may promote the release of salivary compounds that stimulate the growth and regeneration of stomach and intestinal cells. DGL in capsule form has not been shown to be effective.

The standard dosage for DGL is two to four 380-mg chewable tablets between or 20 minutes before meals. Taking DGL after meals is associated with poor results. DGL therapy should be continued for at least 8 to 16 weeks after a full therapeutic response.

Mastic (Pistacia Lentiscus). Mastic is a resin obtained from the mastic tree (*Pistacia lentiscus*). In Greece it is known as the "tears of Chios," being traditionally produced on the Greek island of Chios; like other natural resins, it is produced in "tears" or droplets. Originally liquid, it is sun-dried into drops of hard, brittle translucent resin. When chewed, the resin softens and becomes a bright white, opaque gum. The flavor is bitter at first, but after chewing the gum releases a refreshing, slightly piney or cedar flavor.

People in the Mediterranean region have used mastic gum as a medicine for gastrointestinal ailments for several thousand years. Recent studies indicate that it may have benefit in healing peptic ulcers.

In a double-blind clinical trial carried out on 38 patients with symptomatic and endoscopically proved duodenal ulcer, patients were given either mastic gum (1 g daily) or a placebo for 2 weeks. Symptomatic relief was obtained in 16 (80%) patients on mastic gum and 9 (50%) patients on placebo, whereas endoscopically proved healing occurred in 14 (70%) patients on mastic gum and 4 (22%) patients on placebo.[45]

In another study, 52 patients with *H. pylori* infection were randomized to receive either 350 mg three times daily of pure mastic gum for 14 days (group A); 1.05 g three times daily of pure mastic gum (group B) for 14 days; pantoprazole 20 mg twice daily plus pure mastic gum 350 mg three times daily for 14 days (group C); or pantoprazole 20 mg twice daily plus amoxicillin 1g twice daily plus clarithromycin 500 mg twice daily for 10 days (group D). Eradication of *H. pylori* was confirmed in 4 of 13 patients in group A and 5 of 13 in group B. No patient in group C achieved eradication, whereas 10 of 13 patients in group D did. These results confirm that mastic gum has some bactericidal activity on *H. pylori* in vivo but not enough to produce consistent clinical eradication.[46]

Rheum Species. In cases of active intestinal bleeding, rhubarb (*Rheum* species) preparations can be extremely effective. In one double-blind study, three kinds of alcohol-extracted rhubarb tablets were studied (*Rheum officinale Baill*; *Rheum palmatum* L.; *Rheum tanguticum Maxim ex Balf*).[47] Their efficacies in a group of 312 cases of bleeding gastric and duodenal ulcers were 90.7%, 93.7%, and 92.8% respectively. The time taken for the stool occult blood to change from positive to negative was 57.1, 53.4, and 56 hours respectively. The beneficial actions are due to the presence of astringent anthraquinones and flavonoids.

Plantain Banana. In rats, the dried extract of the unripe plantain banana (*Musa sapientum* var. *paradisiaca*) has been found to have antiulcerogenic activity against various experimentally induced ulcers.[48-50] This effect appears to be similar to that of DGL (i.e., stimulation of mucosal cell growth rather than inhibition of gastric acid secretion).

Zingiber Officinale. Ginger root *(Zingiber officinale)* has traditionally been used for the treatment of gastrointestinal ailments such as indigestion, motion sickness, and nausea associated with pregnancy. One study used in vitro experimentation to test a methanol extract of ginger root as an agent against 19 strains of *H. pylori.* Results showed that growth was inhibited against all 19 strains.[51] Although more research is required to characterize the best form of this botanical medicine and to learn of its efficacy in actual patients, given its safety profile and cost effectiveness, it is certainly worth a try.

Artemisia Douglasiana. Growing on the western slopes of the Rockies, *Artemisia douglasiana* has been used as a folk remedy in Argentina to treat gastric ulcers and skin lesions since the late 1960s. *A. douglasiana* and its active constituent dehydroleucodine are known to act as potent antioxidants and, like DGL and plantain, they confer protection to the gastric lining via significantly enhanced mucus secretion.[52,53]

Allium Sativum. People whose diets are high in garlic and onions are well known to have a lower incidence of stomach cancer. *H. pylori* is a risk factor for stomach cancer as well as peptic ulcers, and in vitro studies have demonstrated that garlic does indeed inhibit its growth. Also noteworthy is the report that garlic can be useful for antibiotic-resistant strains as well. The author of this paper points out that human clinical trials are necessary in order to verify the efficacy of this low-cost treatment option.[54]



THERAPEUTIC APPROACH

Peptic ulcer disease should be recognized as a heterogeneous group of disorders with a common final pathway leading to an ulcerative lesion in either the gastric or duodenal mucosa. Patients must be carefully evaluated to determine which of the previously mentioned factors is most relevant to their health problem. This is difficult, however; therefore a more general approach may be necessary.

The first step is to identify and eliminate or reduce all factors implicated in the etiology of peptic ulcers: food allergy, cigarette smoking, stress, and drugs—especially aspirin and other NSAIDS. Once the causative factors have been controlled, attention should be directed at healing the ulcers, inhibiting exacerbating factors (e.g., reducing excess acid secretion if present), and promoting tissue resistance. Finally, the proper diet and lifestyle should be developed to prevent further recurrence.

Peptic ulcer complications—hemorrhage, perforation, and obstruction—represent medical emergencies that require immediate hospitalization.

Psychological Considerations

The physician should assist the patient in developing an effective stress reduction program, eliminating or controlling of stressors, and designing a regular relaxation plan.

Diet

The patient should eliminate allergic food, eat foods high in dietary fiber and low in refined sugars, and eat various members of the cabbage family and garlic.

Supplements

- Vitamin A: 20,000 IU three times a day
- Vitamin C: 500 mg twice a day

- Vitamin E: 100 IU twice a day
- Flavonoids: 500 mg twice a day
- Zinc: 20 mg/day
- Glutamine: 500 mg three times a day
- Bismuth subcitrate: 240 mg twice a day before meals

Botanical Medicines

- Deglycyrrhizinated licorice: 380 to 760 mg three times a day 20 minutes before meals
- Mastic gum: 350 to 1000 mg three times a day

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CHAPTER 199

Periodontal Disease

Michael T. Murray, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- Gingivitis—inflammation of the gingiva characterized by erythema, contour changes, and bleeding
- Periodontitis—localized pain, loose teeth, demonstration of dental pockets, erythema, swelling, or suppuration; possibly also alveolar bone destruction seen on radiograph

GENERAL CONSIDERATIONS

Periodontal disease is an inclusive term used to describe an inflammatory condition of the gingiva (gingivitis) or periodontium (periodontitis) or both. Periodontal disease usually involves a disease process that typically progresses from gingivitis to periodontitis.[1,2] It may be a manifestation of a more systemic condition such as diabetes mellitus, collagen diseases, leukemia or other disorders of leukocyte function, anemia, or vitamin deficiency states.[1] Periodontal disease may also contribute to systemic disease. For example, periodontal disease has been linked to atherosclerosis via an increased level of serum C-reactive protein, a marker for inflammation and a strong risk factor for coronary artery disease.[3]

Because alveolar bone loss may be noninflammatory, our definition of periodontal disease excludes the processes causing only the loss of teeth (the majority of which are due to osteoporosis or endocrine imbalances).[1] These conditions reflect systemic disease, with local factors playing only a minor role; therefore the focus should be on treating the underlying condition rather than the "periodontal disease." In this context, noninflammatory alveolar bone loss should be viewed as a separate entity, since it involves a different etiology (see Chapter 194).

The focus of this chapter is the use of nutrition and lifestyle improvement as an adjunctive therapy to aid in the control and prevention of the causes of inflammatory periodontal disease. This is a good example of a condition that is probably best treated with combined expertise (i.e., a dentist or periodontist and a nutritionally minded physician). Although oral hygiene is of great importance in treating and preventing periodontal disease, it is insufficient in many cases. The host defense must be normalized if development and progression of the disease are to be controlled.[1,4] To a large extent, the nutritional status of the individual determines the status of host defense factors.

Prevalence and Epidemiology

The prevalence of periodontal disease increases directly with age. The rate of periodontal disease is approximately 15% at age 10, 38% at age 20, 46% at age 35, and 54% at age 50. As a group, men have a higher prevalence and severity of periodontal disease than women. Periodontal disease is inversely related to increasing levels of education and income. Rural inhabitants have a higher level of severity and prevalence than their urban counterparts.[1]

Pathophysiology

Understanding the underlying pathophysiology of any disease process leads to a more effective treatment plan. In periodontal disease this involves understanding the normal host protective factors in the periodontium. Page and Schroeder[4] concluded: "Clearly bacteria are essential agents, but their presence is in itself

insufficient; host factors must be involved if the disease is to develop and progress."

Factors involved in host resistance include the following:

- The environment of the gingival sulcus
- Bacterial factors
- Leukocyte function
- Complement activation
- Immunoglobulin (Ig)E and mast cell function
- Amalgam restoration
- Miscellaneous local factors
- The structure and integrity of the collagen matrix of the periodontium and gingiva

Gingival Sulcus

The gingival sulcus, a V-shaped crevice that surrounds each tooth, is bounded by the surface of the tooth on one side and the epithelium lining the free margin of the gingiva on the other. The anatomy of the gingival sulcus is ideal for bacterial growth, because it is resistant to the washing and cleansing action of saliva. Furthermore, the gingival fluid (sulcular fluid) provides a rich nutrient source for microorganisms. The clinical determination of the depth of the gingival sulcus is an important diagnostic parameter. Patients with periodontal disease should be monitored; biannual visits to the dentist should be sufficient in most cases.

Bacterial Factors

Bacterial plaque has long been considered the etiologic agent in most forms of periodontal disease.[1] However, an appreciation of host defense factors has now developed.[1,4] Bacteria are known to produce and secrete numerous compounds that are quite detrimental to the status of the host's defense mechanisms. These compounds include the following[1]:

- Endotoxins and exotoxins
- Free radicals and collagen-destroying enzymes
- Leukotoxins
- Bacterial antigens, waste products, and toxic compounds

Polymorphonuclear Leukocytes

Polymorphonuclear neutrophils (PMNs) constitute a first line of defense against microbial overgrowth. Defects in PMN functions are "catastrophic" to the periodontium.[1,4] PMN functions are depressed in the geriatric population as a whole and in patients with diabetes, Crohn's disease, Chédiak-Higashi syndrome, Down syndrome, and juvenile periodontitis.[1,4] These patients are at extremely high risk for developing rapidly progressing periodontal disease, as are people with transient neutropenia. Transient defects in PMN function may be responsible for the periods of quiescence and exacerbation noted in periodontal disease. In addition to serving a vital role in protecting against periodontal disease, PMNs also play a major role in tissue destruction. PMNs release numerous free radicals, collagenases, hyaluronidases, inflammatory mediators, and an osteoclast stimulator.[1,4]

Macrophages and Monocytes

These leukocytes are found in increased numbers in periodontal disease. They serve to phagocytize bacteria and debris and are the primary source of prostaglandins in the diseased gingiva, releasing large quantities of enzymes believed to play a major role in collagen destruction.[1,4]

Lymphocytes

The major role lymphocytes play in periodontal disease involves lymphokine production. Their role in periodontal disease is overshadowed by the roles of the other immune system components discussed, but lymphokines are involved in promoting PMN and monocyte chemotaxis, fibroblast destruction, and osteoclast activation.[1,4]

Complement

The complement system is composed of at least 22 proteins and accounts for more than 10% of the total serum globulin. On activation, complement components act in a cascade fashion. Complement can be activated via the classic or alternative pathway. The complement system plays a critical role in immunologic and nonspecific resistance to infection and in the pathogenesis of tissue injury. The products of complement activation regulate a number of events, including the release of mediators from mast cells; promotion of smooth muscle contraction; chemotaxis of PMNs, monocytes, and eosinophils; and phagocytosis by immune adherence.[5] The net effect is an increase in gingival permeability, resulting in the increased penetration of bacteria and bacterial by-products and, in essence, the initiation of a positive feedback cycle.[1,4]

Other effects of complement activation include solubilization of immune complexes, cell membrane lysis, neutralization of viruses, and the killing of bacteria.[5] In periodontal disease, activation of complement via the alternative pathway within the periodontal pocket is possibly the major factor in tissue destruction.

Mast Cells and Immunoglobulin E

Mast cell degranulation is also a major factor in periodontal disease. Degranulation results in the release of inflammatory mediators (i.e., histamine, prostaglandins, leukotrienes, kinins, serotonin, heparin, and serine proteases).[1] Mast cell degranulation can be initiated by IgE complexes, complement components, mechanical trauma, endotoxins, and free radicals. The finding of increased IgE concentrations in the gingivae of patients with periodontal disease suggests that allergic reactions may be a factor in the progression of the disease in some patients.[6]

Amalgam Restorations

Faulty dental restorations and prostheses are common causes of gingival inflammation and periodontal destruction.[1] Overhanging margins provide an ideal location for the accumulation of plaque and the multiplication of bacteria. If the restoration is a silver amalgam filling, there may be even more involvement due to decreased activities of antioxidant enzymes. Mercury accumulation results in a depletion of the free radical–scavenging enzymes glutathione peroxidase, superoxide dismutase, and catalase.[7] The proteoglycans and glycosaminoglycans of the collagen matrix are particularly sensitive to free radical damage.[8]

Miscellaneous Local Factors

Numerous local factors favor the progression of periodontal disease; these include the following:

- Food impaction
- Unreplaced missing teeth
- Malocclusion
- Tongue thrusting
- Bruxism
- Toothbrush trauma
- Mouth breathing
- Tobacco (discussed later)

Tobacco and Alcohol

Tobacco smoking is associated with increased susceptibility to severe periodontal disease and tooth loss.[1,9,10] (In fact, tobacco

smoking is associated with increased susceptibility to virtually every major chronic disease.) Many of the harmful effects of tobacco smoking result from free radical damage, particularly to epithelial cells. Furthermore, smoking greatly reduces the levels of ascorbic acid, thereby potentiating its damaging effects.[11] Carotenes and flavonoids have been shown to greatly reduce some of the toxic effects of smoking.[12,13]

In addition to cigarette smoking, there is a dose-dependent association between alcohol consumption and periodontal disease.[14] Presumably the combination of smoking and drinking alcohol produces an even greater negative effect on periodontal health.

Structure and Integrity of the Collagen Matrix

The collagen matrix of the periodontal membrane serves as periosteum to the alveolar bone and enables the dissipation of the tremendous amount of pressure exerted during mastication.[15] The status of the collagen matrix of the periodontium, specifically the extracellular proteoglycans of the gingival epithelium, determines the rate of diffusion and the permeability of inflammatory mediators, bacteria and their by-products, and destructive enzymes from the oral cavity.[16,17] Owing to the high rate of protein turnover in periodontal collagen, the integrity of the collagen matrix in this area is extremely vulnerable to atrophy when the necessary cofactors for collagen synthesis (e.g., protein; vitamins C, B_6 and A; zinc; copper) are absent or deficient.[15]

The collagen of the periodontium is particularly rich in glycosaminoglycans.[15-18] Heparin sulfate, dermatan sulfate, and chondroitin sulfate proteoglycan 4 are the major glycosaminoglycans present. Stabilization of collagen is the major treatment goal (see later).

THERAPEUTIC CONSIDERATIONS

Therapeutic goals in treating periodontal disease from a nutritional perspective follow:

- Decrease wound healing time (because the time span for wound healing is longer in patients who are more susceptible to periodontal disease[19]).
- Improve membrane and collagen integrity.
- Decrease inflammation and free radical damage (inflammation can induce a vicious cycle and promote periodontal disease).
- Enhance immune status (defects in the immune system, particularly PMNs, are catastrophic to the periodontium).

Individual nutrients are discussed later in the context of their roles in achieving these therapeutic goals.

Nutrition

Vitamin C

Vitamin C (ascorbic acid) plays a major role in preventing periodontal disease, as is evident from many experimental studies.[1,20-24] The classic symptom of gingivitis seen in scurvy illustrates the vital function of vitamin C in maintaining the integrity of membrane and collagen as well as supporting immunocompetence. Deficiency of vitamin C is associated with defective formation and maintenance of collagen, ground substance, and intercellular cement substance in mesenchymal tissue.[1] The deficiency effects on bone include retardation or cessation of osteoid formation, impaired osteoblastic activity, and osteoporosis. Subclinical vitamin C deficiency plays a significant role in periodontal disease via these effects, which also include delayed wound healing.[1,20-24]

Decreased vitamin C levels are also associated with increased permeability of the oral mucosa to endotoxin and bacterial byproducts as well as impaired leukocyte functions (particularly with regard to PMNs). The role vitamin C plays in increasing chemotaxis and phagocytosis by PMNs is best exemplified by its effect on Chédiak-Higashi syndrome. This autosomal recessive trait is associated with compromised PMN and monocyte chemotaxis and phagocytosis, all of which are responsive to vitamin C supplementation.[25] This syndrome is also associated with an extremely rapidly progressing periodontitis.[1,4]

Vitamin C's other effects on immune status include enhancing lymphoproliferative response to mitogens and increasing interferon levels, antibody response, immunoglobulin levels, and the secretion of thymic hormones. Vitamin C also possesses significant antioxidant and antiinflammatory properties and decreases wound healing time.

Vitamin D

Low vitamin D is associated with gingivitis; it is a likely cause of both gingivitis and periodontal disease. In a study that analyzed data from 77,503 gingival units (teeth) in 6700 never smokers ages 13 to 90, those with the highest levels of vitamin D had a 30% decreased incidence of gingivitis. This was found consistent across racial or ethnic groups and was similar among men and women as well as among users and nonusers of vitamin and mineral supplements.[26a] A similar association is found for periodontal disease, in that men in the highest quintile experienced 39% less bone loss, while women experienced 26% less. Supplementation reduces bone loss.[26b] To further strengthen the case for the causal role of vitamin D deficiency, a study found a much higher incidence of the TT VDR (vitamin D receptor) polymorphism and aggressive periodontitis.[26c]

This low vitamin D status likely contributes to the link between periodontal disease and breast cancer in women.[26d]

Sucrose

Sugar is known to significantly increase plaque accumulation while simultaneously decreasing PMN chemotaxis and phagocytosis.[1,27] This inhibition of PMN function is due to osmotic effects and competition with vitamin C.

Vitamin C and glucose are known to compete for intracellular transport sites, with this intracellular transport being largely insulin-dependent. (See Chapter 56 for further information on nutrient factors and immune function.)

Considering the fact that the average American consumes in excess of 175 g/day of sucrose and other refined carbohydrates, it is safe to say that most Americans have a chronically depressed immune status that puts them at increased risk for periodontal disease.[28]

Vitamin A

Vitamin A deficiency predisposes people to periodontal disease. Deficiency of vitamin A is associated with the following[1]:

- Keratinizing metaplasia of the gingival epithelium
- Early karyolysis of gingival epithelial cells
- Inflammatory infiltration and degeneration
- Periodontal pocket formation
- Gingival calculus formation
- Increased susceptibility to infection
- Abnormal alveolar bone formation

Vitamin A is necessary for collagen synthesis and wound healing, maintaining the integrity of epithelial and mucosal surfaces and their secretions, and enhancing numerous immune functions.

Beta-carotene may be a more advantageous supplement owing to its affinity for epithelial tissue and potent antioxidant activity.[13]

Zinc and Copper

Zinc functions synergistically with vitamin A in many metabolic processes.[29] The severity of periodontal disease is positively associated with increased serum copper levels while zinc levels are significantly decreased (i.e., an increased copper-to-zinc ratio).[30] This is consistent with other causes of chronic inflammation and signifies activation of metallothionein, which increases ceruloplasmin formation while increasing zinc sequestration in response to inflammation.[29]

Zinc's importance in treating periodontal disease cannot be overstated. In the United States, marginal zinc deficiency is widespread, particularly in the elderly.[30,31] This may be a factor in the increasing prevalence of periodontal disease with age, although the geriatric population as a whole is at higher risk for development of numerous nutrient deficiencies. The functions of zinc in the gingiva and periodontium include the following[29,31-33]:

- Stabilization of membranes
- Inhibition of calcium influxes
- Antioxidant activity
- A metallocomponent in at least 40 enzymes, including those for DNA, RNA, and collagen synthesis
- Inhibition of plaque growth
- Inhibition of mast cell degranulation
- Numerous immune activities including increased PMN chemotaxis and phagocytosis

Zinc is also known to significantly reduce wound healing time.[26,29]

Zinc's positive effects in established periodontal disease are also due to its action on calcium- and calmodulin-mediated processes such as mast cell degranulation, tissue damage induced by endotoxin, and increased vascular permeability.[29] These calcium-mediated events are responsible for much of the tissue destruction seen in periodontal disease.[34]

Regular (twice daily) use of a mouthwash that contains a 5% zinc solution inhibits plaque growth.[32] However, lower concentrations or less frequent mouth washing are not particularly successful.

Vitamin E and Selenium

These two nutrients function synergistically in antioxidant mechanisms and seem to potentiate each other's effects. Vitamin E alone has been demonstrated to be of considerable value in patients with severe periodontal disease.[1,35] This can largely be attributed to the decreased wound healing time associated with vitamin E.[36] The antioxidant effects of vitamin E are particularly needed if silver amalgam is present. Mercury depletes the tissues of the antioxidant enzymes superoxide dismutase, glutathione peroxidase, and catalase. In animal studies, this toxic effect of mercury is prevented by supplementation with vitamin E.[7] Selenium and vitamin E's antioxidant activities also deter periodontal disease, as the effects of free radicals are extremely damaging to gingival proteoglycans and glycosaminoglycans.[8]

Coenzyme Q_{10}

Ubiquinone, an essential coenzyme involved in mitochondrial oxidative phosphorylation, is also an effective antioxidant.[37,38] Coenzyme Q_{10} (CoQ_{10}) is widely used in Japan for many conditions including periodontal disease. A review of seven studies using CoQ_{10} found that 70% of the 332 patients involved responded favorably to supplementation.[37] A double-blind study comprising 56 subjects found that the supplemented group responded significantly, while the placebo group displayed very little change in periodontal pocket depth and tooth mobility.[38]

Flavonoids

As a group, these compounds are perhaps the most important components of a program to alleviate periodontal disease. Flavonoids are extremely effective in reducing inflammation and stabilizing collagen structures. Flavonoids affect collagen structure by doing the following[39-44]:

- Decreasing membrane permeability, thereby decreasing the load of inflammatory mediators and bacterial products
- Preventing free radical damage with their potent antioxidant properties
- Inhibiting enzymatic cleavage by hyaluronidases and collagenases
- Inhibiting mast cell degranulation
- Cross-linking with collagen fibers directly

The more biologically active flavonoids (e.g., anthocyanidins and proanthocyanidins) should be supplemented, because rutin has little collagen-stabilizing effect. Perhaps the most useful source is grape seed extract, because its proanthocyanidins have been reported to possess a wide range of biological properties that are useful against periodontal disease.[45] In one study in mice, the effects of a grape seed proanthocyanidin extract (GSE) on the production of reactive oxygen species (ROS) and on the protein expression of inducible nitric oxide synthase (iNOS) by murine macrophages stimulated with lipopolysaccharides (LPS) of periodontopathogens was investigated. GSE strongly decreased iNOS and ROS production.[46]

The flavonoid components of *Camellia sinensis* (green tea) have demonstrated not only activity against gingival bacteria but also direct antiinflammatory effects. Epidemiologic studies have shown green tea intake to protect against periodontal disease and tooth loss.[47] Clinical studies have focused on direct local effects with either soft chewable candy or hydroxypropylcellulose strips impregnated with green tea catechin. In the study with the hydroxypropylcellulose strips, the pocket depth and the proportion of pathogenic bacteria were markedly decreased.[48] The study using the soft candy was double-blinded; it indicated by the approximal plaque index (API) and the sulcus bleeding index (SBI) scores that the green tea soft chews significantly reduced plaque and the degree of gingival inflammation.[49] A double-blind study also showed that chewing gum containing procyanidolic oligomers also minimizes gingival bleeding and plaque accumulation.[50]

Folic Acid

The use of folate, either topically or systemically, in double-blind studies produced significant reductions of gingival inflammation as determined by reduction in color changes, bleeding tendency, gingival exudate flow, and plaque scores.[51-55] The folate mouthwash, 0.1% folic acid, is significantly more effective than oral supplementation of either 2 or 5 mg/day, suggesting a local mechanism of action.[53,54] Folate has been demonstrated to bind plaque-derived endotoxin.[53-56] The use of folate mouthwash is particularly indicated for pregnant women and oral contraceptive users as well as for conditions associated with an exaggerated gingival inflammatory response or folate antimetabolites (e.g., phenytoin, methotrexate).[53,54]

Epithelial cells of the cervix and the oral cavity appear to suffer from a similar "end organ" deficiency of folic acid under the

hormonal influences of pregnancy and oral contraceptive use.[54,56,57] The cervical dysplasia associated with oral contraceptive use also responds to pharmacologic doses of folic acid (i.e., 8 to 30 mg/day).[56,57] (Whitehead's work[56] was the inspiration for the use of folic acid by Pack and Thomson[53,54] in the treatment of gingivitis of pregnancy.) The sera and leukocytes of pregnant women and oral contraceptive users contain a macromolecule that binds folate, which, more than malabsorption or decreased intake, appears to be the major factor for end-organ folate deficiency.[58] Double-blind studies have shown that the beneficial effects of folic acid are not limited to women,[49,50,53] and the positive effects are not limited to gingivitis because periodontitis improves as well.[55]

Botanical Medicines

A number of botanical compounds have shown an ability to inhibit plaque formation, but perhaps the most popular botanical medicine in a toothpaste is an alcoholic extract of *Sanguinaria canadensis* (bloodroot). This extract contains a mixture of benzophenanthridine alkaloids, but chiefly sanguinarine is available in commercial toothpastes and mouth rinses. Sanguinarine demonstrates properties useful in preventing the formation of dental plaque. It has broad antimicrobial activity as well as antiinflammatory properties. In vitro studies indicate that the antiplaque action of sanguinaria is due to its ability to inhibit bacterial adherence. Electron microscopic studies of bacteria exposed to sanguinarine demonstrate that bacteria aggregate and become morphologically irregular.[59] Sanguinarine appears to be less effective than chlorhexidine mouthwash, but it is effective in many cases and does have the advantage of being a natural compound versus a synthetic.[59,60]

Another useful botanical medicine in periodontal disease is the triterpenoid extract of *Centella asiatica* (gotu kola). This extract has demonstrated impressive wound healing properties (see Chapter 75). One study demonstrated that *Centella* extract was helpful in speeding up recovery after laser surgery for severe periodontal disease.[61]

THERAPEUTIC APPROACH

As discussed earlier, many factors are involved in the initiation and promotion of periodontal disease. Effective therapy requires that all relevant factors be controlled. Because there are as yet no clear guidelines for determining which factors are most important for a given patient, a general approach is recommended here. All patients who smoke should be helped to stop, because continued smoking greatly decreases the success of any therapy for periodontal disease. Because those factors that increase the risk for osteoporosis (e.g., low calcium and vitamin D, cigarette smoking, etc.) also predispose individuals to the risk for periodontal disease and tooth loss, attention should be directed to Chapter 194 as well as to the recommendations given here.

Hygiene

Patients should visit a dentist periodically, as needed, to eliminate accumulated plaque and calculus. Brushing after meals and daily flossing are necessary.

Diet

A diet high in dietary fiber may have a protective effect via increased salivary secretion.[20] Avoidance of sucrose and all refined carbohydrates is extremely important.

Supplements

- Vitamin C: 3 to 5 g/day in divided doses
- Vitamin D: 2000 to 6000 IU/day
- Vitamin E: 400 to 800 IU/day
- Beta-carotene 50,000 IU/day
- Selenium: 400 mcg/day
- Zinc: 30 mg/day; used as a mouthwash with 15 mL of a 5% solution twice a day
- Folic acid: 800 mcg/day; used as a mouthwash with 15 mL of a 0.1% solution twice a day

Botanical Medicines

High-flavonoid–containing extracts such as those from bilberry *(Vaccinium myrtillus),* hawthorn (*Crataegus* species), grape seed *(Vitis vinifera),* or green tea *(Camellia sinensis)* can be used according to the dosages in the corresponding chapters. Of these extracts, grape seed extract or green tea extract (or the liberal consumption of green tea as a beverage) may offer the greatest protection. For a grape seed extract with a 95% proanthocyanidolic oligomer content or a green tea extract with a 90% polyphenol content, the dosage would be 150 to 300 mg a day. Additional recommendations follow:

- *Sanguinaria canadensis:* toothpaste containing extract
- *Centella asiatica* triterpenoids: 30 mg twice a day of pure triterpenoids

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CHAPTER 200

Porphyrias

Thomas A. Kruzel, BA, MT, ND

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Diet, *1721*
Supplements, *1721*

DIAGNOSTIC SUMMARY

- Unexplained abdominal pain, possibly including nausea and vomiting
- Acute peripheral or central nervous system dysfunction
- Mental abnormalities ranging from confusion to acute psychosis
- Urinary porphobilinogen during attack
- Most carriers are usually asymptomatic except when exposed to drugs or chemicals that exacerbate the condition

GENERAL CONSIDERATIONS

Until recently, porphyrias have been considered rare. It has only been within the past decade or so that an increasing number of patients have been diagnosed with these disorders, leading some clinicians to question their prevalence. Although allopathic medicine offers therapies that are effective in treating them, naturopathic medicine possesses a considerable array of therapeutic modalities that are effective in combating these diseases and preventing their recurrence.

Porphyria as a disease was first described three centuries ago by Sir Theodore Turquet de Mayerne of France, physician to the English court of King James I. He described accounts of paralysis, bilious urine, colic, insanity fits, permanent insanity, deaths at childbirth, and premature death in those afflicted. The disease probably afflicted King George III of England and was thought to have impaired his judgment during the American Revolution.[1]

In 1911, Günther described what is now known as the classic triad of abdominal pain, constipation (or diarrhea), and vomiting. Waldenström later added to the understanding of these diseases by describing acute intermittent porphyria (AIP) as characterized by periods of exacerbation and remission.[2]

Various classifications of porphyria were arrived at as greater recognition of their variations occurred. Genetic and environmentally induced manifestations of the disease were found, with considerable variations in the clinical presentations of the different forms.

The genetic deficits of porphyria affect all tissues but primarily the blood-forming tissues of the bone marrow and the cytochrome P-450 system in the liver because of the greater number of porphyrin precursors required. The liver is the major site where inherited or acquired deficits in heme synthesis occur.[3]

Classifications of Porphyria

Porphyrias are classified as being either hepatic or erythropoietic in origin. In both classes they are characterized by the overproduction of porphyrin or their precursors. Biosynthesis of heme is controlled differently in liver and bone marrow, with the rate-limiting enzyme in liver being aminolevulinic acid (ALA) synthase, whereas the biosynthesis of heme in the bone marrow is partly regulated by the uptake of iron.

Acute hepatic porphyrias are characterized by a rapid onset of symptoms that are largely neurologic; the erythropoietic variety manifests primarily in the skin, leading to cutaneous photosensitivity (Box 200-1).

Signs and Symptoms of Hepatic Porphyrias

Acute attacks are comprised of a wide variety of symptoms, ranging from skin lesions to abdominal pain to neurologic manifestations of varying intensity. Abdominal,

BOX 200-1 **Primary Porphyrias**

Hepatic Porphyrias	Erythropoietic Porphyrias
ALA-dehydrase-deficiency porphyria	X-linked sideroblastic anemia
Acute intermittent porphyria	Congenital erythropoietic porphyria
Porphyria cutanea tarda	Erythrocytic protoporphyria
Hereditary coproporphyria	
Variegate porphyria	

Modified from Braunwald E, ed. Harrison's principles of internal medicine, ed 15. New York: McGraw-Hill, 2001.
ALA, Aminolevulinic acid.

back, or extremity pain grows in intensity over a 24- to 48-hour period, which may lead the clinician to consider appendicitis or an acute abdomen. Rebound tenderness is not usually present.

Nausea and vomiting are frequently seen, as are anxiety and restlessness. Often these patients have some degree of constipation that worsens as the condition develops. Tachycardia may also be present, suggesting an infectious process or increased bowel toxicity.

In general the severity of the symptom pattern seems to the clinician to be out of proportion to the manifesting signs. It is thought that the bowel symptoms are due to a neurologic disturbance of normal function.

Mental abnormalities can range from confusion to acute psychosis and may be the first presentations of an attack. With prolonged attacks, sensory and motor functions are impaired and can result in respiratory paralysis and death.[5] Many patients are diagnosed with schizophrenia, and a considerable number confined to mental institutions are thought to be afflicted with one of the porphyrias.[6,7]

The majority of carriers are usually asymptomatic except when they are exposed to drugs or chemicals that exacerbate the condition. Neurologic symptoms and the sequelae of an acute or prolonged attack can take months to clear, but eventual recovery occurs in the majority of cases.

BIOCHEMISTRY OF PORPHYRIA

The biosynthesis of heme is the main purpose of the porphyrogenic pathway. Heme, a high-molecular-weight metalloprotein, is a member of a group of chemicals that include cytochromes (oxidation/reduction reactions), chlorophyll (photosynthesis), and vitamin B_{12}. Heme is formed from succinyl coenzyme A (CoA) and glycine; after being combined with globin chains, it is ultimately involved in aerobic metabolism. These globin chains are synthesized on the ribosomes in the plasma of the developing erythrocyte. In the liver, heme production is largely used for the production of cytochrome P-450 in response to the body's need to eliminate toxic substances. Heme synthesis begins and ends in the mitochondrion, with part of it occurring in the cytoplasm. All tissues form heme, but the primary sites are the bone marrow and liver.

The rate-limiting enzyme for heme synthesis is ALA synthase, which is the initial enzyme in the cascade. ALA synthase requires vitamin cofactors and energy input. All other reactions in the sequence are the result of thermodynamics and are irreversible once initiated.

ALA synthase is regulated by a feedback mechanism that is responsive to the tissues' demand for heme production. With the formation of uroporphyrinogen, branching occurs and results in different porphyrin isomers. Isomer I proceeds only as far as coproporphyrin I and normally is considered inconsequential. Isomer III results in the formation of uroporphyrinogen III, which undergoes modification to render it more lipophilic so that it can be excreted from the body. Thus, most of the pathway favors heme production.

Heme Formation

Final heme formation is regulated by the action of ferrochelatase in the mitochondria. Reducing substances such as ascorbic acid, cysteine, or glutathione are required. Iron must be in the ferrous rather than ferric form. Ferrochelatase activity is inhibited by high concentrations of heme. Thus, the feedback system prevents further formation. Heme concentration also feeds back on ALA synthase, the rate-limiting step in the biosynthetic pathway.

Because heme formation is essential for aerobic metabolism, its absence would be lethal. Therefore, multiple control systems have evolved to regulate the metabolic pathway, which has made it difficult to elucidate the exact mechanism of the deficit, be it genetic or acquired. Recent advances in identifying specific DNA encoding the heme biosynthetic enzymes, however, has resulted in a more precise diagnosis of the specific genetic deficit.

Red blood cell (RBC) incorporation of heme, iron, and glycine occurs in maturing cells up through and including reticulocytes but is eventually lost as the red cell ages. Hypoxia and erythropoietin will increase ALA synthase activity in RBCs but not the liver, whereas drugs and chemicals will affect the liver but not erythropoietic tissues. Figure 200-1 illustrates heme synthesis and porphyria.

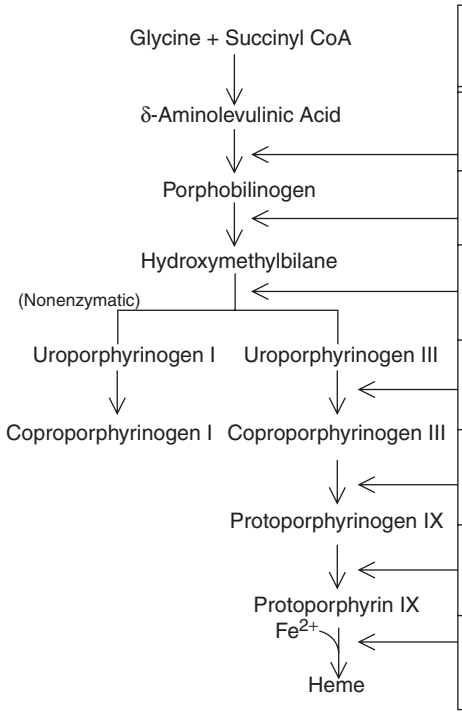
MANIFESTATION OF PORPHYRIA

In patients with porphyria, specific genetic or acquired deficiencies limit the flow of heme precursors through the cascade of steps needed to form hemoglobin. The deficiency can become manifest owing to an increased demand for heme precursors. Certain drugs, chemicals, steroids, estrogens, oral contraceptives, progesterone, testosterone, or any substance that places an excess burden on the cytochrome P-450 system can act to precipitate an acute attack. This results from the partial removal of the feedback mechanism on delta-ALA synthase. Depending on the specific enzyme deficit present, heme precursors follow different pathways resulting in their accumulation in the tissues. Their presence affects the skin and nervous system and manifests as the signs and symptoms of the disease.

Attacks occur more frequently in women than men, especially premenstrually. As the person ages, the likelihood of exposure of an underlying porphyria deficit increases because of increased exposures to environmental toxins and the aging body's decreasing ability to adapt.

Cutaneous manifestations occur because some porphyritic precursors absorb light at 400 nm, resulting in photosensitivity. The absorption of light raises the potential energy of the molecule to an "excited" state, resulting in a highly reactive oxygen species. The release of histamine and proteolytic enzymes then results in oxidative damage. Beta-carotene protects against these injuries.[3,4,8]

Neuropsychiatric changes occur in the hepatic porphyrias (ALA-dehydrase-deficiency porphyria, AIP, porphyria cutanea tarda, hereditary coproporphyria, and variegate porphyria) with excess production of ALA and porphobilinogen (PBG), and there is a somewhat linear relationship between their concentration and the severity and duration of symptoms. A buildup of porphyrin intermediaries has been found in various tissues and may induce the neuropsychiatric symptoms accompanying acute flareups.[9,10] The exact mechanism whereby porphyrins affect the central nervous system is not well understood.



Enzyme	Disease	Major Symptoms	Accumulation Products
δ-Aminolevulinate Dehydratase	ALA-Dehydrase-Deficiency Porphyria	Neurovisceral	Urinary ALA
Porphobilinigen Deaminase	Acute Intermittent Porphyria	Neurovisceral	Urinary ALA and PBG
Uroporphyrinogen III Cosynthase	Congenital Erythropoietic Porphyria	Photosensitivity	Erythrocyte and Urinary Uroporphyrin I and Coproporphyrin I
Uroporphyrinogen Decarboxylase	Porphyria Cutanea Tarda; Hepatoerythropoietic Porphyria	Photosensitivity	Urinary 7-Carboxylate Porphyrin; Fecal Isocoproporphyrin
Coproporphyrinogen Oxidase	Hereditary Coproporphyria	Neurovisceral and Photosensitivity	Urinary ALA, PBG, and Coproporphyrin; Fecal Coproporphyrin
Protoporphyrinogen Oxidase	Variegate Porphyria	Neurovisceral and Photosensitivity	Urinary ALA and PBG; Fecal Protoporphyrin
Ferrochelatase	Erythropoietic Protoporphyria	Photosensitivity	Erythrocyte, Plasma, and Fecal Protoporphyrin

FIGURE 200-1 The heme synthesis and porphyria. (From Sassa S, Kappas A. The porphyrias. Scientific American medicine. New York: Scientific American, 2003:9:V:1-9.)

Patients with familial porphyria cutanea tarda (PCT) usually present at a younger age than those who develop PCT spontaneously, despite the fact that there is no difference in the biochemical features of the disease.[11] This may be because of a corresponding genetic predisposition to sequester ferritin in the liver or an increased sensitivity to ethanol ingestion.[11,12] Additionally, even in families with known genetic deficits, manifestations of the disease among family members vary.

Etiologic Agents Triggering Porphyria

Numerous agents that trigger episodes of porphyria have been identified, and patients afflicted must be careful when taking prescription medications, estrogens, and some herbal medicines; they must also avoid environmental exposures to heavy metals, organophosphates, and any substance that places an excess burden on the cytochrome P-450 system. In particular, exogenous estrogens—whether from oral contraceptives, estrogen patches, or estrogen replacement therapy—are strong contributors to an underlying porphyria deficit.[13,14] This is one reason why acute attacks of porphyria are seen more often in women than men, especially premenstrually. Additionally, some studies have suggested that estrogens enhance the porphyrin-inducing activities of other agents, making women more vulnerable to environmental exposures than their male counterparts.[15,16]

Herbicide-induced porphyria has been shown to decrease the activity of several enzymes involved in the porphyritic pathway as well as to increase the porphyrin content in nerve tissue.[16,17] A considerable number of chemicals have also been linked to porphyria or porphyrinuria in humans; these generally involve chronic industrial exposures or environmental exposures. An example of an epidemic of PCT produced by the accidental ingestion of wheat treated with the fungicide hexachlorobenzene occurred in Turkey in the 1950s.

Some researchers have hypothesized that several otherwise unexplained chemical-associated illnesses such as multiple chemical sensitivity syndrome (MCSS) may represent mild chronic cases of porphyria or other acquired abnormalities in heme synthesis.[18,19]

According to William Morton, who has written extensively on porphyrias, MCSS as first described by Cullen in 1979 may, in fact, be porphyria. Morton speculates that exposures to porphyrogenic chemicals, medications, or severe infection overpower the already deficient enzyme system, resulting in an accumulation of the specific porphyrin because of diminished enzyme function. He proposed that the resultant symptoms are due to an increase of the porphyrinogen and not an accumulation of the toxin itself. Many diagnosticians have tried to expedite the distinction between "real" porphyria and secondary porphyrinopathies by requiring that a porphyria diagnosis be based on urinary or fecal porphyrin excretions or both 2 to 20 times the upper limit of normal. This classification would exclude individuals demonstrating lesser degrees of porphyrinogenic activity, possibly some of those whose conditions are in remission or not subject to environmental exposures.[20]

The intensity of porphyria symptoms varies widely. About 10% of the cases present with acute severe attacks, whereas approximately 25% are seen with chronic symptomatology of varying degrees. The remaining percentage (65%) present with no symptoms but may become susceptible under the right circumstances.[21]

Not all researchers agree with Morton's and others' premise that environmental toxicities induce underlying genetic deficits leading to symptomatic porphyria. According to Hahn and Bonkovsky, "patients with multiple chemical sensitivity syndrome may, at times, have modest increases in urinary coproporphyrin excretion; this is a common finding found in many asymptomatic subjects or patients with diverse other conditions (e.g., diabetes mellitus, heavy alcohol use, liver disease, and many kinds of anemia). Such secondary coproporphyrinuria does not indicate the existence of coproporphyria."[22]

Regardless of which view is correct, an increasing number of cases are being diagnosed by clinicians. Certainly, with the increasing levels of pollutants in the environment, hormonal additives to

the food chain, and the unmonitored multiple pharmacy prescriptions encountered by most humans, the potential for unmasking an underlying deficit increases.

LABORATORY DIAGNOSIS OF PORPHYRIA

Small amounts of porphyrins are excreted in normal human urine, the most predominant of which is coproporphyrin. Coproporphyrin is also present in the bile and feces. ALA, PBG, and uroporphyrin are largely excreted in the urine, whereas coproporphyrin is preferentially and protoporphyrin exclusively excreted in the bile and feces.

Fecal excretion is also affected by diet and bowel flora, thus contributing to its wide variation. Geographic distribution, dietary preferences, ethnic diversities, and differences in test methodologies make it difficult to arrive at "normal" values.

PBG excretion in the urine of healthy individuals is usually below 1.5 mg/day and is undetectable by conventional testing. The Watson-Schwartz qualitative test for PBG will be positive in acute attacks of AIP and variegate porphyria and hereditary coproporphyria in latent periods.[23] There is a high false-negative rate owing to its subjective nature. A false increase in porphyrins from a substance present in yeast tablets has been demonstrated to produce a false-positive Watson-Schwartz test.[24]

A cost-effective strategy for the diagnosis of porphyric syndromes in the presence of acute symptoms has been suggested:

> *If neurovisceral features suggest an acute porphyric syndrome, a rapid screening test for urinary porphobilinogen should be performed. If clinical features suggest a cutaneous porphyria, then for solar urticaria and acute photosensitivity (suggesting protoporphyria) screening tests for increased erythrocytic porphyrins should be done; for vesiculobullous formation (suggesting porphyria cutanea tarda, hereditary coproporphyria, or variegate porphyria) a screening test for urinary porphyrins should be done. Positive screening tests should be confirmed with targeted quantitative testing.*[25]

Enzymatic assays and DNA-based testing are not usually necessary for the rapid diagnosis or management of symptomatic subjects with acute disease. Such tests are, however, useful for evaluation and genetic counseling. Isolation of specific DNA encoding the heme biosynthetic pathway enzymes makes it possible to now provide precise heterozygote identification as well as prenatal diagnosis in families with known defects.[4,25,26]

Other cell markers may also help in identifying porphyria patients in the absence of symptoms. Leukocyte concentrations of manganese, calcium, iron, zinc, and erythrocyte calcium have been shown to be present at different concentrations between groups classified as AIP gene carriers. Of the cell markers, manganese was found to be the most discriminative component of all the variables investigated. An increase in cellular manganese by a factor of four suggests an increase in the likelihood of development of AIP.[27]

Because of the many possible genetic deficits leading to porphyria, it is important that the specific deficit be determined, because successful treatment outcomes depend on the correct diagnosis.

See also Chapter 29 for more discussion of the diagnosis of porphyrinopathies.

THERAPEUTIC CONSIDERATIONS

It is important to identify patients who are predisposed and susceptible to the development of porphyritic episodes. On seeing a patient with a past medical history of periodic psychotic episodes or nervous breakdown, unexplained abdominal pain, or unusual symptoms that have led to numerous diagnoses, the physician should be alerted to the possibility of an underlying porphyria. Prevention is clearly the first option, because porphyritic episodes can be difficult to control once initiated.[28]

The treatment of patients afflicted with acute episodes of porphyria can be demanding and owing to the severity of the condition and the unstable clinical picture. Each patient presentation is different depending on the degree of toxicity, genetic component, and patient response to therapy.

Homeopathic treatment has proved successful, but different homeopathic medicines are required depending on the clinical picture, which, as has been mentioned, can change quickly. Constitutional prescribing does not seem to work as well when the patient is in an acute state, and several prescriptions may be necessary to help the patient to become stable. The prescriptions may have to be changed frequently as the patient progresses through the varying stages of the disease.

During an acute episode, frequent follow-up is necessary in order to assess the clinical state. In some cases, patients must be seen daily and medications altered depending on the presentation.

Education of the patient as to his or her condition is one of the most important tasks. Often the patient does not want to believe that a genetic affliction exists and will seek another diagnosis. He or she has often received various diagnoses and may still believe that this condition is another disorder. It will be important to delineate which symptoms go with each condition, but they will all probably be related to the porphyria. Additionally, informing other physicians seen by the patient as to his or her condition will help to keep prescription drugs to a minimum, thus decreasing the likelihood of an exacerbation.

The course of therapy required for the patient to reach a state where he or she is not as susceptible to environmental toxins is usually long and involves periods of exacerbation and remission. Helping the patient to understand this will facilitate the recovery.

Environmental and chemical exposures must be eliminated by identifying offending agents and limiting exposures. Lists of prescription medicines and environmental toxins that cause exacerbation of porphyria are available (Boxes 200-2 and 200-3). A complete history as to environmental and work-related exposures is in order. Often, simply by changing the patient's work environment, exposures will be decreased and attacks eliminated.

BOX 200-2 Toxins Known to Cause or Exacerbate Porphyria

Intoxications
- Alcoholism
- Foreign and environmental chemicals (e.g., hexachlorobenzene, polyhalogenated biphenyls, dioxins [2,3,7,8-tetrachlorodibenzo-p-dioxin], vinyl chloride, carbon tetrachloride, benzene, chloroform)
- Heavy metals such as lead, arsenic, and mercury
- Drugs

Adverse Effect of Drugs
- Analgesics
- Sedatives
- Hypnotics
- Anesthetics
- Sex hormones
- Sulfa-drug antibiotics

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Diet

During attacks of AIP, an increased intake of complex carbohydrates can help to alleviate symptoms. Often the patient is ingesting high amounts of carbohydrates when first seen, and weight gain often follows. Intravenous glucose can also be given (300 to 400 g/day). A more complete parenteral nutritional regimen is preferable, however. Fasting or rapid-weight-loss diets can precipitate AIP and should be avoided.

A diet rich in high-fiber fruits and vegetables has been shown to be remarkably effective in improving several measures of porphyria. A 3-week study of 13 male PCT patients found that 500 kcal/day of fruits and vegetables resulted in a significant decrease in body-mass index from 26.8 to 25.8, serum ALT activity from 122 to 75.6 U/L, serum AST from 91.8 to 55.2 U/L, serum iron levels from 188.6 to 140.2 mg/dL, and serum ferritin concentrations from 574 to 499 ng/mL. Skin lesions also improved, and urinary coproporphyrin excretion decreased. There was a statistically insignificant reduction in uroporphyrin excretion.[30]

BOX 200-3 Drugs Known to Cause or Exacerbate Porphyria*

- Antipyrine
- Aminopyrine
- Aminoglutethimide
- Barbiturates
- Captopril
- Carbamazepine
- Carbromal
- Chloral hydrate
- Chloramphenicol
- Chlordiazepoxide
- Chlorpropamide
- Danazol
- Dapsone
- Diazepam
- Diclofenac
- Diltiazem
- Diphenhydramine
- Diphenylhydantoin
- Doxycycline
- Ergot preparations
- Erythromycin
- Estrogen
- Ethanol (acute)
- Ethchlorvynol
- Ethinamate
- Furosemide
- Glutethimide
- Griseofulvin
- Hydralazine
- Hydrochlorothiazide
- Imipramine
- Isopropyl meprobamate
- Lidocaine
- Mephenytoin
- Meprobamate
- Methyldopa
- Methylprylon
- Metoclopramide
- Metronidazole
- N-butylscopolammonium bromide
- Nifedipine
- Nitrous oxide
- Novobiocin
- Oral contraceptives
- Orphenadrine
- Oxycodone
- Pentazocine
- Phenobarbital
- Phenylbutazone
- Phenytoin
- Piroxicam
- Pivampicillin
- Primidone
- Progesterone
- Pyrazimide
- Pyrazolone preparations
- Sodium valproate
- Succinimides
- Sulfonamide antibiotics
- Sulfonethylmethane
- Sulfonmethane
- Synthetic estrogens, progestins
- Terfenadine
- Tetracyclines
- Theophylline
- Tolazamide
- Tolbutamide
- Trimethadione
- Valproic acid
- Verapamil

Modified from Sassa S, Kappas A. The porphyrias. Scientific American medicine. New York: Scientific American, 2003:9:V:1-9.
*Although this list includes many of the better-known drugs that can exacerbate porphyria, it should not be considered complete.

Antioxidants

Antioxidant therapy, along with homeopathy, is the mainstay of case management during acute porphyritic episodes.[31] Once the patient has stabilized, an ongoing regimen of antioxidants such as vitamin C, vitamin E, glutathione, beta-carotene, and *N*-acetylcysteine should be undertaken in order to prevent recurrence.[32] Vitamin C has been found to be low in PCT patients.[33] Subjective evaluation of the use of high-dose vitamin C (1 g a day) compared with placebo was conducted in 12 patients with erythropoietic protoporphria photosensitivity for a period of 4 weeks. Although there was no statistical significance to the fact that patients fared better on the high-dose vitamin C, 8 of the 12 participants reported less sensitivity to sunlight.[34]

High-dose vitamin E supplementation (1 g/day of alpha-tocopherol) in patients with PCT decreased urinary excretion of uroporphyrins (50% of the C8 carboxyls), with clinical improvement in all patients.[35] The effect lasted only as long as vitamin E was being supplemented. Treatment with vitamin E was found to reduce residual oxidative stress while not affecting increased plasma and whole-blood viscosity present in PCT patients who were receiving only phlebotomy treatment prior to clinical remission.[36]

Combinations of antioxidants are also being looked at as a mode of treatment for the various porphyrias. A study comparing the protective ability of several antioxidants used concurrently for the phototoxicity of protoporphyrin IX (PP IX) and uroporphyrin I (UP I) was conducted on cell cultures. The researchers found that cell growth and cell membrane protection showed differences in protection for the two types of porphyrias. Both beta-carotene and lycopene and the combination of beta-carotene, ascorbic acid, and alpha-tocopherol offered cell protection against PP IX phototoxicity. For membrane protection, there was significant protection against UP I by the combination of beta-carotene, ascorbic acid, and alpha-tocopherol as compared with any of these antioxidants alone. The authors concluded that a combination of beta-carotene, ascorbic acid, and alpha-tocopherol offers membrane protection against the phototoxicity of both porphyrins, which is believed to occur as a result of synergistic processes. Their results suggest that the treatment of porphyria cutanea tarda and erythropoietic protoporphyria may be improved by the use of a combination of the antioxidants studied.[37]

Additionally, it is thought that the increase in oxidative damage from photodermatitis would contribute to lower vitamin D levels. Lower levels of vitamin D have been implicated more recently as contributing to a number of medical conditions such as stroke, osteoporosis, hip fracture, and muscle weakness.[38] A cohort of 201 patients with known erythrocytic protoporphyria (EPP) was evaluated over a 7-month period for the deficiency of vitamin D levels due to lowered sun exposure. Thirty-four patients (17%) were deficient in vitamin D and 126 (63%) were found to have insufficient levels of vitamin D. Both insufficiency and deficiency were significantly associated with the total erythrocyte protoporphyrin concentration and inversely with the time in minutes to the onset of symptoms following sunlight exposure. The authors concluded that in patients with porphyrias associated with photodermatitis, vitamin D therapy should be considered.[39]

In two studies, melatonin as an antioxidant was evaluated for its effects on delta-aminolevulinic acid–induced oxidative toxicity in neural tissue and as a cotreatment in patients suffering from disturbances related to ALA accumulation. In in vivo experiments it was demonstrated that lipid peroxidation induced by delta-aminolevulinic acid (40 mg/kg) in the cerebellum and hippocampus was reduced by

acute melatonin (10 mg/kg) administration.[40] In the other study it was concluded that melatonin had marked efficacy in protecting against ALA-related oxidative stress and its oncostatic properties. Moreover, it was concluded that its low toxicity constituted a reason to consider the use of melatonin as a cotreatment in patients suffering from disturbances related to ALA accumulation.[41]

B-Complex Vitamins

Because pantothenic acid is required for the formation of succinyl CoA (generated by the tricarboxylic acid cycle) and glycine, which are the precursors to formation of ALA, supplementation is helpful. Additionally, a step in the transformation of succinyl CoA requires a vitamin B_{12}–dependent enzyme, and evaluation of vitamin B_{12} and folic acid status may be in order. The initial reaction is oxygen-dependent, which may mean that oxygen therapy is contraindicated in delta-ALA porphyria.

ALA formation requires and is dependent on pyridoxal-5-phosphate; hence, any substance that inhibits enzyme systems is countered in part by the addition of pyridoxal-5-phosphate. However, experimental models suggest that this agent does not play an important role.[3]

Carotenoids

All cutaneous porphyrias can be alleviated by the avoidance of sunlight. Treatment of erythropoietic protoporphyria with large doses of beta-carotene has been effective and may improve tolerance to sunlight.[42] Another study showed that mixed carotenoids (alpha-carotene, beta-carotene, and lycopene) were effective in cell cultures, although any one of these used alone was ineffective.

Iron

Several lines of evidence suggest that excessive iron stores and consumption aggravate some porphyrias.[43] Iron should be avoided unless supplementation is clearly indicated by low iron stores.

Detoxification

Detoxification of the liver and colon is indicated as an ongoing process to eliminate toxins that may exacerbate the condition. Regardless of whether the toxin actually precipitates an attack of porphyria, elimination on an ongoing basis reduces the chance of an acute flareup of the disease. Detoxification can be achieved through colon hydrotherapies, constitutional hydrotherapies, saunas, antioxidants, or oxygen therapies such as ozone.

Supplementation with lipotrophic factors that enhance the function of the liver's cytochrome P-450 system are contraindicated during acute attacks but useful when the patient is in a period of normality. Incorporating them, as well as high doses of antioxidants, helps decrease the number of acute attacks.

Additionally, chelation therapies with ethylenediamine tetraacetic acid and ethanol extracts of botanical medicines are contraindicated in patients with a predisposition to developing porphyria.

Constitutional Hydrotherapy

Constitutional hydrotherapy during an acute flareup is effective in normalizing liver function as well as neurologic symptoms. Daily sessions may be necessary to accomplish this, while allowing the physician to monitor the patient closely.[44]

Ozone Therapy

Ozone therapy is primarily indicated when there is a deficit of coproporphyrinogen oxidase, resulting in a deficit of coporphyrinogen in hereditary coproporphyria. It is contraindicated when there is a deficit of ALA synthase, because higher amounts of oxygen enhance the pathway and exacerbate the symptoms.

THERAPEUTIC APPROACH

The primarily clinical approach is to identify the condition early and avoid irritating and aggravating factors. Sun exposure should be limited when cutaneous manifestations are present.

Diet

The patient's diet should be rich in fruits and vegetables and low in iron.

Supplements

- Vitamin E: 400 to 1200 IU/day
- Mixed-carotenes: 100,000 to 150,000 IU/day
- Vitamin C: 3000 to 5000 mg/day
- Vitamin D: 5000 to 10,000 IU/day (measure blood levels to determine optimal dosage)
- Melatonin: 3 mg/day

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CHAPTER 201

Pregnancy Health and Primary Prevention of Adult Disease

Pina LoGiudice, ND, LAc, and Peter B. Bongiorno, ND, LAc

INTRODUCTION

Pregnancy provides a unique opportunity for the practitioner to help create a healthful environment for the benefit of the mother and to positively affect the future offsprings health. The health care provider can use this time to educate and empower parents to create optimal conditions for the future health of the family.

There is a growing body of evidence suggesting that increased susceptibility to chronic disease in adulthood originates in part during fetal development.[1] In utero gene expression is highly sensitive to environmental changes, which can lead to altered function, metabolism, and hormone production.[2] In utero environmental exposures alter phenotypic expression via DNA methylation, histone acetylation, messenger RNA expression, and chromatin structure modification. These epigenetic changes occurring in the womb are replicated throughout life, and may even be passed to subsequent generations.

Preconceptive Work

It should be noted that if the practitioner has the opportunity to work with the pregnant mother before pregnancy, natural considerations to detoxify, replete deficient nutrients, and lower stress would be ideal before conception in order to optimize the in utero environment.

Pregnancy Death Rates and Premature Births

According to the World Health Organization (WHO), the pregnancy death rate has decreased by 30% in the last 20 years. This decline is due to both a worldwide increase in the training of midwives as well as higher quality pregnancy care in higher-risk community health centers and hospitals. Pregnancy deaths are about 36 times greater in a developing country versus a developed country. The main causes of such deaths are severe bleeds after childbirth, infections, hypertension, and improper abortion.[3] With more than 540,000 yearly premature births, the United States has a significantly higher rate of infant mortality compared with other developed countries owing to the inadequate pregnancy care received by poor women, increased infertility treatments (which raise the odds of multiple births), and early labor and delivery.[4]

Weight Gain

On average, women should expect to gain from 25 to 35 pounds during a normal pregnancy, with a typical 3- to 4-pound gain during the first trimester (Table 201-1). Low weight gain is associated with increased intrauterine growth restriction risk and perinatal mortality. The overall weight gain represents two components: (1) the products of conception (fetus, amniotic fluid, and placenta) and (2) maternal accretion of tissues (expansion of blood and extracellular fluid, enlarged uterus and mammaries, and adipose stores).

Obesity in Pregnancy

Animal studies reveal that high maternal weight or weight gain during pregnancy leads to changes in the hypothalamus, pancreatic islet cells, fat tissue, endocrine physiology, and metabolic pathways affecting homeostatic weight control.[5] Excessive gains are

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TABLE 201-1 **Current Recommendations for Weight Gain During Pregnancy**

Prepregnancy BMI	BMI (kg/m^2) (WHO)	Total Weight Gain Range (lb)	Rates of Weight Gain 2nd and 3rd Trimesters (lb/wk)
Underweight	<18.5	28–40	1 (1–1.3)
Normal weight	18.5–24.9	25–35	1 (0.8–1)
Overweight	25.0–29.9	15–25	0.6 (0.5–0.7)
Obese (includes all classes)	≥30.0	11–20	0.5 (0.4–0.6)

Data from the Institute of Medicine. Weight Gain During Pregnancy: Reexamining the Guidelines.Washington DC: National Academy Press; 2009.

associated with gestational hypertension, labor augmentation, high birth weight, cesarean sections, neonatal metabolic abnormalities, and fetopelvic disproportion complicates the risk.[6]

According to the Centers for Disease Control (CDC), 20% of women are obese at the onset of pregnancy. Babies born to obese women are nearly three times more likely to die within the first month of birth, and stillbirth rates are doubled. Very obese women, or those with a body-mass index of 35 or higher, are three to four times as likely to deliver their first baby by cesarean section versus first-time normal-weight women.[7] Weight gains of 6.7 to 11.2 kg (15–25 lb) in overweight and obese women, and less than 6.7 kg (15 lb) will reduce risk. Interestingly, in morbidly obese women, poor weight gain was associated with 30% less use of epidural analgesia and an overall reduction in negative outcomes.[8]

Thyroid

With normal thyroid function needed for pregnancy success, the need for thyroxine increases in many women.[9] Preterm delivery, preeclampsia, hypertension, diabetic complications, placental abruption, miscarriage, and adverse fetal effects have all been reported with hypo- or hyperthyroidism during pregnancy.[10]

Normal thyroid stimulating hormone (TSH) levels alone do not assure proper thyroid function. Normal TSH accompanying autoimmunity creates a twofold risk for pregnancy loss.[11] Although TSH laboratory values range between 0.45 and 4.5 mIU/L, studies suggest that that the upper range cutoff in the pregnancy TSH should be around 2.5 mIU/L.[12] Miscarriage and preterm delivery increase with higher levels. Furthermore, women with positive antibodies and no replacement therapy also have higher rates of miscarriage than women with positive antibodies and levothyroxine replacement (13.8% vs. 3.5%).[13]

Women planning to undergo fertility treatment may benefit from thyroid antibody screening and thyroid replacement if antibodies are found, especially if clinical symptoms are present. Symptoms can include fatigue, dry skin, constipation, slowed mentation, and low body temperature. Women with otherwise unexplained previous pregnancy losses probably should be treated if their TSH level is above 2.5 mIU/L and/or they have a positive test for antibodies.

One study of 4,123 thyroid antibody–free women found a 3.6% rate of pregnancy loss in women with a TSH level greater than 2.5 mIU/L and double that rate (6.1%) in women with TSH levels between 2.5 and 5.0 mIU/L. Age, obstetric history, and even thyroid function tests did not differ between those who miscarried and those who did not. Statistically, the risk of miscarriage increased by 15% for each elevation of 1 mIU/L in the TSH level. Preterm and very preterm delivery risks did not differ with TSH levels.[14]

BOX 201-1 **Adjuvant Ingredients**

- Squalene
- Polysorbate 80
- Sorbitan triolate
- Sorbitan oleate
- Polyethylene cetostearyl ether
- Mannitol
- Aluminum hydroxide
- Aluminum phosphate
- Aluminum hydroxyphosphate sulfate

Preeclamptic women are more likely to have hypothyroidism before conception or in late pregnancy. After the onset of preeclampsia, predelivery TSH increased 2.42 times above baseline versus 1.48 times in controls. Toward the end of pregnancy, women with preeclampsia had, in general, much higher levels of TSH than women with no history of preeclampsia.[15]

Flu Shots and Vaccines

In pregnancy care, it is generally recognized as reasonable to avoid any unnecessary treatment. Vaccination during pregnancy is a controversial topic in both conventional and natural medicine.

Vaccination is recommended in several countries, and no studies demonstrate an increased risk of maternal or fetal adverse effects with inactivated, unadjuvanted shots.[16,17] The U.S. Advisory Committee on Immunization Practices recommends the influenza vaccine in pregnancy, citing increased risks of flu complications in pregnant women. There is a 41% decreased incidence of flu in infants born to vaccinated women as well as a 39% decrease in influenza-like illness and hospitalization. Infant antibody titers were significantly higher with vaccinated pregnant mothers. It should be noted that one of the study authors received grants from three companies that manufacture influenza vaccine.[18]

Newer vaccines, such as the influenza/H1N1 vaccine, now include adjuvant, which may induce a stronger immune response in pregnant individuals, because they have been shown to be more sensitive to proinflammatory stimuli than those who are not pregnant.[20] An adjuvant (Box 201-1) is a substance that, when administered in combination with a specific antigen, enhances the immune response against the antigen when compared with use of the antigen alone. Many pregnant women were vaccinated with the adjuvanted H1N1 pandemic influenza vaccine at a time when its safety had not been tested.[20]

The CDC Advisory Committee on Immunization Practices in pregnancy[21] supports giving pregnant women a number of vaccinations during pregnancy and lists only two as contraindicated. These are listed in Box 201-2.

LIFESTYLE FACTORS

Hydration

Vital for a healthful pregnancy, appropriate fluid intake hydrates all body cells and provides a normal 40% volume expansion in the pregnant woman.[22] About 32 ounces of fluid surround the baby as amniotic fluid, which is replaced every third hour. Insufficient fluid intake can cause constipation, preterm labor, temperature dysregulation, cystitis, miscarriage, and fatigue. Proper hydration is also important for subsequent breast milk production and flow.

BOX 201-2 Vaccination Recommendations from the CDC Advisory Committee on Immunization Practices in Pregnancy

Tetanus, diphtheria, pertussis	**Contraindicated Vaccines:**
Hepatitis A	Measles, mumps, rubella
Hepatitis B	Varicella
Influenza	
Pneumococcus	
Polio	
Typhoid-nonlive	

Data from Zain A, Al-Safi Valerie I, Shavell VI, Gonik B. Vaccination in pregnancy. *Women's Health* 2011;7(1):109-119.

With 96 ounces of fluid loss via urination and perspiration per day, each pregnant women needs between 8 and 12 eight-ounce glasses of water or other beverages per day. Weather that is warmer than usual and dry, cold weather both increase moisture loss. The pregnant woman should avoid heavily caffeinated drinks and sugary beverages. It is best to drink at regular intervals and not wait for the feeling of thirst.

Energy Needs and Diet

Pregnancy is a demanding anabolic state that hormonally redirects nutrients to maternal reproductive tissues and the developing infant.[23] Pregnancy leads to a modest increase of energy needs on the order of 375, 1200, and 1950 kJ daily for the first, second, and third trimesters of pregnancy respectively,[24,25] which can normally be met by modest increases in consumption of a balanced diet. The 2002 Dietary Reference Intake Report set a minimum level of 175 g carbohydrate per day for pregnancy, which includes an additional 33 g carbohydrate for fetal brain development and functioning over nonpregnant women. There is no indication that recommendations for dietary total fat intake, expressed as a percentage of energy intake, need to differ from those for nonpregnant women.[26] With micronutrient deficiencies common during pregnancy (even in well-fed populations),[27] it is important to consider a prenatal multivitamin along with a healthful diet.

Under- and Overnutrition

Undernutrition during pregnancy and low birth weight epigenetically increase the risks of diabetes and cardiovascular disease in adulthood.[28] In birth cohorts conceived during the height of the Dutch Hunger Winter famine of 1944–1945[29] and the severe China famine, from 1958–1961,[29,30] fetal effects included higher weight and waist circumferences, higher adult BMIs, increased risk of hypertension, impaired glucose tolerance,[31] increased risk for cardiovascular disease[32] and diabetes,[33] and a twofold increase in the incidence of schizophrenia[34] and both mood and schizoid personality disorders.[35]

Excess and unbalanced food choices will also have a negative impact on the health of the offspring via high birth weight, which increases the risks for obesity and diseases such as cancer and asthma later in life. It is appropriate for a baby to be born with some adipose tissue, but excess fat is indicative of abnormal fetal development.[5]

Healthful dietary changes after a baby is born may not be able to reverse the original fetal insult. Pregnant rats fed an unhealthy diet are more likely to have offspring that develop breast cancer, likely due to the in utero effect on mammary remodeling. Even when daughters eat healthily, their disease risk is still not ameliorated. Interestingly, daughter rats with grandmothers who ate a fatty diet were even more at risk. In one study at 20 weeks, 50% of the rats whose grandmothers ate a normal diet developed breast tumors, whereas 80% of rats with two grandmothers fed a high-fat diet grew tumors and 68% of the rats with just one such grandmother developed cancer. These animal studies strongly suggest that a fatty diet may cause epigenetic DNA modifications that can be passed on to future generations.[36]

The brain and nervous system are also subject to the epigenetic changes of a high-fat diet. One study looked at three different pregnancy diets: the first diet was high in saturated fat, the second was high in unsaturated or "trans" fat, and the third was a control low-fat diet. At weaning and in adulthood, proinflammatory cytokine expression was strikingly increased in the periphery and hippocampus following a bacterial challenge in the high-fat and trans-fat groups compared with controls. Anxiety was significantly increased in fat-exposed offspring, particularly males, and there was a negative effect on learning. These effects were all observed in adulthood, even after the pups were placed on standard chow at weaning, suggesting that these outcomes were programmed in utero. The findings suggest that maternal diet will program brain changes that begin before birth and that these cannot be reversed in the offspring with a change in diet.[37]

Healthy Foods

Fruits and Vegetables

Pregnant women require more fruits and vegetables than usual because of the extra demands on the body. One study of 1034 women reported dose-dependent reductions in urinary tract infection with an increased intake of *both* fruits and vegetables, not either alone.[38] The recommendation is seven servings per day of fruits and vegetables during pregnancy. A serving size for fruit or vegetables is one half cup. Less dense greens like spinach and lettuce have a serving size equal to one full cup.[39]

Folic Acid–Containing Foods

Given the well-known association between deficiency of folic acid during the prenatal period with spina bifida and other neural tube defects,[40] pregnant women should be encouraged to eat foods specifically higher in folic acid. Foods containing excellent to good sources of folic acid are fortified grains, spinach, lentils, chick peas, asparagus, broccoli, peas, Brussels sprouts, corn, and oranges. However, research suggests that diet alone is unlikely to provide levels similar to those from folate-multivitamin supplementation.[41]

Apples

In two birth cohort studies of children, maternal intake of apples or apple juice had a protective effect on the children, with a 40% decreased rate of wheeze and about a 50% lowered risk of asthma at age 5.[42,43] Apples have a powerful phytochemical content, which includes flavonoids, isoflavonoids, and phenolic acids. Because apple juice is a high-sugar food, whole apples are advised.

Vegetarian Diets

Although vegetarian diets are associated with healthier pregnancy weight,[44] strict vegan diets have been reported to cause low

pregnancy vitamin B_{12} status, anemia, and delayed infant development.[45] The American Dietetic Association (ADA) proffers that properly planned vegetarian or vegan diets can be "healthful, nutritionally adequate, and may provide health benefits in the prevention and treatment of certain diseases." The ADA also suggests that well-planned vegetarian diets are appropriate for individuals during all stages of the life cycle, including pregnancy and lactation.[46]

Soy

Soy is a staple in many vegetarian diets. The use of soy during pregnancy is controversial. A Danish analysis suggests that a pregnancy diet lacking fish and meat was associated with a more than fourfold increased risk of hypospadias,[47,48] possibly due to increased soy intake. Suspected estrogenic effects[49] may disrupt male masculinization through interference at the pituitary-gonadal axis.[50] Study of animal perinatal genistein exposure resulted in alterations in the male reproductive system (i.e., smaller anogenital distance and testis size, delayed preputial separation, lowered testosterone). Maternal exposure to the daidzein in rats during pregnancy had a masculinization effect on female offspring in regard to memory and social behavior.

Generations of Asian cultures have consumed soy. At this point, there is no clear evidence of reproductive damage or untoward effects in humans.[51] As a prudent measure, it may be helpful to balance soy protein with other sources of protein.

Fish

Eating fish during pregnancy can support future brain development and reduce the risk of asthma and atopy in offspring by 40%; it can also help to prevent postpartum mood disorders in the mother.[52] As a rich source of the essential long-chain n-3 (omega-3) polyunsaturated fatty acids (PUFA), fish provides structural and physiologic support for neurologic, immune, and cardiovascular system development. In pregnancy, the desired minimum intake of 200 mg docosahexaenoic acid (DHA) per day[26] can be reached with the consumption of one to two portions of sea fish per week, including oily fish such as herring and salmon.[26,53]

Unfortunately, fish contributes significantly to dietary exposure to methylmercury, dioxins and polychlorinated biphenyls, brominated flame retardants, camphechlor, and organotin.[54] Bioaccumulative contaminants tend to concentrate in larger fish.

Mercury. The greatest susceptibility to the critical contaminants methylmercury and the dioxin-like compounds occurs during early development. Methylmercury is particularly toxic to the developing brain and may also adversely affect child growth.[55-57] A woman can effectively decrease methylmercury levels in her body by reducing the intake of contaminated foods in the months prior to and during pregnancy. Compared with other foods, salmon is relatively low in mercury as well as in levels of 18 other trace metals; however, the levels are three times higher in wild salmon than in farmed. Total mercury intake from both is lower than from many other foods[58] (Box 201-3).

Dioxins. Unwanted by-products of a variety of industrial and combustion processes, dioxins have also been found in fish. Because they break down very slowly, avoiding them right before and during pregnancy will not decrease fetal exposure.

The highest levels of dioxins are found in herring, and wild/farmed salmon. The European Food Safety Authority suggests that two portions of fish per week are unlikely to exceed the tolerable weekly intake of dioxin during pregnancy. Very high levels are found in Baltic Sea fish, and should be avoided.

BOX 201-3 Mercury in Fish

High-mercury fish	Low-mercury fish
• Marlin	• Salmon (farmed has less mercury than wild)
• Pike	• Herring
• Swordfish	• Anchovies
• Shark	• Sardines
• Tuna	• Rainbow trout
• Halibut	• Calamari
• Mackeral	• Flounder
• Bass	• Tilapia
• Lobster	• Trout

Data from National Resources Defense Council. *Consumer Guide to Mercury in Fish.* http://www.nrdc.org/health/effects/mercury/guide.asp. Accessed February 15, 2012.

Polychlorinated Biphenyls (PCBs). Although PCB use ceased in the 1970s, virtually all samples of human blood, fat, or breast milk show some detectable PCBs.[59] They are found at the highest levels in fish and inorganic butter; moreover, farmed salmon contains significantly higher levels of PCBs than wild varieties of the fish. It was therefore concluded that eating farmed Atlantic salmon, "may pose health risks that detract from the beneficial effects of fish consumption."[60]

The ingestion of PCB-contaminated fish before and during pregnancy can contribute to low birth weight, small head circumference, earlier birth, a depressive response in the infant, and impaired vision and memory. At age 11, children who had been exposed to PCBs had thrice the risk of low verbal IQ and twice the lag in reading comprehension/attention issues as children who had not been so exposed.[61]

The U.S. Food and Drug Administration (FDA) and Environmental Protection Agency recommend that pregnant women and youngsters eat no more than two servings of salmon or other low-mercury fish each week.[62] However, the benefits of eating fish may outweigh the risks. It may be prudent to have pregnant women focus on fish with lower mercury and PCB content and to avoid eating the skin and fat typically found along the ventral, lateral, and abdominal areas, where PCBs are most heavily deposited.

Flaxseed

Flax is considered a good source of fiber and omega-3 fatty acids in the form of alpha-linolenic acid, and it is the richest source of the lignan secoisolariciresinol diglycoside (SDG), a phytoestrogen precursor. Flaxseed consumption during pregnancy is thought to be beneficial for fetal brain development based on its omega fat content. Because of SDG, there has been concern about the ingestion of flax during pregnancy.

Rat studies using a high percentage of dietary flax in pregnancy have shown lower birth weights, female offspring with shortened anogenital distance, greater uterine and ovarian relative weights, lighter body weight at puberty, as well as lengthened estrous cycle and persistent estrus; the males had reduced postnatal weight gain, greater sex gland and prostate relative weights, and delayed puberty.[63] An analysis of 3191 study subjects found that exposure to flax oil during the last two trimesters of pregnancy quadrupled the risk of preterm birth. The authors of this study were not clear on doses or whether the effect of flax on prematurity is explained by a phytoestrogenic effect.[64]

Caffeine

Caffeine intake, most often in the forms of coffee or black and green tea, is commonplace during pregnancy. Although rat studies using 24-cup human-equivalent doses of black tea found no changes in pregnancy outcomes,[65] a study of 1063 pregnant women who consumed 200 mg/day or more of caffeine (the amount in 10 ounces of coffee or 25 ounces of tea) revealed a doubling in the risk of early miscarriage (12.5% to 24.5%). The increased risk was associated with caffeine itself and was separated from confounders such as smoking or advanced maternal age.[66] An 8-year analysis of 3346 case infants and 6642 controls found no teratogenic consequences of maternal caffeine intake.[67,68]

Cocoa/Theobromines[69]

Having increased in per capita intake over the last four decades, cocoa and chocolate have enjoyed popularity and perceived health benefit with little pregnancy outcome information. One large study has nonconclusively suggested that maternal prenatal intake of cocoa could be associated with both hypospadias and testicular cancer in male offspring. Moreover, a study comprising a 2291-woman cohort found that theobromine concentrations in cord serum from five or more servings of chocolate was inversely associated with preeclampsia when compared with women who consumed less than one serving of chocolate weekly.[70] Another study found no correlation.[71]

Stevia

Stevia is a small perennial shrub that yields a white crystalline compound (stevioside) commonly used as a natural sweetener. With no calories, it is over 100 to 300 times as sweet as table sugar. Animal studies suggest no effect on growth or reproduction.[72-74] Although no human trials are available, the FDA rates stevia as generally recognized as safe (GRAS).

Peanuts

About 1% of the population reports peanut or tree nut allergy.[75] Studies have found that the babies of mothers who ate a greater number of peanut products during pregnancy were more likely to test positive for peanut allergies (showing up as allergic factors in the blood).[76] What is particularly interesting in this study is that all sensitized infants also tended to have either milk or egg allergy and/or significant eczema. It is possible that this underlying inflammatory response may cause increased reactivity to peanut. Although not conclusively known, maternal peanut consumption during pregnancy may accelerate child peanut sensitization.

Sleep

Anecdotally thought of as a 'preparation for life with the newborn," interrupted sleep during pregnancy is a challenge to the health of the mother-to-be as well as to her expected child. Pregnancy itself will also affect the quality of sleep, with difficulty in assuming the usual sleep positions, discomfort from fetal movements, cramps, and poor sleep quality, with the latter being influenced by the previous complaints. Pregnancy is associated with some specific sleep disorders, such as obstructive sleep apnea and restless legs syndrome. Decreases rapid-eye-movement sleep during the last trimester can be explained by progesterone and estrogen alterations.[77]

Animal pregnancy studies show that sleep deprivation affects child renal development negatively.[78] Human sleep deprivation (less than 8 hours per day) during pregnancy risks a 3.8 times increase in first-trimester miscarriage,[79] impairs the mother–infant relationship, and promotes postpartum depression.[80]

TABLE 201-2 **Recommendations for Exercise During Pregnancy**

AGENCY	RECOMMENDATIONS
ACOG	• Not recommended if a woman has risk factors for preterm labor, vaginal bleeding or premature rupture of membranes. • Safe exercises, even for women who do not exercise before pregnancy, include walking, swimming, cycling, and aerobics. • In women who are active before pregnancy, running, racquet sports, and strength training may be safe to continue in moderation. • Skiing, contact sports, and scuba diving should be avoided. • If just beginning to exercise, women should start with 5 minutes of exercise a day and add 5 minutes each week until 30 minutes of activity a day is tolerable. • Avoid exercises that require lying prone after the first trimester and exercises that may cause overheating or dehydration.
DH-UK	• If inactive before pregnancy, do not suddenly start strenuous exercise. • Keep active on a daily basis. Half an hour of activities a day, such as walking, keeping in mind that any amount is better than nothing. • Avoid strenuous exercise in hot weather. • If attending exercise classes, ensure the instructor is qualified and aware of the pregnancy and gestational age. • Swimming will support increased weight, and many pools offer aquanatal classes.
HHS-US	• Healthy women not already highly active or doing vigorous-intensity activity should get at least 150 minutes (divided) of moderate-intensity aerobic activity per week during pregnancy and the postpartum period. • Pregnant women who habitually engage in vigorous-intensity aerobic activity or are highly active can continue physical activity during pregnancy and the postpartum period provided that they remain healthy and discuss activity adjustment with a health practitioner.

Recommendations based on the following:

Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Gen Hosp Psychiatry* 2009;31(5):403-413.

American College of Obstetricians and Gynecologists (ACOG). *Exercise during Pregnancy.* American College of Obstetricians and Gynecologists, Washington, DC; 2003.

Department of Health (DH-UK): *The Pregnancy Book 2007*. London: Department of Health; 2007.

U.S. Department of Health and Human Services (HHS-US). *2008 Physical Activity Guidelines for Americans*. Washington, DC: U.S. Department of Health and Human Services; 2008.

Exercise

Recommended by all major health departments as well as the American College of Obstetricians and Gynecologists (ACOG), the Department of Health, and the U.S. Department of Health and Human Services, exercise during pregnancy has shown improvement in positive well-being, moderate effects on psychological distress, a large reduction of fatigue in the second trimester,[81] as well as lower miscarriage[79] and depression risk[82] (Table 201-2).

Commonsense physical activity recommendations include avoiding contact sports, engaging in low-impact activities,

wearing an athletic support bra, drinking ample water, and eating a snack 30 minutes before exercise to assure adequate blood sugar levels.

Pregnant women may have to avoid exercise if there is high or malignant blood pressure, asthma, or a threat of miscarriage.

Studies suggest that regular exercise during pregnancy can have a positive effect on a baby's birth weight without putting the pregnancy or child at risk. Regular exercise was associated with lower birth weights (within the normal range) and reduced cord concentrations of growth-related peptides, suggesting an influence of exercise on endocrine regulation of fetal growth.[83]

One interesting case of exercise during pregnancy is that of Paula Radcliffe, an English champion long-distance runner. Ms. Radcliffe ran throughout her pregnancy, avoiding heart rates above 160 beats per minute, and she agreed to uterine imaging every month after month five. For the first 5 months, she ran twice a day, 75 minutes in the morning and 30 to 45 minutes in the evening. After month 5, she ran 1 hour in the morning and then used a stationary bike at night. She ran up to the day before she gave birth to a healthy baby. Twelve days after her daughter's birth, she started running again.[84]

Alcohol

Fetal alcohol syndrome is the leading cause of mental retardation in the United States. Sources suggest that earlier gestational exposure to alcohol, often during the time before a woman has become aware of her pregnancy, may be most detrimental. According to studies, 60.2% of women said they did not drink during their pregnancies, and 25.9%, 5.5%, and 2.5% were categorized as light, moderate, and heavy/binge drinkers, respectively.[85] Social factors such as being single or divorced, and intimate partner violence increased alcohol consumption risk.[86]

The Millennium Cohort Study of 11,513 children born in the United Kingdom between September 2000 and January 2002 found that by limiting alcoholic beverages during pregnancy to one or two per week, the resulting offspring were 30% less likely to have behavioral problems at age 5. Cognitive testing showed no behavioral or cognitive deficits. The authors cautioned that this observational study focused on light drinkers and there is still no precedent that any level of alcohol consumption is safe, because the long-term effects are unknown.

Smoking

Smoking during pregnancy is among the leading preventable causes of adverse maternal and fetal outcomes.[87] About 37% of women smoke before becoming pregnant, and 27% continue to do so during their pregnancies. Pregnancy smoking leads to fetal growth restriction, retroplacental hematoma, increased preterm birth, shorter fetal crown-to-rump lengths, placenta previa, and death in utero.[88,89] Smoking cessation is an important goal for the woman thinking about pregnancy, and it is urgent in pregnant women.[90]

Cannabis

Cannabis is the most frequently used illicit drug among pregnant women, and prenatal cannabis exposure is associated with fetal growth restriction, decreased birth weight, reduced length, smaller head circumference, and newborn cognitive, motor, and emotional issues.[91-93] Increases in offsprings' later tobacco use and adolescent psychosis have also been noted.[94]

Betel Nut

The fourth most commonly used drug in the world after tobacco, alcohol, and caffeine is the betel nut. It is the seed of the Areca palm, which grows in much of the tropical Pacific, Asia, and parts of east Africa. It is customarily wrapped in betel leaves and chewed. In Taiwan, 23.7% of aboriginal women were found to have chewed betel during pregnancy versus almost no nonaboriginals.[95] Studies in mice have shown that betel alkaloids cause skeletal immaturity,[96] and cases of human newborns showing withdrawal symptoms are documented.[97]

Stress and Mind-Body Modalities

High stress triples the risk of pregnancy hypertension, causes adverse birth outcomes, and doubles preterm delivery risk.[98] Whereas low and moderate anxiety in the first or early second trimester did not significantly affect birth outcomes,[99] anxiety in the second and third trimesters is linked to smaller infant size, lower Apgar scores, increased obstetric complications, lower birth weight, and shorter birth length, after adjustment for confounders, as well as shortened gestational age.[100,101]

Stress during pregnancy also alters regulation of the fetal hypothalamic-pituitary-adrenal (HPA) axis,[102-105] with altered hippocampal glucocorticoid receptor density and sensitivity. Maternal anxiety or depression during pregnancy is linked with HPA axis overreactivity and higher cortisol in infants and children.[106-108] Impaired functioning of the HPA axis is associated with metabolic syndrome,[109] fibromyalgia, depression,[110] and posttraumatic stress disorder[111,112] and likely increases the susceptibility of offspring to stress-related disorders.

Mind-body modalities may hold the greatest promise in balancing HPA axis function. There is evidence that pregnant women benefit from mind-body therapies used in conjunction with conventional prenatal care. In a meta-analysis, progressive muscle relaxation was the most common intervention used in pregnant women. Other studies used a multimodal psychoeducation approach or a yoga/meditation intervention and found modest evidence for the efficacy of mind-body modalities during pregnancy. Treatment group outcomes included healthier birth weight, shorter labor, fewer instrument-assisted births, and reduced perceived stress and anxiety.[113]

Sunlight

Several studies have shown that the month of birth can affect the birth weight and height of children. The mechanism of this phenomenon is not fully explained, but the importance of hours of sunlight may play a role. An evaluation of 10,631 neonates found that higher temperature, more hours of sunlight, greater rainfall, and lower humidity are associated with greater birth length.[114] Prenatal sunlight is one of the most significant determinants of height.[115] These findings signify that better nutrition and more active lifestyles of pregnant women, with a longer warm period, may have beneficial outcomes.

Conversely, diseases in offspring may be encouraged by minimal sun exposure. An Australian study reports that low maternal exposure to sunlight during the first trimester of pregnancy may increase the risk of offspring later developing multiple sclerosis.[116] Other autoimmune diseases may also play a role this relationship.

A likely factor in sunlight benefit is the role of vitamin D for both healthy pregnancies and healthy offspring. Pregnancy is a vulnerable time for vitamin D deficiency because of increased

physiologic needs and reduced maternal outdoor activity.[117] Although there are some vitamin D–rich foods, their benefit is minimal in comparison with sun exposure. The importance of vitamin D in pregnancy is discussed further later in this chapter.

Environmental Toxins

Earlier in this chapter, mercury and PCBs from fish were discussed.

Generally, most pregnant women take elaborate steps to protect their babies' health by avoiding alcohol, caffeine, tobacco, and sometimes even soft cheeses and deli meats. In spite of these efforts, studies report that the typical pregnant woman has dozens of potentially toxic or even cancer-causing chemicals in her body, including ingredients from flame retardants and rocket fuel.

Environmental factors are known to trigger epigenetic changes in the fetus, which may not manifest until years later. For example, spray-cleaning products have been associated with wheezing and impaired lung function in children up to 8.5 years of age.[118] Environmental pollutants may trigger genetic changes that can affect a person's health and that, in some cases, may be passed on to future generations.

One CDC study of 268 women showed detectable levels of eight types of chemicals in their blood or urine, and many of these agents pass easily through the placenta to concentrate in the fetus. Included were pesticides, flame retardants, perfluorocarbons used in nonstick cookware, phthalates, pollution from car exhaust, perchlorate, and PCBs.[119] Other studies have found these chemicals in babies' umbilical cords.

Pthalates/BPA

The FDA has expressed "some concern" that bisphenol A (BPA), an estrogen-like industrial petrochemical found in 96% of pregnant women, affects the brain, prostate, and behavioral development in children exposed both before and after birth. In one study, 9 of 10 randomly selected samples of cord blood tested positive for BPA.[120] Phthalate exposure during childhood was associated with attention deficit hyperactivity disorder (ADHD) in a cross-sectional study of Korean children between the ages of 8 and 11 years.[121]

Pthalates are found in plastics, solvents, antifoam agents, alcohol denaturants, vinyl flooring, wall covering, pesticides, and personal care products (fragrances, shampoos, cosmetics, and nail polish). Human exposure occurs through inhalation, ingestion, and dermal contact.[122]

A 4-year evaluation of prenatal phthalate exposure in 404 subjects in New York City found increased concentrations of phthalate metabolites associated with poorer scores on aggression, conduct, attention, and emotional control, especially among boys. Prenatal pthalate exposure likely plays a role in children clinically diagnosed with conduct disorders or ADHD.[123] Pregnant women should avoid phthalates as much as possible.

Cell Phone Radiation

There is some evidence regarding prenatal and postnatal exposure to cell phone use and behavioral problems in children.[124] An evaluation of mothers of 13,159 children reported almost twice the incidence of behavioral problems in children who had possible prenatal or postnatal cell phone exposure. More studies are needed, but it may be prudent to reduce such exposure by following Newton's law of radiation; that is, by increasing distance. Speakerphones may be of benefit here.

Arsenic and Perchlorates

Arsenic is poisonous to any organism, and arsenic exposure during pregnancy (in tested as concentrations of metabolites of inorganic arsenic in maternal urine samples) was associated with increased morbidity due to infectious diseases during infancy.[125] Perchlorate in drinking water during pregnancy was assessed in 497,458 newborns in California; the results suggest that higher perchlorate levels are associated with higher-than-normal neonatal TSH levels.[126] Water filters can prevent exposure.

Lead

Higher maternal lead levels can lead to complications such as preeclampsia or eclampsia, potentially deadly seizures that can also increase a woman's future risk of heart attack as well as cognitive deficits in her infant.[127] Maternal tibial-patellar lead levels suggest that the genomic methylation of the developing fetus can be influenced by maternal cumulative lead burden, which may influence long-term epigenetic programming and disease susceptibility.[128]

Air Pollution

Both outdoor and indoor air pollution may play a role in pregnancy and the health of offspring.

Air pollution can affect fetal health through direct effects on the fetus via placental exposure and by effects on the mother's health.

Inconclusive studies of exposure to traffic-related airborne pollutants have been associated with an array of health effects, including pulmonary and cardiovascular challenges, asthma, low birth weight, and preterm delivery.[129,130] Like maternal smoking, air pollution may encourage premature rupture of membranes, placental abruption, and lower birth weight.

Indoor air pollutants are likely a stronger player in pregnancy health. Indoor air studies have looked at thousands of South Asian, African, and Latin American women who were commonly exposed to indoor air pollutants such as smoke secondary to third-world cooking fuels. Among such women, poorer pregnancy outcomes and correlations with stillbirth were found as compared with women who cooked with cleaner fuels.[79] Indoor air quality can be improved by improving choices in cooking, cleaning products, paint, furniture, carpeting, and anything brought into the home. Also, the use of air filters that can filter particulate matter as well as chemicals, volatile compounds, and solvents is recommended.

GENERAL SUPPLEMENTATION

Although the research is scant, one study suggests that about 62% of pregnant women use supplements (Box 201-4). They tend to rely on friends and relatives for advice in deciding to use these. A British study reports that dietary supplement use during

BOX 201-4 Supplements Used During Pregnancy

Folate: 70%
Iron: 38%
Multivitamin: 27%
Ginger: 7% to 20%
Echinacea: 8%
Raspberry leaf/pregnancy tea: 8% to 9%

Data from Patterns of vitamin, mineral and herbal supplement use prior to and during pregnancy. *Aust N Z J Obstet Gynaecol* 2002;42(5):494-496.
Maats FH, Crowther CA. *Am J Obstet Gynecol* 2001;185(2):433-437.
Tsui B, Dennehy CE, Tsourounis C. A survey of dietary supplement use during pregnancy at an academic medical center. Am J Obstet Gynecol. 2001 Aug;185(2):433-7.

pregnancy declined from 82% of women in the first trimester of pregnancy to 22% in the second trimester and 33% in the third trimester.[131]

Multivitamins and Folic Acid

A 2008 review of medline, PubMed, and Cochrane databases found that the use of folic acid and a multivitamin supplement among women of reproductive age reduced the incidence of birth defects (anencephaly, myelomeningocele, meningocele, oral facial cleft, structural heart disease, limb defect, urinary tract anomaly, hydrocephalus).[41] With concerns about folic acid masking a vitamin B_{12} deficiency, this study concluded that 5 mg of folic acid supplementation will not mask a vitamin B_{12} deficiency (pernicious anemia).

Excellent sources of folate are spinach, asparagus, romaine lettuce, turnip greens, mustard greens, calf's liver, collard greens, cauliflower, broccoli, parsley, lentils, and beets.[132] This study, however, points out that it is unlikely that diet alone can provide levels similar to those obtained from folate-multivitamin supplementation, because nutrient densities in foods are poor. A study by the ADA—comprising over 70 dietary analyses of 20 different diets from a cross section of people, including athletes and sedentary people—showed that all diets including food alone fell short of the recommended daily allowance (RDA) of micronutrients. Even more, it was shown that the more active the person, the greater the tendency toward deficiency.[133] Pregnancy is clearly a condition of increased nutrient need; therefore, a multivitamin seems to make sense.

Folate is particularly important in the synthesis of purines and pyrimidines, in the conversion of homocysteine to methionine, and in the interconversion of serine and glycine.[134,135] Prenatal folate deficiency may influence the risk of schizophrenia in offspring by inhibiting optimal neurogenesis and allowing homocysteine to accumulate in the fetal brain.[34,136]

A folate-supplemented diet with additional daily supplementation of multivitamins with 5 mg of folic acid should begin at least 3 months before conception and continue until 10 to 12 weeks postconception. From 12 weeks postconception and continuing throughout pregnancy and the postpartum period (4 to 6 weeks or as long as breastfeeding continues), supplementation should consist of a multivitamin with folic acid (0.4 to 1.0 mg).

The form of folic acid may also play a role in efficacy. According to some studies, metabolism of folic acid into its form 5-methyltetrahydrofolate may be impeded, and up to half of women may have this difficulty due to common genetic mutations.[137] As such, L-methylfolate forms of this nutrient may be more efficacious.

Three patient scenarios with specific folic acid recommendations are as follows[138]:

1. Patients with no personal health risks, planned pregnancy, and good compliance:
 - Folate-rich diet
 - Multivitamin with folic acid (0.4 to 1.0 mg) daily for at least 2 to 3 months before conception and throughout pregnancy and postpartum period (4-6 weeks and through breastfeeding)
2. Patients with health risks, including epilepsy, insulin-dependent diabetes, obesity (BMI >35 kg/m^2), family history of neural tube defect:
 - Increased folate-rich foods
 - Multivitamins with 5 mg of folic acid daily, beginning at least 3 months before conception and continuing until 10 to 12 weeks postconception. From 12 weeks postconception and continuing throughout pregnancy and the postpartum period (4 to 6 weeks and through breastfeeding) a multivitamin with folic acid (0.4-1.0 mg) daily
3. Medicated patients with a poor compliance history as well as poor diet, no consistent birth control, and teratogenic substance use (alcohol, tobacco, recreational nonprescription drugs):
 - Counseling regarding prevention of birth defects and health problems
 - Folic acid (5 mg) with a multivitamin daily

Essential Fatty Acids

The benefits of EFAs are numerous, as previously discussed in regard to fish intake. Essential omega-3 polyunsaturated fatty acids (PUFAs) are critical during pregnancy and must be obtained through diet.

DHA is a necessary structural component of the brain and retina, with uptake maximal during the second half of gestation and infancy.[139] It is known that preterm infants have delayed mental development, likely because the third trimester is a period of rapid brain growth and development that requires DHA for brain cell structure and communication.[140] National nutritional surveys have shown that the average intake of DHA during the last trimester of pregnancy is between zero and 100 mg,[141] with 90% of women well below the minimal recommendation of 300 mg a day and the United States having the third lowest intake of DHA in the world.[151]

In totality, clinical studies support the use of fish oil in pregnancy. Two recent independent meta-analyses reveal that omega-3 fats healthfully prolonged gestation by a mean of 1.6 or 2.6 days, accompanied by a slight increase in birth weight (of 47 or 54 g) and reduced the risk of preterm birth before 34 weeks of gestation by 31% in normal pregnancies and by 61% in high-risk pregnancies.

A recent double-blind multicenter randomized controlled trial of 2399 women found that those who took fish oil supplements also enjoyed a significantly lower risk of very preterm birth (defined as delivery before 34 weeks' gestation) than did women in the control group. The rate of very preterm birth was 1.1% with DHA-rich supplements (13 such births) compared with 2.3% with placebo (27 such births). The downstream benefits of that difference included lower rates of low birth weight, fewer admissions to the neonatal intensive care unit, and a nonsignificant 30% reduction in infant mortality. Interestingly, 64% of the women who were initially screened but ineligible to take part in the trial were excluded because they were already taking prenatal supplements containing DHA. It is possible that earlier intervention with fish oil might have yielded even better results. Possibly, supplementation with higher levels of eicosapentaenoic acid (EPA) relative to 800 mg of DHA, as found in nature, might also have improved benefits. However, no effect was seen on postpartum depression or cognitive and language development in the offspring during early childhood. Dosages of 800 mg/day of DHA and 100 mg/day of EPA may have been low in EPA for emotive or cognitive benefit.[142]

In regard to dosing, pregnant women should aim to achieve a minimum 300 mg/day of DHA. Intakes of up to 1 g of DHA or 2.7 g/day of total omega-3 long-chain fatty acids have been used in randomized clinical trials without significant adverse effects.[26] Fish in various doses and fish oil capsules in doses ranging from 0.1 to 2.8 g, from weeks 17 to 27 of gestation until delivery, showed no increase in spontaneous deliveries versus the control group.[143]

Fish oil supplementation may be a healthier source of fatty acids than fish because of environmental toxins, which can easily be removed from fish oil.[144,145] Except for some reported discomfort such as belching and unpleasant taste, no adverse effects have been detected up to the highest intake of 2.8 g of total omega-3 fats.

Although vegetable oils contain varying levels of healthy fats, the conversion from the parent omega-3 PUFA, alpha-linolenic acid, to the more biologically active long-chain omega-3 PUFAs, DHA and EPA, is inefficient. Therefore, fish oils are likely a better choice than plant oils.[146]

Evening Primrose Oil (EPO)

EPO is rich in omega-6, containing both linoleic acid (LA) and gamma linolenic acid (GLA). Pregnant rats given alcohol and EPO found a significant reduction in the embryopathic activity of ethanol. Chronic ethanol intake causes a depletion of EFAs. It is possible that in pregnant women who consume excess alcohol and will not cease that intake, EPO may be protective by reducing alcohol's teratogenic potential.[147]

Anecdotal reports suggest that EPO may hasten cervical ripening, shorten labor, and decrease the postdate pregnancy likelihood. One study supplementing from the thirty-seventh gestational week until birth does not support this.[148] Although EPO is rated as GRAS, the use of orally administered EPO may be associated with an increase in the incidence of prolonged rupture of membranes, oxytocin augmentation, arrest of descent, and vacuum extraction.[149] Therefore, it is not recommended except in the case of alcohol intake with pregnancy.

Vitamin D

Although it was thought in the 1960s to cause fetal heart defects, mental disabilities, and elflike facial features, recent genetic studies have identified the cause as Williams syndrome, a rare genetic deletion disorder affecting vitamin D metabolism.[150]

Vitamin D is a preprohormone that supports calcium homeostasis, bone health,[151] and general immune function.[152] Vitamin D plays a role in pregnancy immune tolerance, insulin resistance,[153] and preeclampsia risk.[154] The vitamin appears to increase the amount of blood flowing to the placenta, bringing more oxygen and nutrients to the fetus and promoting healthier growth.[155] The effects of inadequate vitamin D are listed in Box 201-5.

Adequate vitamin D may prevent premature delivery, offspring wheezing,[156,157] and multiple sclerosis.[116] One study comprising 494 women found that those taking 4000 IU/day of vitamin D halved their the risk of premature delivery as compared with women who took only 400 IU. Interestingly, the women taking part in this study were living in sunny Charleston, South Carolina. In this population, 85% had insufficient or "frankly deficient" vitamin D levels at study onset, which corroborates other studies of women living in sunny places.[150]

BOX 201-5 Risks of Vitamin D Deficiency

Low vitamin D in pregnancy increases the risk of:

- Adverse musculoskeletal effects
- Bacterial vaginosis
- Small-for-gestational-age babies
- Preeclampsia
- Flu

Prepregnancy obesity predicts poor vitamin D status in mothers and their neonates.[158] Serum 25(OH)D levels should be tested before pregnancy if possible as well as during early pregnancy to help decide on appropriate supplementation. Levels of 50 to 80 ng/mL would be adequate.

Magnesium

Mounting research demonstrates that low magnesium status may play a role in several pregnancy-related disorders. These include vasospasm, coagulation defects, premature delivery, hypertension and eclampsia, intrauterine growth restriction, and muscle cramping.

A meta-analysis involving 2689 women showed that oral magnesium supplementation given before the 25th week of gestation supported a 30% lower preterm birth frequency, 33% lower low-birth-weight frequency, 30% fewer small-for-gestational-age infants, and 62% fewer cases of antepartum hemorrhage compared with placebo. However, reviewers of this study concluded that poor-quality trials had led to a bias in favor of magnesium supplementation.[159]

Low protein intake will negatively affect magnesium absorption. Studies report that protein intakes of more than 0.4 g/kg of body weight resulted in a magnesium absorption of more than 40%. And a protein intake of 0.36 g/kg of body weight resulted in a magnesium absorption of 28%.[160] The magnesium intake of pregnant women must be increased by either dietary means or supplements, especially among low-income women in soft-water states. Excessive intakes of calcium and phosphorus may be detrimental to magnesium absorption.[161]

Vitamin A

According to the WHO, vitamin A deficiency affects 19 million pregnant women worldwide, and supplementation can reduce infant mortality in regions where this micronutrient deficiency is common (with Africa and Southeast Asian countries affected the most).[162,163] Retinol (vitamin A) and other retinoids are essential nutrients required by the early embryo and fetus for gene expression, cell differentiation, proliferation, and migration.[164] Vitamin A is important in regulating early lung development and alveolar formation and to prevent night blindness.[165] Because it is important for central nervous system (CNS) morphogenesis, inadequate vitamin A can cause hydrocephalus, anencephaly, spina bifida,[166,167] and an underdeveloped posterior hindbrain.[168,169] As antioxidants, retinoids may also help to protect the developing brain from a number of potential insults that generate free radicals.[170]

Because hypovitaminosis can contribute to problems, excess vitamin A has potent teratogenic effects and is contraindicated during pregnancy. Like thalidomide, isotretinoin and vitamin A–related acne medications are responsible for a high incidence (25%) of malformations of the CNS, heart, and thymus as well as craniofacial defects.[171] The risk of birth defects owing to supplements containing a synthetic vitamin A analogue has already been documented in humans, and recently the ingestion of excess vitamin A (25,000 IU or more) as retinol/retinyl esters during pregnancy has been associated with some birth defects in a small number of case reports, although it is not known that the relationship is causal.[172]

The National Research Council's recommended dietary allowance for vitamin A during pregnancy is 1000 retinol equivalents per day, which is equivalent to 3300 IU as retinol or 5000 IU of

vitamin A obtained from the typical American diet as a combination of retinol and carotenoids (e.g., beta-carotene). An average balanced diet contains approximately 7000 to 8000 IU of vitamin A derived from different sources. The RDA established by the FDA is 8000 IU/day. Supplementation of 8000 IU of vitamin A (as retinol/retinyl esters) per day should be considered the recommended maximum prior to or during pregnancy. Beta-carotene is not metabolized or stored in the same way as vitamin A, has not been associated with vitamin A toxicity in animals or humans, but may not have the ability to prevent deficiency issues because of differences in absorption and metabolism.[173,174]

Antioxidants

Oxidative stress has been implicated in many pathologic processes during pregnancy, childbirth, and the postnatal period but the possible preventive or therapeutic effects of antioxidants remain unclear.[175,176] Overt deficiency of antioxidant status is a detriment to pregnancy. In a Ugandan rural cohort, 400 mg of vitamin C allowed 42.2% of women in the vitamin C group to avoid pregnancy hospitalization compared with 27.9% in the control group.

Beneficial effects have been seen regarding maternal vitamin E intake in respect to wheezing in the second year of life.[177] Beneficial associations have also been found between maternal zinc intake[178] during pregnancy and asthma and eczema in children at the age of 5 years. Forty milligrams of zinc gluconate effectively increased mean birth weight among anemic and iron-deficient women but not among women with elevated iron stores in early pregnancy.

Pre-2005 studies involving 6082 women suggest that supplementation of one or more antioxidants was associated with a 39% reduction in the risk of preeclampsia and a 35% risk reduction of having a small-for-gestational-age infant.[179] However, two more recent trials, with supplementation of high dosages of both vitamins C and E, did not show any reduction of preeclampsia. In one of these trials, supplementation with vitamins C and E was associated with a significantly higher rate of low-birth-weight infants.[180,181]

Overall, the currently available data[182-186] do not provide a basis for recommending antioxidant intakes for pregnant and lactating women in excess of reference nutrient intakes. Women with risk factors for preeclampsia may consider additional low-dose antioxidant support.

Iron

During pregnancy, low iron and anemia can compromise oxygen delivery to the developing fetus.[187] Factors associated with deficiency include poor fetal brain and intrauterine development, prematurity, and low birth weight.[188] These lead to a poor growth trajectory in infancy, childhood, and adolescence and low adult height. Indirect indicators of fetal hypoxia have been associated with increased susceptibility to schizophrenia,[189] in which the hippocampus is believed to be particularly vulnerable to hypoxic insult.

Studies in India, where iron deficiency is the highest in the world, show that anemia is directly or indirectly responsible for 40% of maternal deaths in that country, with an 8- to 10-fold increase in morbidity and mortality rates when the hemoglobin falls below 5 g/dL.

Iron is an important component of any prenatal vitamin. A dose between 30 and 60 mg of elemental iron is common but may not be enough to prevent gestational anemia.[190]

Probiotics

The newborn gut is first colonized by microbes picked up from the mother as the baby moves through the birth canal[191]; however, this is minimized with delivery by cesarean section. Newborns delivered in this way go on to have higher rates of celiac disease.[192]

Strain of bacterium used is important to its effectiveness. *Lactobacillus* GG dosing twice daily neither reduced the incidence or severity of atopic dermatitis but was associated with increased wheezing bronchitis.[193] In a second study, pregnant mothers who were carrying infants at high risk for allergy received a mixture of four probiotic species (*Lactobacillus rhamnosus* GG and LC705, *Bifidobacterium breve*, and *Propionibacterium freudenreichii* ssp *shermanii*) 4 weeks before delivery. As a result, antibiotics were prescribed slightly less often and there were less frequent respiratory infections.[194]

Oral and intravaginal yogurt and probiotics have also been used to amelioriate bacterial vaginosis in pregnant patients. Such treatment may be a first choice in pregnant patients seeking to avoid antibiotic treatment.[195]

Probiotics seem quite safe during pregnancy, with no increased neonatal morbidity, feeding-related difficulties (such as infantile colic), or serious adverse events. A 1505-patient meta-analysis of *Lactobacillus* and/or *Bifidobacterium* found no malformations and no adverse effects on the incidence of cesarean section, birth weight, or gestational age. The safety of *Saccharomyces* during pregnancy is unknown.[196]

Choline

The rapid rate of cell division during pregnancy, the expansion of the maternal kidneys and uterus, the growth of placental and fetal tissue, as well as the increased lipoprotein required for nervous system development all deplete choline stores. Higher levels of blood choline are associated with a 2.5-fold reduction in the risk for neural tube birth defects.[197] Third-trimester fetal organ growth is extremely rapid and large amounts of choline are required for membrane biosynthesis, because neonates have choline levels three times higher than those in maternal blood.

Most pregnant women are not getting enough choline and certain genetic variants may increase requirements further. The recommended intake is 450 mg/day during pregnancy.[198] Because choline is not found in most varieties of prenatal vitamins, the focus should be on choline-rich foods (Table 201-3). Studies of choline supplementation in pregnancy are not available.

TABLE 201-3 **Dietary Sources of Choline**

FOOD	MILLIGRAMS OF CHOLINE
Egg, large[226]	115
Beef steak, 3 oz	110
Salmon, 3 oz	100
Baked beans, 1 c	70
Navy beans, 1 c	60
Brussel sprouts, 1 c	60
Kidney beans, 1 c	60
Broccoli cooked, 1 c	60

Data from Caudill MA. Pre- and postnatal health: evidence of increased choline needs. *J Am Diet Assoc* 2010;110(8):1198-1206.

Carnitine

Carnitine is an essential constituent of intermediary metabolism, and the total plasma carnitine level in nonpregnant fertile women averages around 40 µmol/L.[199] During gestation, plasma carnitine concentrations decrease precipitously. By delivery, they may be at 15 µmol/L,[200,201] a level also found in carnitine-deficient individuals.[202] It is unclear whether low carnitine in pregnant women has adverse effects on their metabolism or on the metabolism of the fetus.[203]

Plasma carnitine reduction in pregnancy is safely prevented by supplementation with 500 mg of L-carnitine L-tartrate from week 13 of gestation to term. A study of 26 women found that supplementation prevented reductions in plasma carnitine versus placebo.[204] Some evidence suggests that infant diets may have to supply supplemental carnitine to satisfy the neonate's metabolic needs.[205] L-carnitine supplementation during pregnancy may help to prevent the development of gestational diabetes, especially in overweight women, by decreasing elevated free fatty acids. Lower L-carnitine downregulates the expression of enzymes involved in fatty acid metabolism. A daily supplement containing 2 g of L-carnitine in over 80 pregnant women starting in the twentieth week increased the relative mRNA levels of these enzymes.[206]

Meat, poultry, fish, and dairy products are the richest sources of L-carnitine, whereas fruits, vegetables, and grains contain relatively little L-carnitine.

Botanicals

As in the general population, the use of botanicals in pregnancy is increasing. One midwife review of 578 expectants who were at least 20 weeks pregnant found that 60% used herbals.[207] A 2010 obstetric analysis of 4239 women who delivered infants without major birth defects found that about 10.9% reported use of an herbal product 3 months before or during pregnancy.[208] Herbal use was highest during the first trimester (6.9%), with substantial second- (5.1%) and third- (5.2%) trimester use. This study extrapolated that about 9.4%, or an estimated 395,000 births, involved antenatal exposure to at least one herbal product.

Studies show ginger as the most used, followed by cranberry, raspberry leaf, chamomile, peppermint, and *Echinacea*. Herbal teas and chamomile were most commonly used in later pregnancy. Other commonly used herbals were mint or peppermint and primrose oil. It is clear by comparing these studies that the population of women who use midwives skew toward greater use of botanicals.

Raspberry Leaf (Rubus idaeus)

Used since the sixth century, the raspberry leaf plant is "the best known and oldest of all the herb infusions and [is] included as a proved aid in maternity in the most ancient of herbal books."[209]

Feline intravenous experimentation from the 1940s found that raspberry leaf extract had a relaxant effect on the uterine musculature.[210] A retrospective Australian comparison study of 109 women showed safety, with first stage labor being shorter, as were the second and third stages. There was one preterm labor and birth in the control group compared with none in the treatment group. The percentage of normal births in the raspberry leaf group (77.2%) was slightly higher than that in the control group (66.7%).[211]

A second 192-woman study dosed 1.2 g twice daily of raspberry leaf from 32 weeks gestation until labor; it found no adverse effects for mother or baby. However, raspberry leaf did not shorten the first stage of labor, although it did shorten the second stage by an average of 9.59 minutes, accompanying a higher rate of vaginal deliveries and less use of forceps between the treatment group and the control group (19.3% vs. 30.4%).[212] Less intervention means a reduction in midwifery and medical time in labor and an increase in maternal satisfaction.[213] To allay concern that raspberry leaf may cause preterm labor and birth, it should be noted that the study of gestation lengths was similar.

Common complaints of nausea, vomiting, and diarrhea were equally distributed between the two groups. Four constipation reports were the only raspberry-exclusive complaints. Although common in pregnancy,[214-216] constipation may also be attributed to the astringent raspberry leaf.[217]

Glycyrrhiza glabra (Licorice)

Known for its hepatoprotective and pulmonary support, licorice has been studied in pregnancy. Although there is no effect on maternal blood pressure or birth weight at the high exposure of 500 mg glycyrrhizin per week,[218] children show more behavioral problems, poor attention spans, and symptoms of ADHD in a dose-dependent manner.[219]

Salivary cortisol tests show higher offspring cortisol levels as well.[220] Glycyrrhizin is a natural licorice constituent that potently inhibits 11β-hydroxysteroid dehydrogenase type 2. This enzyme blocks the fetus from receiving maternal cortisol. Using licorice can induce higher cortisol levels in utero and may alter HPA axis function in children, contributing to altered mood and stress response. Therefore, the ingestion of licorice is not recommended for pregnant women.

Gingko biloba

A murine study of ginkgo at 78 mg/kg per day (equivalent to the human dose) up to 100 mg/kg per day showed significant malformations in the eye and orbit; syndactyly; malformed pinnae, nostrils, lips, and jaws; and decreased weight as well as crown-rump length of fetuses in the 100-mg group with no change in the 78-mg or control groups.[221] A second study in pregnant rats found no embryonic death, growth restriction, or fetal malformations.[222] At this time, given the lack of human data and suggestive teratogenicity in animal data, ginkgo is not recommended during pregnancy.

Scutellaria (Scutellaria baicalensis)

There are anecdotal reports that *Scutellaria baicalensis* has some fetal calming effects. A mouse study showed higher liver and kidneys weights in the mothers who took scutellaria in high doses as compared with the controls, with dosing below 32 g/kg of scutellaria extract per day not causing significant fetal external or skeletal malformations.[223] Human research is needed.

Bitter Melon (Momordica charantia)

Well used in Asian cultures for blood sugar regulation and cancer care, bitter melon contains the abortifacient proteins trichosanthin, α-momorcharin, and β-momorcharin, which can inhibit cellular protein synthesis. The momorcharins and the ribosome-inactivating proteins isolated from bitter melon seeds have been shown to have abortifacient activity in pregnant mice.[224] The use of bitter melon during pregnancy is not recommended.

Podophyllum

This agent has historically been used to remove benign dermatologic lesions. There is a case study of a pregnant woman who used its resin topically 5 times for a duration of 4 hours each time from the 23rd to the 29th week of pregnancy in order to remove warts.

At birth, a simian crease on the left hand and a preauricular skin tag were noted on the child. It was not clear whether the topical treatment was the cause.[225]

Therapeutic Approach

Support

A midwife should be considered for optimal prenatal care, with conventional medical backup support for urgent care if needed. Psychological therapy is beneficial for those with anxiety or mood disorders.

Foods

Dietary therapies should include an organic whole-foods diet with adequate hydration and protein and seven servings of fruits and vegetables daily. Fish with toxic contaminants as well as peanuts (minimal intake), flax, and caffeinated beverages are best avoided.

Sleep

Eight hours each night.

Exercise

Daily as appropriate for the individual.

Lifestyle

Daily sunlight exposure.
Cigarettes, cannabis, and betel nuts should be avoided.
Meditation and relaxation work.
Use of filters to ensure toxin-free water and indoor air.

Nutritional Supplementation

High-quality prenatal multivitamin with 1000 to 5000 mcg of folic acid, 1000 mg of calcium, and no more than 5000 IU of vitamin A.
Essential fatty acids: 800 mg of DHA and corresponding EPA.
Vitamin D: dosed according to specific need based on laboratory findings.
Probiotic.

Botanical Medicine

According to specific health needs.

CONCLUSION

Pregnancy care is an unparalleled opportunity to improve the health of the pregnant woman as well as safeguard the childhood and adult health of the offspring by preventing disease. Natural medicine therapeutics have many options toward this goal.

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CHAPTER 202

Premenstrual Syndrome

Tori Hudson, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- Recurrent signs and symptoms that develop during the late luteal phase of the menstrual cycle and disappear by the end of the full flow of menses
- Symptoms typically including decreased energy, tension, irritability, depression, headache, altered sex drive, breast pain, backache, abdominal bloating, and edema of the fingers and ankles

GENERAL CONSIDERATIONS

Premenstrual syndrome (PMS) refers to the cyclic constellation of troublesome symptoms that appears during the luteal phase of the menstrual cycle—more so in the late luteal phase—disappear by the end of the full flow of menses, and do not appear during the follicular phase.[1] Although some 150 symptoms have been listed as premenstrual, the most common symptoms are as follows (Box 202-1):

- Decreased energy
- Tension
- Irritability
- Anger
- Food cravings
- Depression
- Headache
- Altered sex drive
- Breast pain
- Muscle aches
- Abdominal bloating
- Edema of the fingers and ankles

PMS is estimated to affect between 30% and 40% of menstruating women; 80% of women experience premenstrual emotional or physical changes but do not have much difficulty. Peak occurrence is among women in their 30s and 40s. In most cases symptoms are relatively mild; however, in about 2.5% to 5% of women symptoms can be severe enough to have a negative impact on their lives, putting home life and work in jeopardy. Severe PMS with depression, irritability, and severe mood swings is referred to as *premenstrual dysphoric disorder* (PMDD)[2] and has a separate diagnostic category in the fourth edition of the American Psychological Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

Although PMS has been a well-defined clinical entity for more than 60 years, some physicians still argue that it really does not exist.[3] Therefore, many women suffering from PMS do not receive proper treatment. Until the advent of therapy with selective serotonin reuptake inhibitors (SSRIs), conventional mainstream medicine had not been able to offer women a known cause for PMS, nor has it been able to offer satisfactory interventions. Women were by and large left to self-care or to seek the advice of alternative medicine practitioners.

The etiology of PMS has not yet been fully understood, but endocrine studies have clarified that the premenstrual symptoms are not a result of a simple excess or deficiency of any given hormone.[4] Several theories have been proposed to explain the causes of PMS; currently strongest is an interaction between the ovarian steroids and the brain's neurotransmitters. Genetic predispositions and sociocultural beliefs about menstruation may also influence what women experience. At present, the dominant thinking is that cyclic changes in the ovarian steroids estrogen and

BOX 202-1 Signs and Symptoms of Premenstrual Syndrome

Behavioral
- Nervousness, anxiety, and irritability
- Mood swings and mild to severe personality change
- Fatigue, lethargy, and depression

Gastrointestinal
- Abdominal bloating
- Diarrhea and/or constipation
- Change in appetite (usually craving of sugar)

Female
- Tender, enlarged breasts
- Uterine cramping
- Altered libido

General
- Headache
- Backache
- Acne
- Edema of fingers and ankles

progesterone cause changes in many body systems, including brain neurotransmitters, which then have emotional and physical manifestations.[5] Therefore, normal ovarian function, and not a true hormonal imbalance, triggers the central nervous system and predisposes a woman to hormone-induced instability.[6] We do not currently know why women differ in their sensitivity to the changes in ovarian steroid-induced neurotransmitters. Of the neurotransmitters studied, serotonin is the principal one implicated in the pathogenesis of PMS and PMDD.[7,8] Whether PMS and PMDD are related to absolute levels or reduced blood levels of serotonin or to serotonin transport remains unclear.[9]

Other neurotransmitter systems may also be involved in PMS and PMDD. They include the adrenergic, opioid, and gamma-aminobutyric acid (GABA) systems. Research over the last 10 to 15 years has shown that SSRIs can alleviate both the psychological and physical symptoms in most women with PMDD. Fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and venlafaxine have all been found to be significantly more effective than placebo for the treatment of PMDD.

DIAGNOSIS AND CLASSIFICATION

The diagnosis of PMS is usually made through the association of the symptoms attributed to PMS with their occurrence during the luteal phase of the menstrual cycle. To aid in the diagnosis, symptom questionnaires are often used. Recalled information is less accurate; therefore, so in addition to a symptom questionnaire, the patient may be asked to keep a menstrual symptom diary. This helps to document improvement as well as to further clarify the symptom pattern.

The key defining feature of both PMS and PMDD is the timing of symptoms, which appear only during the luteal phase and disappear before or during menstruation. Fundamental to making the diagnosis is to rule out other psychiatric and medical disorders. The clinician should obtain a medical and psychiatric history and be aware that many mental and physical disorders mimic premenstrual symptoms and may also coexist with them. The results of the medical, psychiatric, and psychosocial evaluations along with the symptom diary offered by the patient can help the clinician to determine whether the symptoms represent PMS or PMDD, a psychiatric or medical illness only, coexisting PMS or PMDD and another illness, or premenstrual exacerbation of an underlying psychiatric or medical illness.

Only one of the following symptoms is required for a diagnosis of PMS: mild psychological discomfort, bloating and weight gain, breast tenderness, swelling of hands and feet, various aches and pains, poor concentration, sleep disturbance, and change in appetite. The symptoms must (1) occur only in the luteal phase, (2) peak close to menstruation, and (3) subside at the onset of menses or during menstrual flow. A diagnosis of PMDD is reserved for women who have at least five of eleven specific symptoms at a severe level such that they interfere significantly with daily life and relationships and occur in the premenstrual phase of the cycle.
- Markedly depressed mood, hopelessness, self-defeating thoughts
- Marked anxiety, tension
- Feeling overwhelmed
- Marked anger, irritability
- Marked lability
- Decreased interest in usual activities
- Difficulty concentrating
- Lethargy, fatigue
- Change in appetite, food cravings
- Sleep disturbance
- Additional physical symptoms (breast tenderness, bloating, headache)

THERAPEUTIC CONSIDERATIONS

Even though it is now understood that there is no frank increase or decrease in serum estrogen or progesterone levels, a possible relative excess or insufficiency in terms of its effect on the central nervous system should still be considered. Owing to the lack of scientific understanding in this area and the clinical experience in improving estrogen metabolism in women with PMS, some clinical considerations from the past should still be recalled.

Estrogen Metabolism

In the early 1940s, Morton Biskind observed an apparent relationship between B-vitamin deficiency and PMS.[10,11] He postulated that PMS, as well as excessive menstruation and fibrocystic breast disease, was due to an excess in estrogen levels caused by decreased detoxification and elimination in the liver as a result of B-vitamin deficiency. The liver uses various B vitamins to detoxify estrogen and excrete it in the bile.

There appears to be support for Biskind's theory. Estrogen excess is known to produce *cholestasis*, a term that signifies diminished bile flow or stasis of bile. Naturopathic physicians often refer to this condition as a "sluggish liver." It reflects minimal impairment of liver function because normal indicators of liver status (such as concentrations of the liver enzymes alkaline phosphatase, serum glutamic oxaloacetic transaminase, serum glutamate pyruvate transaminase, and gamma-glutamyl-transpeptidase) are not elevated. These enzyme measurements, the conventional means of assessing liver status, are not very useful, because they serve only to indicate liver damage, being elevated only when the liver is compromised. They have little correlation with liver function. Because of the liver's important role in numerous metabolic processes, even a minor impairment of liver function can have profound effects.

Cholestasis can be caused by a large number of factors besides estrogen excess (Box 202-2). The presence of cholestasis may be a predisposing factor in PMS, because with cholestasis there is

BOX 202-2 **Causes of Cholestasis**

- Estrogen excess or birth control pills
- Pregnancy
- Presence of gallstones
- Alcohol
- Endotoxins
- Hereditary disorders such as Gilbert's syndrome
- Anabolic steroids
- Various chemicals and drugs
- Nutritional deficiencies

reduced estrogen detoxification and clearance. Hence, a positive feedback scenario is produced. The high incidence of gallstones is a clear indication that many American women suffer from cholestasis.

Again, even though elevated serum estrogen values cannot be confirmed in PMS studies, it is interesting to note that estrogen excess during the luteal phase affects endorphin levels negatively. One study found a direct correlation between an increased estrogen/progesterone ratio and endorphin activity in the brain.[12] In essence, when the estrogen/progesterone ratio was increased, there was a decline in endorphin levels. This reduction is significant considering the known ability of endorphins to normalize or improve mood. Other studies have shown that low endorphin levels during the luteal phase are common in women with PMS.[13] Endorphins are lowered by stress and raised by exercise. The role of endorphins is discussed further later.

Estrogen Impairs Vitamin B_6

The way in which estrogen levels during the luteal phase negatively affect neurotransmitter and endorphin levels may be secondary to impairment of the action of vitamin B_6. It is well known that estrogens affect vitamin B_6 function negatively. Vitamin B_6 levels are typically quite low in depressed patients, especially women taking estrogens (birth control pills or conjugated estrogens [Premarin]).[14,15] Vitamin B_6 supplementation has been shown to have positive effects on all PMS symptoms, particularly depression, in many women (discussed in greater detail later). This improvement is achieved via a combination of a reduction in midluteal estrogen levels and an increase in midluteal progesterone levels.

Dietary Considerations

Women suffering from PMS typically eat a diet that is even worse than the standard American diet. Abraham[16] reports that, compared with symptom-free women, PMS patients consume the following substances:

- 62% more refined carbohydrates
- 275% more refined sugar
- 79% more dairy products
- 78% more sodium
- 53% less iron
- 77% less manganese
- 52% less zinc

A diet that is higher in dairy products may also contribute to some PMS symptoms. A survey of 39 women with PMS and 14 women without reported that the women with PMS consumed fivefold more dairy products and threefold more refined sugar than the women without PMS.[17] Another study observed that women with PMS also have an increased intake of dietary fat, carbohydrates, and simple sugars and decreased protein intake.[18]

Food cravings are often also higher in women with PMS; this may in part be due to a decrease in serotonin during the luteal phase in PMS sufferers. Therefore, serotonergic treatments may be helpful in controlling such food cravings.[19]

Another nutritional factor in PMS is the effect of refined sugars on rapid increases in insulin, which then causes the retention of sodium and subsequent water retention, with swelling in the hands and feet, abdominal bloating, and breast engorgement. Sugar has several detrimental actions in PMS. Eating foods high in simple sugars increases insulin secretion and can be harmful to blood sugar control, especially if the patient is hypoglycemic or diabetic. Sugar, especially combined with caffeine, also has a detrimental effect on PMS and mood (discussed later).[20] A high intake of sugar also impairs estrogen metabolism. The evidence is based on the higher frequency of PMS symptoms in women consuming a high-sugar diet and the fact that a high sugar intake is also associated with higher estrogen levels.[21] One study found that a low-fat, high-complex-carbohydrate diet alleviated premenstrual breast tenderness.[22]

C-reactive protein, a marker of inflammation, has been correlated with the severity of both physical and psychological symptoms of PMS.[23] A diet that stimulates inflammatory pathways includes sugar, poultry, eggs, cheese, milk, white flour, white rice, and partially hydrogenated oils. Foods that can reduce inflammation include fresh fruits, especially berries, green leafy vegetables, fish, nuts, seeds, turmeric, garlic, and onions.

Vegetarian women have been shown to excrete two to three times more estrogen in their feces and to have 50% lower levels of free estrogen in their blood than omnivores.[24,25] These differences are thought to be due to the lower fat and higher fiber intake of the vegetarian women. These dietary differences may also explain the lower incidence of breast cancer, endometriosis, and uterine cancer in vegetarian women. They may also play a role in PMS.

At the very least, the clinician should recommend a diet lower in saturated fat and cholesterol (achieved by reducing or eliminating the consumption of animal products) and higher in fiber-rich plant foods (fruits, vegetables, grains, and legumes).

Decreasing the percentage of calories as fat, in particular saturated fat, has dramatic effects on the reduction of circulating estrogen.[26,27] In one study, when 17 women switched from the standard American diet (composed of 40% of calories as fat and only 12 g as fiber daily) to a low-fat, high-fiber diet (consisting of 25% of calories as fat and 40 g as fiber daily), there was a 36% reduction in blood estrogen levels, with 16 out of the 17 women demonstrating significant reductions in only 8 to 10 weeks.[28]

It should be noted that not all nutrition research shows a clear-cut association with PMS. In the Study of Women's Health Across the Nation, a cross-sectional analysis was conducted of PMS symptoms in a multiethnic sample of 3302 midlife women.[29]

They sought to determine if the frequency of physical or emotional premenstrual symptoms was associated with dietary intake of phytoestrogens/fiber/fat or calcium, consumption of alcohol or caffeine, cigarette exposure, lack of physical exercise, and race/ethnicity or socioeconomic status. In this study, most dietary factors were not related to PMS. Fat intake was negatively associated with craving and bloating. Fiber intake was positively associated with breast pain. Alcohol intake was negatively associated with anxiety, mood changes, and headaches. Cigarette smoke exposure, whether passive or active, was positively associated with cramps and back pain. Ethnic differences in the reporting of symptoms and comorbidity associations were observed as well.

BOX 202-3 Negative Coping Styles in Women with Premenstrual Syndrome

- Feelings of helplessness
- Overeating
- Watching too much television
- Emotional outbursts
- Overspending
- Excessive/irrational behavior
- Dependence on chemicals: drugs, legal and illicit; alcohol; cigarettes

Thyroid Function

Low thyroid function (hypothyroidism) has been shown to affect a large proportion of women with PMS.[30,31] For example, in one study, 51 of 54 subjects with PMS demonstrated low thyroid status compared with 0 of 12 in the control group.[30] In another study, 7 of 10 subjects in the PMS group had low thyroid status compared with 0 of 9 in the control group.[31] Other studies have also shown hypothyroidism to be only slightly more common in women with PMS than in controls.[32,33] Many women with PMS and confirmed hypothyroidism who are given thyroid hormone experience complete relief of symptoms.[30] For more information, see Chapter 177.

Stress, Coping Style, and Depression

Study of the interaction of stress/serotonin and PMS has shown that serotonin levels in women with PMS fall after ovulation. Those without PMS had much higher levels of serotonin during the last half of the menstrual cycle. In a holistic/natural medicine approach to PMS, the identification of stressors and stress management should not be overlooked.[34] Many women with PMS tend to employ "negative" coping styles,[35] examples of which are listed in Box 202-3. It is important to identify the manner in which the patient deals with stress and to counsel her on more positive ways of coping.

There are some important relationships between PMS and depression. Depression is a common feature in many cases of PMS, and PMS symptoms are typically more severe in depressed women.[1] The reason appears to be a decrease in the brain level of various neurotransmitters, with serotonin and GABA being the most significant.[36,37] The most common class of prescription medications recommended for moderate to severe PMS/PMDD is an SSRI. When they are used for chronic depression, SSRIs must be taken daily. When used for PMS/PMDD, they can be taken just on the days of the month when the symptoms are the most problematic. This would suggest that when used in this way, they are not really increasing neurotransmitter levels but work by altering the neurophysiology and electrical conduction in the brain. Several SSRIs have been used, including fluoxetine, sertraline, and paroxetine. However, various psychotherapy methods have been equally if not more successful in improving the psychological aspects of PMS. In particular, biofeedback and short-term individual counseling (especially cognitive therapy) have documented clinical efficacy.[38,39] One of the advantages of cognitive therapy over antidepressant drug therapy in the treatment of PMS is that learning techniques such as cognitive-behavioral coping skills can produce excellent results that are maintained over time.

Exercise

Several studies have shown that women engaged in a regular exercise program do not suffer from PMS nearly as often as sedentary women.[40-42] In one of the more thorough studies, mood and physical symptoms during the menstrual cycle were assessed in 97 women who exercised regularly and in a second group of 159 women who did not exercise.[40] Mood scores and physical symptoms assessed throughout the menstrual cycle showed significant effects of exercise on negative mood states and physical symptoms. The regular exercisers obtained significantly lower scores for impaired concentration, negative mood, behavior change, and pain.

In another study, 143 women were monitored for 5 days in each of the three phases of their cycles (midcycle, premenstrual, and menstrual).[41] The women were 35 competitive athletes, two groups of exercisers (33 high-frequency exercisers and 36 low-frequency exercisers), and 39 sedentary women. The high-frequency exercisers experienced the greater positive mood scores and sedentary women the least. The high-frequency exercisers also reported the least depression and anxiety. The differences were most apparent during the premenstrual and menstrual phases. These results are consistent with the belief that women who exercise frequently (but not competitive athletes) are protected from PMS symptoms. In particular, regular exercise protects against the deterioration of mood before and during menstruation.

These studies provide evidence that women with PMS should partake of the benefits of exercise. Exercise may reduce PMS symptoms by elevating endorphin values, improving glucose tolerance, decreasing catecholamines, and modulating estrogen levels.[43]

Nutritional Supplements

Nutritional supplements have been widely used in the treatment of PMS by alternative practitioners and most definitely by women taking things into their own hands. Despite the inconsistent evidence, the positive results do show that nutritional supplements can offer safe, affordable solutions for many problems.

Vitamin B_6

The first use of vitamin B_6 in the management of cyclic conditions in women was in the successful treatment of depression caused by birth control pills, as noted in several studies in the early 1970s. These results led researchers to try to determine the effectiveness of vitamin B_6 in relieving PMS symptoms. Since 1975 at least a dozen double-blind clinical trials have been performed. Some of these studies have shown no effect, but most of the studies have shown a significant effect on the whole range of PMS symptoms at dosage ranges from 50 to 500 mg/day.[44] For example, in one double-blind crossover trial, 84% of the subjects had a lower symptom score during the vitamin B_6 treatment period.[45] In another double-blind crossover trial, 50 mg/day of vitamin B_6 was effective in decreasing premenstrual depression, fatigue, and irritability.[46] Although PMS has multiple causes, vitamin B_6 supplementation alone appears to benefit most patients.

It is important to note, however, that not all double-blind studies of vitamin B_6 have shown a positive effect.[44,47] The negative results in some trials may have been caused by many factors, such as the inability of some women to convert vitamin B_6 to its active form owing to a deficiency in another nutrient (e.g., vitamin B_2 or magnesium) that was not supplemented. These results suggest that supplementing pyridoxine by itself may not produce adequate clinical results for all women suffering from this disorder and that some women may have difficulty converting vitamin B_6 into its active form, pyridoxal-5-phosphate. To overcome this conversion difficulty, it may be necessary to use a broader-spectrum nutritional supplement or injectable pyridoxal-5-phosphate.

For most indications, the therapeutic dosage of vitamin B_6 is 50 to 100 mg/day. This dose level is generally regarded as safe, even

for long-term use. With use of doses greater than 50 mg, it may be important to divide it into 50-mg doses taken throughout the day. A single dose of 100 mg of pyridoxine did not lead to significantly higher pyridoxal-5-phosphate levels in the blood than a 50-mg dose, possibly indicating that a 50-mg oral dose of pyridoxine is about all the liver can handle at once.[48]

Vitamin B_6 is one of the few water-soluble vitamins associated with some toxicity when taken in large doses or in moderate dosages for long periods. One-time doses larger than 2000 mg/day can produce symptoms of nerve toxicity (tingling sensations in the feet, loss of muscle coordination, and degeneration of nerve tissue) in some individuals. Long-term intake of doses larger than 500 mg a day can be toxic if taken for many months or years.[49] There are also a few rare reports of toxicity occurring at long-term dosages as low as 150 mg/day.[49-51] The toxicity is thought to occur when supplemental pyridoxine overwhelms the liver's ability to add a phosphate group to produce the active form of vitamin B_6 (pyridoxal-5-phosphate). As a result, it is speculated that pyridoxine either is toxic to the nerve cells or actually acts as an antimetabolite by binding to pyridoxal-5-phosphate receptors, thereby creating a relative deficiency of vitamin B_6. Another possibility is that minute amounts of contaminants or vitamin B_6 analogs may have been introduced during synthesis. Although not a problem at normal doses of vitamin B_6, contaminants present in larger doses may block vitamin B_6 activation sites. Again, it appears to make sense to limit doses to 50 mg at a time. If more than 50 mg/day is desired, the doses should be spread out throughout the day.

Vitamin B_6 has the ability to increase the synthesis of several neurotransmitters in the brain including serotonin, dopamine, norepinephrine, epinephrine, taurine and histamine. There are also extensive interactions between vitamin B_6 and magnesium, which work together in many enzyme systems. In fact, another mechanism by which vitamin B_6 may improve the symptoms of PMS is by increasing the accumulation of magnesium within body cells.[52] Without vitamin B_6, magnesium does not get inside the cell.

Magnesium

Magnesium deficiency has been implicated as a causative factor in PMS.[53] Red blood cell (RBC) magnesium levels in patients with PMS have been shown to be significantly lower than in normal subjects.[16,54] Because magnesium plays such an integral part in normal cell function, magnesium deficiency may account for the wide range of symptoms attributed to PMS. Furthermore, magnesium deficiency and PMS have many common features, and magnesium supplementation has been shown to be an effective treatment of PMS. In one study involving 32 women with PMS, 360 mg of magnesium three times daily was given from midcycle to the onset of menstrual flow.[55] Relief of premenstrual mood fluctuations and depression during magnesium treatment was significant.

A recent study designed to improve understanding of the association between magnesium and the menstrual cycle measured plasma, RBC, and mononuclear blood cell (MBC) magnesium concentrations in 26 women with confirmed PMS and in a control group of 19 women during the follicular, ovulatory, early luteal, and late luteal phases of the menstrual cycle.[56] Although there were no significant differences in plasma magnesium levels between PMS patients and control subjects and there was no menstrual cycle effect on plasma magnesium, women with PMS had significantly lower RBC magnesium concentrations than those in the control group, which was consistent throughout the menstrual cycle.

The observation of low RBC magnesium concentrations in patients with PMS has now been confirmed by four independent studies. In general, it is thought that women with PMS have a "vulnerability to luteal phase mood state destabilization"[56] and that chronic and enduring intracellular magnesium depletion serves as a major predisposing factor for destabilization.

In addition to emotional instability, magnesium deficiency in PMS is characterized by excessive nervous sensitivity with generalized aches and pains and a lower premenstrual pain threshold. One clinical trial of magnesium in PMS showed a reduction of nervousness in 89%, breast tenderness in 96%, and weight gain in 95% of subjects.[16] In another double-blind study, high-dose magnesium supplementation (360 mg three times daily) was shown to dramatically relieve PMS-related mood changes.[55]

Although magnesium has been shown to be effective on its own, even better results may be achieved by combining it with vitamin B_6 and other nutrients. Several studies have shown that when PMS patients are given a multivitamin/multimineral supplement containing high doses of magnesium and pyridoxine, they experience a substantial reduction in PMS symptoms.[57,58]

The optimal intake of magnesium should be based on body weight, 6 mg/kg. For a 50-kg woman, the recommendation would be 300 mg; for a 90-kg woman, 540 mg. Because these doses are difficult to achieve by diet alone, supplementation is recommended. In the treatment of PMS, a dose of twice this amount, 12 mg/kg, may be needed.

Magnesium bound to aspartate or one of the Krebs cycle intermediates (malate, succinate, fumarate, or citrate) is preferred to magnesium oxide, gluconate, sulfate, or chloride because of better absorption and fewer side effects (laxative effects).[59,60]

Calcium

Calcium has emerged as a common nutrient to supplement for PMS. Because calcium regulation and calcium deficiency can actually mimic some PMS symptoms, supplemental calcium has been tested as a treatment. An important multicenter clinical trial was conducted in 479 women who were given either 1200 mg of calcium carbonate or placebo for three menstrual cycles.[61] A significantly lower symptom score was observed in the calcium group during the luteal phase of the cycle for both the second and third cycles. By the end of the third cycle, calcium resulted in a 48% reduction in total symptom scores from baseline compared with a 30% reduction in the placebo group. Other studies also show improvements in PMS symptomatology with calcium supplementation (1000 to 1336 mg).[62,63] In one of the later studies, calcium and manganese supplementation (1336 and 5.6 mg, respectively) improved mood, concentration, and behavior. In another study, 1000 mg/day improved mood and water retention.[62]

Zinc

Zinc levels have been shown to be low in women with PMS.[64] Zinc is required for proper action of many body hormones, including the sex hormones, as well as in the control of the synthesis and secretion of hormones. In particular, zinc serves as one of the control factors for prolactin secretion.[65] When zinc levels are low, prolactin release increases, and high zinc levels inhibit this release. Hence, in high-prolactin states, zinc supplementation is very useful. An effective dose range for zinc supplementation for elevated prolactin levels in women is 30 to 45 mg in the picolinate form.

Vitamin E

Although vitamin E research concerning PMS has focused primarily on breast tenderness, significant reduction of other PMS symptoms has also been demonstrated in double-blind studies.[16,66] Nervous tension, headache, fatigue, depression, and insomnia were all significantly reduced. In one double-blind

study, patients receiving vitamin E (400 IU/day) demonstrated a 33% reduction in physical symptoms (such as weight gain and breast tenderness), a 38% reduction in anxiety, and a 27% reduction in depression after 3 months of use. In contrast, the placebo group reported only a 14% reduction in physical symptoms. The group taking vitamin E also noted higher energy levels, fewer headaches, and fewer cravings for sweets.

See Chapter 165 for further research on vitamin E and mastalgia.

Essential Fatty Acids

Women with PMS have been shown to exhibit essential fatty acid and prostaglandin abnormalities, the chief abnormality being a decrease in gamma-linolenic acid (GLA).[67] GLA is derived from linoleic acid. This conversion requires adequate levels of vitamin B_6, magnesium, and zinc, because these nutrients function in delta-6-desaturase, the key enzyme responsible for this conversion. Given that a deficiency of one or more of these nutrients is common in PMS, decreased GLA levels could almost be expected.

Evening primrose, black currant, and borage oils contain GLA, typical levels being 9%, 12%, and 22% respectively. Although these essential fatty acid sources are quite popular, the research on GLA supplements in the treatment of PMS shows no benefit over placebo. In the four double-blind crossover controlled trials of evening primrose oil, this issue may be complicated by a very high response in the placebo group.[68,69] One of these studies used 3 g/day and the others used 4 g/day. A meta-analysis of the clinical trials of evening primrose oil concluded that it is of little value in the management of PMS.[68]

Multiple Vitamin and Mineral Supplements

A high-quality multivitamin/multimineral supplement providing all of the known vitamins and minerals can serve as a foundation on which to build. Women with PMS have two very sound reasons for taking a high-potency multiple vitamin:

- Nutritional deficiency is relatively common among women with PMS.
- High-potency multivitamin/multimineral formulations have been shown to have significant benefits in PMS.

The frequency of nutritional supplementation and the calculated intake of select nutrients have been shown to be much lower in patients with PMS than in normal women. Women with PMS have been shown to consume vitamins in their food at levels close to the recommended daily allowance, but compared with women who did not have PMS, their intake levels were only 2.2% as much for thiamin, 2.2% for riboflavin, 16.7% for niacin, 8.7% for pantothenic acid, and 2.7% for pyridoxine.[16]

Several double-blind studies have shown that patients with PMS who were given a multivitamin/multimineral supplement containing high doses of magnesium and pyridoxine experience reductions (typically at least a 70% reduction) in both premenopausal and postmenstrual symptoms.[57,58]

L-Trytophan

As discussed earlier in this chapter, decreases in serotonin may be the cause of PMS or at least may exacerbate PMS. Tryptophan is a precursor to serotonin. Studies using L-tryptophan in daily doses of 6 g/day for 17 days from ovulation to day 3 of menses has led to significant reductions in mood swings, insomnia, carbohydrate cravings, tension, irritability, and dysphoria.[70,71] As 5-hydroxytryptophan (5-HTP) has shown superior results to tryptophan in depression, it may also prove to be a more effective option for raising serotonin levels in PMS. For more information, see Chapter 98.

Botanical Medicines

Many plants have been used throughout traditional botanical medicine for cyclic premenstrual symptoms. These have tended to include what are called reproductive tonics, adaptogens, liver detoxification herbs, and "hormonal balancing" herbs. Unfortunately these botanical approaches have not been the subject of clinical evaluation. Instead, modern research has focused on the following botanicals for relief of PMS symptoms: chaste berry, St. John's wort, and *Ginkgo biloba*.

Vitex agnus castus (chaste tree)

The chaste tree *(V. agnus castus)* is native to the Mediterranean, where its berries have long been used for women's health. Chaste berry extract is probably the single most important herb in the treatment of PMS, not only because of its long tradition and known historical uses but also as a result of modern scientific research. In two surveys of gynecologic practices in Germany, physicians graded chaste berry extract as good or very good in the treatment of PMS. More than 1500 women participated in the studies.[72,73] One third of the women experienced complete resolution of their symptoms, and another 57% reported significant improvement.

The beneficial effects of chaste tree in PMS and these other conditions appear to be related to alterations in gonadotropin-releasing hormone and follicle-stimulating hormone-releasing hormone. In other words, it appears that chaste berry extract has profound effects on the hypothalamus and pituitary function. As a result, it is able to normalize the secretion of other hormones—for instance, reducing the secretion of prolactin and reducing the estrogen: progesterone ratio.

In a more recent study, a randomized clinical trial compared a chaste tree standardized extract (20-mg tablet standardized for casticin) with placebo in women with PMS.[74] One hundred and seventy women with PMS were assigned to take either the chaste tree or a placebo once daily for three consecutive menstrual cycles. Women were asked to rate changes in PMS symptoms, such as irritability, mood changes, anger, headache, breast tenderness, and bloating. At the end of the trial, women taking the chaste tree reported a 52% overall reduction in PMS symptoms, compared with only 24% for those taking placebo. Women taking the chaste tree extract reported significantly greater reductions in irritability, mood changes, anger, headache, and breast tenderness than the women taking the placebo. Bloating was the only symptom that did not change significantly with chaste tree. Another study has looked at the effectiveness of chaste tree extract versus fluoxetine in decreasing PMS symptoms and found the two treatments to have comparable results, with the main difference being that fluoxetine was more effective in treating psychological symptoms and chaste berry was more effective with physical symptoms.[75]

In more recent research, Chinese women suffering from moderate to severe PMS were studied in a prospective double-blind placebo controlled parallel-group multicenter clinical trial.[76] The chaste tree extract contained 4.0 mg of dried ethanolic (70%) extract. The mean total Premenstrual Syndrome Diary (PMSD) score decreased from 29.23 at baseline to 6.41 at the end of the third cycle for the chaste tree group and from 28.14 at baseline to 12.64 at the end of the third cycle for the placebo group. The difference in the PMSD score from baseline to the third cycle was significantly lower in the treatment group than in the placebo group. The Premenstrual Tension Syndrome Self-Rating Scale decreased from 26.17 at baseline to 9.92 for the treatment group and from 27.10 to 14.59 for the placebo group—similar positive results as the PMSD scores.

PMS is also very common in perimenopausal women. A study was undertaken to evaluate the effectiveness of a combination of St. John's wort and chaste berry in the treatment of PMS-like symptoms in perimenopausal women.[77] This clinical trial was conducted over 16 weeks and information rating PMS scores in perimenopausal women who were experiencing irregular menses was collected at 4-week intervals. The daily dose of herbal products given was 3 tablets containing 5400 mg of St. John's wort standardized to contain 990 mcg hypericins, 9 mg hyperforin, and 18 mg flavonoid glycosides. The daily dose of chaste tree was one tablet of an extract equivalent to 1000 mg of dried fruit. Participants recorded the severity of their PMS symptoms using the Abraham's Menstrual Symptom Questionnaire. Results for the active treatment group were statistically superior to placebo for total PMS-like symptoms as well as subgroups of PMS depression and PMS food cravings.

Ginkgo biloba

Several compounds and mechanisms of *Ginkgo* may be involved in physical and psychological benefits for PMS (see Chapter 93). In the first randomized placebo-controlled clinical trial evaluating *G. biloba* extract (GBE) in PMS, 165 women of reproductive age who had fluid retention, breast tenderness, and vascular congestion were assigned to receive either a GBE of 25% *Ginkgo* flavone glycosides at 80 mg twice daily or a placebo from day 16 to day 5 of their cycles. Symptom diaries kept by patients and physician evaluation of symptoms demonstrated that *G. biloba* extract was effective against the congestive symptoms of PMS, particularly breast pain and breast tenderness.[78]

In a subsequent study, GBE was evaluated using Beck's Depression Inventory, a daily symptom rating questionnaire containing 19 PMS symptoms according to DSM-IV, and items relative to the inclusion criteria included participants experiencing the symptoms for at least two consecutive cycles before the study and experienced at least 5 of the 19 symptoms for most of the time during the last week before menses. Eighty-five women completed the study. Participants were given 40 mg three times daily of a standardized GBE or a placebo from day 16 of their cycle to day 5 of their next cycle. Overall severity of symptoms in the GBE group was 34.80% before the treatment, which fell to 11.11% after the treatment. In the placebo group, the baseline severity was 34.38%, which dropped to 25.64% after intervention. The severity of the psychological and physical symptoms also declined significantly in both groups, but there was again a significant difference between the two groups, in favor of the GBE.[79]

Hypericum perforatum

Owing to the influence of St. John's wort on serotonin (see Chapter 99), it should not be surprising that this herb would be an important botanical in the treatment of PMS, and research has affirmed this. A randomized double-blind placebo-controlled crossover trial of 36 women with regular menstrual cycles and mild PMS was done in which women were randomly assigned to receive St. John's wort tablets (900 mg/day and standardized to 0.18% hypericin and 3.38% hyperforin) or placebo for two menstrual cycles.[80] After a 1-month no treatment cycle, women were crossed over to the opposite group for two additional cycles. Symptoms were rated using the Daily Symptom Report, State Anxiety Inventory, Beck Depression Inventory, Aggression Questionnaire, and Barratt Impulsiveness Scale. Numerous hormones and physiologic markers were also measured in the follicular and luteal phases: follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, prolactin, testosterone, cytokine, interleukins (IL-1B, IL-6, and IL-8), interferon, and tumor necrosis factor alpha.

St. John's wort was statistically more beneficial than placebo in relieving food cravings, swelling, poor coordination, insomnia, confusion, headaches, crying, and fatigue. There were no significant effects of St. John's wort compared with placebo in any of the biochemical blood measurements. St. John's wort was not statistically more beneficial in anxiety, irritability, depression, nervous tension, mood swing, feeling out of control, and pain-related symptoms during two cycles of treatment. However, these pain-related symptoms appeared to improve more than with placebo toward the end of each treatment period.

In a prospective, open, uncontrolled observational study, 19 women who were diagnosed with PMS completed a daily symptom rating questionnaire for one menstrual cycle and underwent a screening interview with physicians. The participants then took St. John's wort tablets (300 mg St John's wort standardized to 900 mcg of hypericin) for two complete menstrual cycles.[81] Symptoms were rated daily by means of the Hospital Anxiety and Depression scale and modified Social Adjustment Scale, which were administered at baseline and after each of the two cycles. The degree of improvement in overall PMS scores between the beginning of the study and the end was 51%, with more than two thirds of the women having at least a 50% decrease in the severity of symptoms. The mood subscale showed the most improvement (57%); the symptoms with the greatest reductions in scores were crying (92%), depression (85%), confusion (75%), feeling out of control (72%), nervous tension (71%), anxiety (69%), and insomnia (69%).

Saffron (Crocus sativus L.)

Saffron has been previously shown to have an antidepressant effect in women with mild to moderate depression through a serotonergic mechanism, so it is not surprising that it would be beneficial in PMS. A double-blind placebo-controlled trial was done to study whether saffron could be used to relieve PMS symptoms. Fifty women of reproductive age with regular menstrual cycles and PMS symptoms for at least the last 6 months were randomly assigned to receive 15 mg of saffron twice daily or placebo twice daily for four full menstrual cycles.[82] The Daily Symptom Report and the Hamilton Depression Rating Scale were used to evaluate the response. According the Daily Symptom Report, 19 of the 25 women in the saffron group responded with at least a 50% reduction in severity of symptoms versus only 2 of 25 in the placebo group (P <0.0001). A significant difference between the saffron and placebo groups occurred between the third and fourth cycles and was statistically significant by the end of the study (P <0.0001). According to the Hamilton Depression Rating Scale, 15 of 25 women in the saffron group responded to treatment versus only 1 of 25 in the placebo group. (P <0.0001). Again, a significant difference was seen between the third and fourth cycles, with a statistically significant difference by the end of the study (P <0.0001).

Bioidentical Progesterone Therapy

Bioidentical progesterone, also called natural progesterone, is a white crystalline powder most often made by extracting diosgenin from Mexican wild yam and then converting this in a manufacturing laboratory into a progesterone molecule that is biochemically identical to the body's own progesterone. It is not wild yam, nor should it be considered an herbal product. What makes natural progesterone "natural" is not so much that it is made from plant material but rather that it is identical to the progesterone hormone produce in a woman's ovaries. Conventional medical practitioners have historically used a synthetic version, called progestin, which is found in birth control pills as a hormonal treatment for PMS. This

has largely been replaced by using select antidepressants for their effect on serotonin levels. Although bioidentical progesterone has been studied in controlled clinical trials for the treatment of PMS, efforts to consistently demonstrate the superiority of progesterone therapy over placebo have failed (possibly because there is a significant placebo response in PMS).[83-88] The studies showing positive effects have used dosages of 200 to 400 mg twice daily as a vaginal or rectal suppository from 14 days before the expected onset of menstruation until the onset of vaginal bleeding.[87,88] Transdermal creams of natural progesterone generally sold in natural foods/nutrition stores have been a popular self-treatment for PMS. These products vary greatly from an herbal wild yam cream only to wild yam cream with bioidentical progesterone added, up to 20 mg per ¼ tsp. Side effects are few and tend to be generally mild, but they may occur in 4% to 5% of individuals using transdermal creams that include 20 mg of USP progesterone per one quarter teaspoon. In one of the later double-blind studies that did show a positive effect for progesterone therapy (400 mg twice a day by vaginal or rectal administration), adverse events were reported by 51% of patients in the progesterone group compared with 43% in the placebo group.[88] Irregularity of menstruation, vaginal itching, and headache were reported more frequently by the women taking the progesterone.

THERAPEUTIC APPROACH

The approach to the woman with premenstrual symptoms first involves an evaluation of symptoms and the establishment of a diagnosis. In an effort to clarify the treatment approach, the clinician should consider the following seven key steps:

1. Evaluate PMS symptoms by having the patient complete a questionnaire.
2. Rule out psychiatric or other medical conditions.
3. Have the patient adopt the following dietary recommendations for PMS:
 - A vegetarian, low-fat, low-sugar, low-salt, high-fiber diet is advised; if there is mastalgia, caffeine should be avoided.
4. The patient may also benefit from the guidelines for nutritional supplementation given below.
5. Select the appropriate herbal support.
6. Establish a program for stress reduction and recommend regular exercise.
7. If, after at least three complete periods, the patient is not experiencing a significant improvement or complete resolution of symptoms, additional causative factors should be sought, as detailed above, or change made to the treatment program.

Nutritional Supplements

- High potency multivitamin/multimineral formula
- Vitamin B_6: 50 to 100 mg/day (total days dose of vitamin B_6 in a single ingredient or in the multiple vitamin should not exceed 150 mg)
- Magnesium (preferably citrate, malate, aspartate,or glycinate): 250 mg twice a day
- Zinc: 15 to 20 mg/day
- Vitamin E: 200 to 400 IU/day

Botanical Medicines

Vitex agnus castus:
- Standardized extract (0.5% agnuside): 175 to 225 mg a day or 20 mg standardized to casticin
- Liquid extract: 2 mL/day

Ginkgo biloba:
- 80 to 160 mg standardized extract (24% ginkgoflavonglycosides) twice a day

Hypericum perforatum:
- 900 to 1800 mg standardized extract (0.3% hypericin content) a day

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CHAPTER 203

Proctologic Conditions

Thomas A. Kruzel, BA, MT, ND

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ANORECTAL ANATOMY

The anorectal region is divided into the anus, which extends anywhere from 3 to 4 cm above the anal verge to its merge with the rectum, and the rectum, which is 12 to 18 cm long. The anal verge is the demarcation point from perianal skin to anal skin. The anal canal can further be divided into the dentate and anorectal lines. The dentate line is the demarcation point between the ectoderm of the external squamous epithelium and the rectal entodermal mucosa. The anal canal does not contain sebaceous or sweat glands and is innervated by somatic nerves up to and slightly beyond the dentate line, which make it sensitive to pain to varying degrees. Above the dentate line the rectal mucosa is relatively insensitive to pain but registers distention and inflammation as diffuse visceral pain. The anorectal line is the point above which the rectum expands outward into the pelvic bowl.

The area between the dentate and anorectal lines contains the rectal columns, anal valves, anal glands, and anal crypts. The anal glands normally provide mucus for lubrication with passage of stool and empty into the anal crypts. This area becomes the source of an anal fistula or perirectal abscess if the crypt becomes impacted and cannot discharge its mucus. Anal fissures lie below the dentate line. Midway between the dentate and anorectal lines lies the white line of Hilton, or pectinate line. This is the location of the intersphincteric groove, the region that lies between the internal and external sphincters. The internal sphincter is under control of the autonomic nervous system, and the external sphincter is under somatic or voluntary control.

The anorectal region is highly vascularized and receives its blood supply from both the inferior mesenteric artery and the internal iliac artery. Arterial flow is then diverted from these sources through the superior, middle, and inferior rectal arteries. There is considerable anastomosis among these branches. Venous return is facilitated by the superior and middle hemorrhoidal veins, which empty into the inferior mesenteric veins and subsequently the portal vein, and the internal iliac vein, which subsequently empties into the vena cava, bypassing the liver.

The levator ani muscle forms the floor of the pelvis and helps form the puborectalis sling. The pull of the puborectalis sling causes the bowel to change direction as it penetrates the pelvic floor, making passage of stool easier. Along with the internal and external rectal sphincters, these muscles form the sphincter mechanism that controls continence. The anal canal receives its innervation via the pudendal nerves originating from S2, S3, and S4.[1,2]

A wide variety of presenting symptoms are related to disorders of the anorectum. Among them are pain, tenderness, rectal spasm, bleeding, itching, protrusions, eruptions, discharges, constipation, diarrhea, changes in stool pattern, sacral backache, shooting pains down the limbs, crampy and painful menses, urinary disturbances, anemia, prostatitis, restlessness in children, and foreign bodies.[3] The clinician should be aware that seemingly unrelated symptoms might, in fact, have their origin in the anorectal tract.

ANAL DISEASES

Anal Fistula and Anal Abscess

Anal fistula and anal abscess result from an infection of an anal crypt, whose distal end lies near the dentate line. The anal glands, which lie within the intersphincteric

groove and empty into the anal crypts, become infected because of impacted feces. The resulting infection makes its way into the intersphincteric space but generally does not penetrate beyond the external sphincter. Most of the anal glands lie posteriorly; therefore, most abscesses drain from a line posterior to the ischial tuberosities, whereas anterior abscesses drain radially from their points of origin. The presence of a rectal fistula or abscess may point to an internal bowel disease such as diverticulitis, trauma to the area, or immune system incompetence, as with the human immunodeficiency virus (HIV).

Under normal conditions the highly vascularized rectal mucosa is able to provide adequate protection against the spread of infection. The weak points are the anal glands, however, because they may become impacted with fecal matter, setting up an infective process in the anal crypt and intersphincteric space. The surrounding perianal tissue is swollen, red, and painful to palpation. If the infection remains in the intersphincteric space, the patient has rectal pain seemingly without specific findings. Eliciting the pain with pressure upon examination may provide a clue to the source of the lesion. The patient may also present with a fever of unknown origin.

The adjacent ischiorectal fossae are regions filled with fatty tissue that allow for distention of the rectum. Therefore, an abscess has many different directions in which to track, setting up areas for pockets of pus. In a true perianal abscess, incision and drainage are usually not recommended because the bulk of the lesion would remain untouched owing to the probable invasion of the underlying tissues and the propensity of such an access to form caverns of pus. Unlike other abscesses formed by the body, perianal abscesses should not be allowed to come to a head and rupture on their own; such an occurrence can lead to excessive inflammatory necrosis of the anal sphincter.

Generally a surgical consultation is warranted for a rectal abscess. Surgery allows for opening of the tract and healing by second intention. However, localized treatment can be undertaken to help the abscess drain if it has ruptured on its own or the patient presents acutely and immediate referral is not possible. Such treatment affords some relief and helps decrease the morbidity associated with this condition. Irrigation with herbal antibacterial agents such as *Hydrastis*, *Usnea*, and *Calendula succus* in 0.9% saline helps drainage.

Another, often encountered scenario is that of folliculitis with resultant abscess formation. These abscesses can be incised and drained, because they do not involve the anal canal or ischiorectal fossa. Homeopathic medicines such as calcarea sulphuricum, silicea, hepar sulphuris, and *Myristica* are some of the more often indicated medicines. Poultices made of onion, garlic, or potatoes exert a drawing action, bringing the lesion to a head faster. Alternating hot and cold sitz bath is also useful. Once the abscess has broken open or has been incised and drained, irrigation with the previously mentioned solution hastens healing.

Anal Cryptitis

Anal crypts are pockets created between the grooves formed by the rectal columns at their distal points ending at the dentate line. Anal glands empty into the crypts and, as previously mentioned, are believed to be the source of anal fistula. That anal cryptitis is a separate entity is open to some debate, and it is rarely seen. The patient complains of pain that is worse with bowel movement. Examination shows localized tenderness and redness at the dentate line, and there may be some rectal spasm. Rectal fissure should be ruled out. Chronic cases suggest bacterial infection, usually gonorrhea.

Treatment is by herbal suppository, sitz baths, increasing dietary fiber intake, and, if necessary, localized anesthesia. The crypt may be cleaned out with a crypt hook if needed and irrigated with a solution of *Calendula succus* and *Hydrastis* in normal saline.

Anal Fissure

An anal fissure is a slit-like separation of the anal mucosa lying below the dentate line. The majority of fissures are found in the posterior midline region (70% to 80%), but anterior midline lesions (10% to 20%) are more commonly seen in women. Some investigators report that fissures are more common in men than women,[4] but other studies do not bear this out.[5] In some patients the anal sphincter is more oval than round, coming to a Y or narrow point at the posterior midline, making for a greater predisposition for anal fissure. Anal fissure in children is not all that uncommon, often being associated with chronic diarrhea or hard stool.[6] Fissure may also be a complication of a lesion associated with a congenital anal deformity. Lesions located in the anteroposterior vertical axis suggest an internal bowel disease, such as Crohn's disease, squamous cell carcinoma or adenocarcinoma of the rectum, syphilitic fissure, or ulceration due to tuberculosis.

Anal fissures are very painful because of their somatic innervation, which results from spasm of the anal sphincter in response to stretching during the passage of stool. The presence of an anal fissure triggers a vicious cycle of pain, causing sphincter spasm, which contributes to a tightening of the sphincter and increased pain with passage of stool. Patients usually have severe pain during and for some time after defecation, and bleeding is not uncommon. As the lesion enlarges it may ulcerate and become infected. Conventional medical treatment consists of rectal dilation, internal sphincterotomy, electrodessication, or surgical excision.[5]

Anal fissure can be caused by passage of large hard stools, childbirth trauma, chronic diarrhea, trauma, food allergy, or prolonged straining to pass stool. Infants and young children who consume large amounts of cow's milk are more likely to have anal fissures and chronic constipation, especially if they were breast fed for a shorter period.[7] Many of the patients in whom anal fissures develop display intense, compulsive personalities that may contribute to the formation of such fissures as well as the ability to heal. A previous anal or rectal operation, syphilis, or Crohn's disease also predisposes the patient to fissure development.

Examination may be difficult because of the pain and spasm, and anoscopic examination is often out of the question unless anesthesia is used. A localized injection of 1% or 2% lidocaine into the rectal sphincter at the 3-o'clock and 9-o'clock positions can help relax it enough for an examination to occur. One can often see anal fissures without using an anoscope simply by pulling back on the anal skin and examining the tissue. Presence of a sentinel pile or enlarged papilla suggests chronic anal fissure and is the result of inflammation and the body's attempt to protect the inflamed area. Anal spasm may be marked, making it difficult to perform an examination, and anal stenosis and fibrosis may be present if the condition has been chronic.

Clinicians should consider the presence of Crohn's disease, especially if the patient is younger, there is a history of periodic or chronic diarrhea, and the fissure lies in the anteroposterior vertical axis. Squamous cell carcinoma, syphilitic ulcers, and rarely tuberculosis should be considered as part of the differential diagnosis. Spasm of the levator ani muscle may also make one think of anal fissure, but no lesion is present in this case.

Treatment of anal fissure can prove to be one of the more difficult courses of therapy for both the patient and the clinician.

Although surgical intervention removes the lesion and alleviates the pain, the lesion invariably returns because the underlying cause has not been addressed. Additionally, surgical intervention often predisposes to fecal incontinence later in life. Therefore, medical management both in the short and long terms is necessary for complete resolution. Patients must be cautioned that the healing of a rectal fissure has its periods of exacerbation and remission and that continuing with the treatment protocol is important despite the periodic setbacks that are often encountered. Educating the patient on this point upon initiation of therapy is essential to its success.

Treatment

Initial treatment should be to alleviate the pain and spasm, because often they have brought the patient to the office. Homeopathic medicines provide prompt relief if the simillimum is found and aids the healing process. Remedies such as *Chamomilla*, graphites, nitric acid, *Ratanhia*, *Sepia*, silicea, and *Thuja* are some of the more often indicated medicines, but others may also be needed.[8,9] Frequent dosing is generally the rule. Protease 315 mg, two capsules three times daily between meals and again before bed, will help to alleviate pain as well. A preparation of 0.2% glycerol trinitrite can be used topically to relieve rectal spasm,[10] as can 5% lidocaine cream for localized pain. Glycerol trinitrite has been shown in a number of studies to be effective in relieving rectal spasm as well as increasing blood flow to the anal sphincter.[11-13] Reduced blood flow to the anal sphincter has been postulated as one of the precipitating mechanisms for the development of an anal fissure.

A topical cream consisting of vitamins A and E, panthenol, *Calendula*, and *Comfrey* will considerably enhance the healing process by providing nutrients essential for healing by second intention. Some of the commercial preparations also contain boric acid, which acts as a styptic. Initially, the cream should be applied topically after every bowel movement and at bedtime. As healing occurs, twice-daily application usually suffices until the lesion has resolved.

Iontophoresis using a zinc electrode and applying a positive current helps facilitate healing by hardening the underlying fissure, decreasing bleeding, and affording pain relief.[14] The patient lies on the negative dispersing pad and current is applied for 10 minutes at 10 mA.

The patient should be instructed not to strain during passage of stool and to use cotton balls that have been moistened with water rather than toilet paper or chemical or alcohol wipes. Some patients are excessive cleaners; they should be instructed that it is unnecessary to wipe deep into the anal canal because doing so makes the condition worse.

Sitz baths also aid in the healing process by providing increased blood flow to the area. If performing a sitz bath is not possible, alternately spraying hot and cold water on the perineal area will achieve the same result.[15]

Increasing dietary fiber is necessary if the condition is due to chronic constipation, whereas chronic diarrhea can be managed through a variety of therapeutic approaches once the cause is found. Dietary changes are a must, especially if the anal fissure is associated with irritable bowel syndrome or Crohn's disease. The higher rates of hemorrhoids and Crohn's disease seen in blood group O individuals are believed to be due to food intolerance.[16]

As previously mentioned, the clinical course varies from patient to patient and seems to depend partially on whether the patient follows the treatment plan religiously. Frequent follow-up is needed to assess the healing process and reassure the patient. Once healing has occurred, proper bowel function and good dietary and bowel habits must be maintained in order to prevent further episodes. Patients who experience an anal fissure are at risk for further episodes.

HEMORRHOIDS

Affliction from hemorrhoids has been noted in the writings of various cultures throughout history—Babylonian, Hindu, Greek, Egyptian, and Hebrew. In the United States as well as other industrialized countries, hemorrhoidal disease is extremely common. Although most individuals may begin to have hemorrhoids in their twenties, hemorrhoidal symptoms usually do not become evident until the fourth decade of life.[17,18] Estimates have indicated that 50% of persons older than 50 years have symptomatic hemorrhoidal disease at one time or another and up to one third of the total U.S. population has hemorrhoids to some degree.[19]

The causes of hemorrhoidal disease are similar to those of varicose veins. As with varicose veins, predisposition to the development of hemorrhoids depends on genetic makeup. Excessive venous pressure, pregnancy, long periods of standing or sitting, straining at stool, and heavy lifting are considered the major factors. Most patients have more than one predisposing factor.[20]

Because the portal venous system contains no valves, factors that increase venous congestion in the perianal region can precipitate hemorrhoid formation. They include increasing intra-abdominal pressure (e.g., defecation, pregnancy, coughing, sneezing, vomiting, physical exertion, and portal hypertension due to cirrhosis), increase in straining during defecation, and standing or sitting for prolonged periods.

Presenting symptoms are itching, burning, irritation with passage of stool, swelling of the anus and perianal region, blood on the toilet paper or in the bowl, and seepage of mucus. Most patients attribute all rectal symptoms to hemorrhoids; however, internal hemorrhoids are only rarely painful or cause itching. Usually the hallmark of a hemorrhoidal eruption is bleeding or protrusion noted after passage of stool. Pain from internal hemorrhoids occurs when they become strangulated from prolapse and with thrombosis. Any other pain associated with hemorrhoids is usually due to a coexisting lesion such as a fissure. Itching is rarely associated with internal hemorrhoids except if there is excess mucus discharge.

Classification

Hemorrhoids are typically classified according to location and degree of severity. External hemorrhoids occur below the anorectal line. They may be full of either blood clots (thrombotic hemorrhoids) or connective tissue (cutaneous hemorrhoids). A thrombotic hemorrhoid is produced when a hemorrhoidal vessel has ruptured and formed thrombus, whereas a cutaneous hemorrhoid consists of fibrous connective tissue covered by anal skin. Cutaneous hemorrhoids can be located at any point on the circumference of the anus. Typically, they are caused by the resolution of a thrombotic hemorrhoid; that is, the thrombus becomes organized and replaced by connective tissue.

Internal hemorrhoids occur above the anorectal line. Occasionally an internal hemorrhoid enlarges to such a degree that it prolapses and descends below the anal sphincter. Internal hemorrhoids are graded by the degree of prolapse.

Grade I: No prolapse

Grade II: Prolapse upon defecation but spontaneous reduction

Grade III: Prolapse upon defecation and manual reduction
Grade IV: Prolapsed and no reduction possible

Internal-external, or mixed, hemorrhoids are a combination of contiguous external and internal hemorrhoids that appear as baggy swellings. The following types of mixed hemorrhoids can occur:

- Without prolapse: bleeding may be present, but there is no pain.
- Prolapsed: characterized by pain and possibly bleeding.
- Strangulated: the hemorrhoid has prolapsed to such a degree and for so long that its blood supply is occluded by the anal sphincter's constricting action; strangulated hemorrhoids are very painful and usually become thrombosed.

Treatment

In contrast to the United States and the United Kingdom, hemorrhoids are rarely seen in parts of the world where high-fiber diets containing unrefined foods are consumed.[19] A low-fiber diet high in refined foods contributes greatly to the development of hemorrhoids. Individuals consuming a low-fiber diet tend to strain more during bowel movements, because their smaller and harder stools are more difficult to pass. This straining raises the pressure in the abdomen, obstructing venous return. The greater pressure will increase pelvic congestion and may significantly weaken the veins, causing hemorrhoids to form.

A high-fiber diet is perhaps the most important component in the prevention of hemorrhoids. A diet rich in vegetables, fruits, legumes, and grains promotes peristalsis because many fiber components attract water and form a gelatinous mass that keeps the feces soft, bulky, and easy to pass. A high-fiber diet leads to significantly less straining during defecation.

Natural bulking compounds can be used to reduce fecal straining. These fibrous substances, particularly psyllium seeds and guar gum, possess a mild laxative action owing to their ability to attract water and form a gelatinous mass. They are generally less irritating than wheat bran and other cellulose fiber products. Several double-blind clinical trials have demonstrated that supplementing the diet with bulk-forming fibers can significantly reduce the symptoms of hemorrhoids (bleeding, pain, pruritus, and prolapse) and improve bowel habits.[21,22] The use of psyllium seed fiber has been shown to afford significant relief in bleeding and pain within 6 weeks in hemorrhoid suffers.[23]

A placebo-controlled randomized study evaluated the efficacy of fiber supplements in 50 patients with bleeding internal hemorrhoids. Patients in the study group were treated with a commercially available preparation of *Plantago ovata* and those in the control group were treated with a placebo. Endoscopy was performed in every patient before and after treatment to establish the degree of hemorrhoidal prolapse as well as the numbers of congested hemorrhoidal cushions and contact-bleeding hemorrhoids. During the first 15 days of treatment, the average number of bleeding episodes was 4.8 ± 3.8 for the study group versus 6.4 ± 3 for the control group (NS). During the following 15 days, it decreased to 3.1 ± 2.7 in the study group versus 5.5 ± 3.2 (P <0.05) in the control group, and in the last 10 days of treatment a further reduction to 1.1 ± 1.4 was found in the study group compared with 5.5 ± 2.9 in the control group (P <0.001). The number of congested hemorrhoidal cushions diminished from 2.6 ± 1 to 1.6 ± 2.2 after fiber treatment (P <0.01) but no differences were found in the control group. In the fiber group, hemorrhoids bled on contact in 5 out 22 patients before treatment and in none after treatment; no differences were found in the control group. No modification of the extent of prolapse was observed after treatment.[24] Although the effect took a few weeks to develop, the final results were very impressive.

Another important, but only recently recognized dietary factor is breakfast. An age-, gender-, and pregnancy-matched case-control study carried out in an outpatient clinic found a remarkable 7.5-fold increase in the odds of suffering from hemorrhoids or anal fissures in matched subjects who did not eat breakfast![25]

Flavonoid preparations have been shown to be beneficial in the prevention and treatment of hemorrhoids through their strengthening effect on venous tissues. Although early studies primarily used rutin, later research has used hydroxyethylrutosides (HERs).

Several of the studies have been performed in pregnant women, where HERs were shown to be of great benefit in helping to relieve hemorrhoidal signs and symptoms. In one study, 90% of the women given HERs (1000 mg daily for 4 weeks) experienced improvement of symptoms, compared with only 12% in the placebo group.[26] Similar results in hemorrhoids not associated with pregnancy have been reported.[27,28] Another study provided a micronized flavonoid combination (diosmin 90% and hesperidin 10%) for a median of 8 weeks before delivery and 4 weeks after delivery to 50 pregnant women with acute hemorrhoids. Their therapy was very successful, with 66% of patients reporting relief from symptoms by the fourth day of treatment and fewer suffering relapses during the antenatal period.[29] Treatment was well accepted and did not affect pregnancy, fetal development, birth weight, infant growth, or feeding.

In most circumstances, topical treatments for acute or chronic hemorrhoids involving the use of suppositories, ointments, and anorectal pads provide only temporary relief. Many over-the-counter products for hemorrhoids primarily contain natural ingredients, such as witch hazel *(Hamamelis)*, cocoa butter, Peruvian balsam, zinc oxide, allantoin, and homeopathic preparations. Many patients use hydrocortisone cream to help with the itching that they associate with hemorrhoids; prolonged use of this agent can often aggravate the pruritus ani, setting up a cycle of continued use.

Botanical Medicines

Botanical medicines have had a long history of use for hemorrhoids. They can be used topically, as suppositories, or taken orally to support redundant tissue and facilitate healing. Use of rectal suppositories after galvanic, infrared, or laser therapy helps facilitate healing and decrease bleeding. Some of the more commonly used botanical medicines are discussed later in this chapter.

Hydrotherapy

The warm sitz bath is an effective noninvasive treatment for uncomplicated hemorrhoids.[15,18] Although a warm sitz bath is a useful treatment for an acute hemorrhoidal flare-up, alternating hot and cold sitz baths is better suited to facilitate the healing of chronic conditions.

Surgical Treatment

A variety of surgical and nonsurgical methods of treating hemorrhoids exist, the choice of which often depends on the stage of the hemorrhoid and the expertise of the physician. Stage I or II hemorrhoids can often be managed medically, especially if they are acute. Herbal rectal suppositories along with the indicated homeopathic medicine often aid quick resolution of the flare-up. In uncomplicated cases of stage I or II hemorrhoids, unless the patient is exhibiting symptoms, treatment is usually not

recommended except for increasing dietary fiber and addressing the patient's dietary choices.

Injection of sclerosing agents is useful in stage I and stage II hemorrhoids, but such treatment is contraindicated in patients with anal fissure, inflammatory bowel disease, Crohn's disease, leukemia, or portal hypertension. Sclerosing therapy is not usually effective against stages III and IV hemorrhoids.

Rubber-band ligation of hemorrhoids is a widely used in-office procedure that removes redundant tissue and causes scarring, which is replaced then by new tissue. Following such treatment, patients often have a sense of fullness or pressure in the rectum, and pain occurs if the band is placed too close to the pectinate line. Postbanding bleeding can occur, and there have been reports of complications resulting in septicemia and death.[20] Rubber-band ligation is used primarily for stage I, stage II, and occasionally stage III hemorrhoids; its success is largely a function of the physician's ability to place the bands.

Cryosurgery involves the application of liquid nitrogen or nitrous oxide to the hemorrhoid, which causes destruction of the venous plexus, scarring, and eventual tissue replacement. Used primarily for stage II and stage III hemorrhoids, the procedure is also useful if condyloma is present. It is contraindicated for stage IV hemorrhoids, chronic ulcers, and acutely thrombosed hemorrhoids. Pain, swelling, and bleeding may occur after cryosurgery.

Hemorrhoidectomy, or the surgical removal of redundant tissue, is by far the most invasive of the hemorrhoidal procedures. It often requires an outpatient surgical setting and causes the patient to lose time from activities of daily living so that healing can take place. Most patients seek alternative treatments in order to avoid surgery and its complications, such as pain and instability of the rectal sphincter.

The monopolar direct current technique for the management of hemorrhoids is becoming a significant treatment of choice in the United States.[30] According to a report by Machicado et al,[31] this painless outpatient treatment of all grades of hemorrhoids is effective and safe. This methodology warrants consideration as the treatment of choice for hemorrhoidal disease.

The first published work on monopolar direct current (also called inverse galvanism) was published by Keesey[32] of Chicago. Dr. Keesey dated the first use of this approach to 1897, although the technical problems (producing a smooth uninterrupted galvanic current source) were not worked out until approximately 1925. The technique then came into use in general practice. Monopolar ablution of hemorrhoidal tissue lost favor in conventional medicine not because it was ineffective but because newer techniques and advances in surgery made it less attractive. If the naturopathic medical schools had not been teaching the Keesey treatment over the last 60 years, it is very possible that this irreplaceable technique would have been lost to the healing arts.

A later study showed that direct-current electrotherapy also relieves the chronic anal fissures often associated with internal hemorrhoids. All 10 of the patients in the reported study experienced relief of chronic anal pain within two treatments, and anal fissures healed in 9 within 4 weeks. One patient experienced a perianal abscess and fistula, requiring surgery. There were no recurrences in 20 months (mean) of follow-up.[31]

The monopolar direct current technique is purely an office procedure. No anesthesia is needed except a local anesthetic for the occasional hypersensitive or nervous patient (in such instances, a 2% procaine solution is injected directly into the hemorrhoid). To date, there have been no reported cases of stricture or metastatic abscesses, a fact that speaks well for the procedure's safety.

The chemicophysiologic action, which causes the absorption and destruction of a vein, is responsible for the permanence of the cure. The mechanism of action of monopolar direct current is well understood. When introduced into the interior of the hemorrhoid, the negative pole of the galvanic current makes contact with the water of the blood and tissues and generates hydrogen gas and hydroxide ions. The hydroxide destroys the organized structure of the hemorrhoid and its capillary circulation. This produces first a hydrolysis and then a hardening of the hemorrhoid. The final disappearance of the hemorrhoid is brought about in one of two ways. It is either absorbed like any bodily contusion or, if the hemorrhoid is large, it ruptures, causing a discharge of the thrombosed elements into the rectum, followed by a contraction of the residual hemorrhoidal tissues.

What makes the Keesey technique attractive is that the patient may be freely ambulant after completion of the procedure and can return to his or her normal activities. The hemorrhoid disappears 7 to 10 days after the treatment. Each separate hemorrhoid is treated in the same manner, and larger hemorrhoids may have to be treated more than once. Generally it is a good policy to treat only one hemorrhoid or at most two at a time because of the healing that must occur and the higher risk of bleeding with the treatment of several.

Infrared coagulation (IRC) is effective with stage I and stage II hemorrhoids but can be combined with the Keesey treatment for stage III and stage IV lesions. Whereas the Keesey technique uses current, the infrared coagulator utilizes a burst of intense heat generated internally and shot through a blue anodized sapphire tip to the surface of the hemorrhoid. The IRC "coagulates" the redundant tissue to a depth that is a function of the duration of the light burst, usually 1 to 1.5 seconds. As with the Keesey technique, a 7- to 10-day period of healing should occur between treatments. Many naturopathic physicians who use the Keesey treatment also incorporate IRC, as doing so usually reduces the number of treatments needed per hemorrhoid. Compared with rubber-band ligation, laser therapy, and cryotherapy, IRC has been shown to produce better results and less morbidity.[33-35]

Prevention

As with all diseases, the primary treatment of hemorrhoids is prevention. This involves reducing factors that may be responsible for increasing pelvic congestion, such as straining during defecation, sitting or standing for prolonged periods, and underlying liver disease. A high-fiber diet is crucial for the maintenance of proper bowel activity, and nutrients and botanical substances that enhance the integrity of venous structures may also be of benefit.

Warm sitz baths and topical preparations are useful to ameliorate the discomfort but have only transient results. A diet high in complex carbohydrates that are rich in dietary fiber is indicated. The diet should contain liberal amounts of proanthocyanidin- and anthocyanidin-rich foods, such as blackberries, cherries, and blueberries, to strengthen vein structures. Supplements such as vitamins A and B complex, antioxidants such as vitamins C and E, and zinc will help maintain vascular integrity and facilitate healing.

When indicated, the monopolar direct current method, specifically designed for the treatment of hemorrhoids, will give permanent results. This technique is especially useful in advanced hemorrhoidal disease and, when coupled with the necessary diet and lifestyle changes, considerably decreases the likelihood of recurrence.

EXTERNAL HEMORRHOIDS

External hemorrhoids occur when there is dilation of the external rectal plexus or thrombosis after an episode of constipation, diarrhea, heavy lifting, or Valsalva effect from sneezing, coughing, or childbirth. The patient notices an often painful perianal lump, and some bleeding may be associated with it. External hemorrhoids usually pose mild to little discomfort and largely resolve on their own if homeostasis is restored. External anal skin tags found on examination are the remnants of previous external hemorrhoids.

If, however, the hemorrhoid becomes thrombosed, a cycle of acute edema and pain is set up that may lead to surgical intervention. As the lesion becomes increasingly distended, varying degrees of pain and swelling can arise, which are often exacerbated by passage of stool or from prolonged sitting. The patient may report bleeding after stool, which is due to a disruption of the hemorrhoid.[36]

A prolapsed internal hemorrhoid should also be considered as part of the differential diagnosis for external hemorrhoid, as should perianal abscess, rectal fissure with sentinel pile, hypertrophied anal papillae, irritated skin tag, condyloma latum, and condyloma acuminata.

Treatment

Unless the hemorrhoid has thrombosed and the patient is in excessive pain, an external hemorrhoid can usually be managed medically. Initial treatment should be to relieve the pressure and dissolve whatever thrombosis has formed. As healing occurs, long-term management in the form of patient education, dietary changes, and enhancement of vascular integrity should be undertaken to help prevent further episodes.

Initial treatment with the enzyme protease 315 mg, two capsules between meals three times daily and two at bedtime, will help reduce the thrombosis and decrease pain. Alternating hot and cold sitz baths act to relieve pain and increase blood flow. A number of homeopathic medicines, such as *Aesculus*, aloe, *Hamamelis*, muriatic acid, *Ratanhia*, and *Sepia*[8,37] are effective in relieving pain and speeding the course of healing. A clinical repertory or materia medica should be consulted, because there are numerous remedies that will provide relief.

Long-term management should involve identification and removal of the precipitating cause and education of the patient as to the cause and how to prevent further episodes. Dietary changes to eliminate offending foods while increasing dietary fiber in the forms of fruits and vegetables or an over-the-counter fiber supplement are warranted. Herbal medicines such as *Aesculus*, *Collinsonia, Hamamelis,* and *Althea* or *Ulmus*[38] will help restore venous sufficiency and soothe inflamed tissues.

In some cases regulation of bowel function with the use of herbal laxatives may be necessary while normal intestinal and colon function is restored. A variety of commercially available herbal medicines and fiber compounds are effective.

In patients who are experiencing an acute episode of a thrombosed external hemorrhoid, prompt surgical excision or incision is in order. Because the external skin is innervated by somatic nerves, administration of anesthesia is needed before evacuation of the clot. Excision leaves a wound that should not be sutured but should be allowed to heal by secondary intention, although this causes greater postoperative pain. Incision and debridement of the clot allow for less pain, but the wound may close too early, leading to re-formation of the thrombus. A text on minor surgery for diseases of the rectum and colon should be consulted as to the proper surgical technique.

Starting the patient on herbal anodynes such as *Piscidia*, belladonna if pain is due to rectal spasm, and *Hyoscyamus niger* can facilitate postoperative management. Healing and pain relief can be afforded with the topical use of *Arnica*, *Hypericum*, and in particular *Calendula succus*.

Alternating hot and cold sitz baths with ½ oz of povidone-iodine added enhances healing and helps reduce the chance of infection. As with medical treatment, protease 2400 milk clotting units (MCUs) can be added for pain relief. Homeopathic agents such as *Arnica*, *Calendula*, and staphysagria should also be considered for pain relief.

PERIANAL DERMATOLOGIC DISORDERS

Condylomata Acuminata

A patient presenting with condylomata acuminata may complain of a sticking or foreign-body sensation perianally. If the lesion is large enough, defecation can be interfered with and hygiene can become a problem. The lesion is usually soft, moist, reddish pink, and pedunculated. Differentiation from condylomata lata of secondary syphilis is necessary because the treaments differ and the potential for transmission is greater with the latter disorder. A rapid plasma reagin (RPR) test with reflexive fluorescent treponemal antibodies (FTA) is warranted. If dark-field microscopic examination is available, it should also be performed. Diagnosis of condylomata acuminata is made through biopsy.

A solution of 25% podophyllum that is applied topically for 6 to 8 hours, after which it is washed off by the patient, has been shown to be effective. Several applications may be necessary in order to eradicate the lesion.[39] Cryosurgery is also available, as is IRC after subcutaneous injection of 1% or 2% lidocaine.[40]Although naturopathic and homeopathic philosophy decries the "suppression" of lesions as contributing to a deepening of the disease process, concomitant administration of the proper homeopathic medicine coupled with a good nutritional program rarely causes this to happen.

Often administration of homeopathic *Thuja* is indicated, but a number of other homeopathic remedies cover genital warts. The taking of a constitutional case not only helps with the eradication of the lesion but also acts to decrease the patient's susceptibility to development of further lesions, which can often happen.

Condyloma Lata

Condyloma lata, or anogenital wart, is caused by human papillomavirus (HPV) types 6, 11, 16, 18, 31, 33, and 35 and is transmitted by sexual contact. Lesions appear as soft, moist, pink to gray flat to pedunculated excrescences frequently found in clusters. More often located in warm, moist regions of the anogenital region, they are more commonly found clustered around the anus in homosexual men and in women who practice anal intercourse.[41]

Lesions must be differentiated from the flat lesion seen with the condyloma lata of secondary syphilis. A diagnosis of squamous cell carcinoma should be considered if the lesion does not respond to therapy, or biopsy can be performed.[42]

Various naturopathic therapies are available, among them being treatment with 25% podophyllum, *Thuja* ointment, homeopathic prescription, cryotherapy, IRC, and electrosurgical dessication.[43]

Lymphogranuloma Venereum

The infective agent in lymphogranuloma venereum (LGV) is one of the serotypes of *Chlamydia trachomatis*, and the lesion may first appear as a papule that ulcerates and heals rapidly. If the primary lesion is in the rectal mucosa, the patient presents with the signs and symptoms of proctitis. This is then followed by the development of inguinal adenitis or buboes that are extremely painful. The later stages may manifest as fistulization, ulceration, fibrosis, and rectal or anal stenosis and can lead to lymphedema of the legs and genitalia. Non-LGV *Chlamydia* serotypes can also be implicated in proctitis but generally do not have as severe presenting symptoms.

White blood cell counts may reach 20,000/mm^3 if there is lymphatic involvement, and the patient may exhibit anemia. Culture of the chlamydial serotype from an infected lesion is diagnostic, but complement fixation and immunofluorescent antibody tests are available.[44]

If LGV is treated promptly, the prognosis is good; but once the disease has begun to affect cellular changes, the prognosis becomes worse as the degree of pathology can be considerable. For the most part allopathic treatment consists of antibiotics such as doxycycline, erythromycin, and sulfisoxazole, all of which have been found to be effective against LGV.[44] Various homeopathic as well as herbal medicines can be used. See treatments under "Proctitis."

Herpes

Probably the most commonly encountered perianal lesion, herpes simplex typically manifests as a burning, searing pain that may be confused with that of a rectal fissure. Examination reveals vesicles on an erythematous base that soon erode and form ulcerations. In patients with HIV or other immunocompromising conditions, the lesions can form deep ulcerations and have a prolonged course. Diagnosis is by Tzanck smear or viral culture.

Initially, treatment protocols should address the current eruption, because longer-term prevention strategies usually take time to work. Topical preparations consisting of deglycyrrhized licorice (DGL) and *Melissa officinalis* extracts can help alleviate local symptoms of burning and pain as well as facilitate the healing process. Zinc sulfate 2% has also been used topically with some success. Various homeopathic medicines not only address the pain and eruptions but also help decrease the patient's susceptibility to further outbreaks. Stress reduction is important as well because herpes eruptions often occur during periods of excessive stress or other illness.

Long-term strategies include decreasing the arginine-containing foods in the diet, such as nuts, legumes (especially peanuts), and chocolate. Supplementing lysine at 500 to 1000 mg/day is useful in eliminating outbreaks. Antioxidants such as vitamins C and E as well as B complex vitamins, zinc, and copper have all been shown to be of benefit.

Pilonidal Sinus

Pilonidal sinus is a rare congenital tract that runs from the coccyx or sacrum to the perineum with constant drainage. Both congenital and acquired factors play a role in the development of a pilonidal sinus. The condition is most commonly seen in young white adults, rarely in black persons, and almost never in Asians. Congenital postanal dimples predispose to the formation of a pilonidal tract as well as obesity, a deep intergluteal cleft, and excess body hair.

The condition is usually differentiated from anal fistula and furunculosis because of its midline orientation and through the passing of a probe through the sinus, noting its passage toward the sacrum rather than the anus.

Patients seek treatment because of the often chronic nature of the discharge. If the sinus becomes infected, incision and drainage may be needed, but irrigation with the herbal formula mentioned for abscess can be performed. Weight reduction and removal of excess hair in the region also helps reduce the risk of infection and symptoms. Homeopathic medicines selected according to the presentation, such as silicea, calcarea sulphuricum, and hepar sulphuris, have proved useful. Additionally, homeopathic *Thuja* as an intercurrent treatment has resolved a number of obstinate cases.

Proctalgia Fugax

Proctalgia fugax, or levator spasm syndrome, is more common in men than women and manifests as an often searing pain near the coccyx or rectum that lasts for a brief but intense period, usually resolving on its own. The episode often wakens the person from sleep but may occur at any time.

Caused by a spasm of the levator ani or pubococcygeal muscle, proctalgia fugax produces a deep-seated, often heavy aching or searing pain that feels as if it were localized in the rectum and/or prostate in men. Examination reveals a tense and tight levator ani muscle that is tender with pressure and is often drawn up above the anal sphincter.

Mechanisms that are thought to trigger an episode are poor posture, chronic anxiety, and mental fixation on the rectal area as well as misalignment of the coccyx or other bones composing the pelvic bowl.

Differential diagnosis includes lumbar disc disease, coccygodynia, prostatitis, presacral tumor, developing ischiorectal abscess, spinal cord tumor, and rectal lesion.

Treatment often takes the form of reassuring the patient as to the etiology of the condition. Muscle relaxants and hot packs may be of benefit. Spinal and pelvic bone adjustments may also be of use, as is massage to the lower abdomen, lumbosacral spine, and perineum. Chronic cases often respond to deep tissue work such as Rolfing.

Proctitis

Proctitis usually manifests as rectal pain, tenesmus, rectal discharge, and blood in the stool. White blood cells may be present in large numbers, being evident on wet preparation, Gram stain, or Wright stain. Because there are a variety of causes for the inflammation, an anoscopic examination is warranted to examine the rectum for inflammation, mucopurulent discharge, mucosal friability, bleeding, and ulceration. Severe ulceration and bleeding are associated with infection by the LGV *Chlamydia* serotype.

Among the causative agents are *Chlamydia* (usually of the genital immunotypes but also the LGV immunotypes), yeast, bacteria such as *Neisseria gonorrhoeae*, parasites, trauma, lectins, excessive fiber in the diet, external irradiation, syphilis, *Trichomonas*, and Crohn's disease. One study demonstrated a higher risk for development of ulcerative proctitis in smokers and persons who had had an appendectomy.[45]

Determination of the etiologic agent dictates the course of treatment and expected outcomes. If the cause is external-beam irradiation for colon cancer or radium seed implants for prostate cancer, the therapy should commence before cancer treatment and continue during it and for several weeks after treatment has ceased. In a study examining the effects of radiation and antioxidant therapy,[46]

it was demonstrated that a "substantial number of patients with radiation proctitis seem to benefit from antioxidant therapy." Despite admonitions by radiation oncologists that antioxidant therapy should be discontinued, a review by Lamson and Brignall[47,48] demonstrated no ill effects when radiation was combined with antioxidant therapy. As part of the therapeutic regimen for radiation proctitis, concomitant administration of homeopathic radium bromatum 200c before and after treatment helps decrease skin burning. Other homeopathic medicines may also be indicated, such as X-Ray, Sol, and cadmium metallicum.

Additionally, the use of demulcent rectal suppositories helps soothe the inflamed rectal mucosa and decrease pain.

If the proctitis is secondary to an inflammatory bowel condition, treatment of the underlying disease results in healing of the rectum as well. This can be accomplished by addressing the patient's diet, providing adequate fiber, and administering herbal demulcents and enteric-coated peppermint to soothe the inflamed intestinal tract. Short-chain fatty acids administered rectally were shown in one study to alleviate symptoms of proctocolitis, and a deficiency of such acids should be considered as part of the clinical presentation.[49,50]

In cases in which an infective agent such as bacteria, *Chlamydia*, yeast, fungi, trichomonas, or a parasite is identified as the etiologic agent, a variety of naturopathic treatments have been found empirically to be effective. Among them are injection of ozone, use of herbal suppositories, homeopathic medicines, and a retention enema consisting of *Hydrastis*, *Usnea*, *Echinacea*, yarrow for *Trichomonas*, and *Althea* in a base of 0.9% NaCl. This combination can be applied topically during the initial examination to begin treatment. Antioxidants such as vitamins C and E, as previously mentioned, facilitate healing.

As a general rule, treatment of proctitis should continue for 10 to 14 days before reexamination and assessment. In cases of ulcerative disease, treatment may need to be continued longer to allow for complete healing.

Pruritus Ani

Pruritus ani is characterized by chronic itching of the perianal skin with excoriation from scratching and an eventual thickening of chronically affected areas. Patients often scratch at night during sleep or are awakened from sleep by the itching. Patients may complain of intermittent to constant itching, burning, and soreness that often awake them at night. Use of topical ointments may provide some relief, but symptoms return when they wear off. Examination may show varying degrees of erythema, swelling, excoriation, thickening, and fissuring due to scratching.

The stage is set for development of pruritus ani when the normal skin protective barriers have broken down. Various agents contribute to this process, such as excessive wiping with harsh toilet papers; use of "wipes" that are impregnated with drying alcohol, dyes, and antibacterial or fungal agents; reactions to synthetic undergarments or detergents used to launder them; and the wearing of too tight underclothing, which decreases air circulation. Patients with chronic diarrhea or loose stools are at increased risk because of the stools' often acidic nature.[51,52] In some cases, removal of normal hair growth for cosmetic purposes also contributes because it disrupts the normal bacterial flora in this region of the body.

Pinworms and *Candida* are the two most common infecting agents in pruritus ani. In particular, a history of perianal itching largely at night should alert the physician to the possibility of *Enterobius vermicularis* infestation (pinworms). This is a common etiologic agent in children and can be spread to other members of the family with considerable ease. A wet preparation will demonstrate *Candida*, and a clear adhesive tape preparation for pinworms helps establish the diagnosis.

Patients with episodes of periodic or chronic diarrhea are also at increased risk of pruritus ani. It can occur because of the acidic nature of the stool but most often is due to aggressive cleaning of the area afterward. Compulsive cleaners should be instructed on the use of cotton wipes, bath or shower cleansing, or the use of moist towels.

The frequent use of soaps, detergents, bleaches dyes, or perfumes can also contribute to the development of pruritus ani. A recent onset may be due to a change in a product, and the physician should ask about it. Certain foods that frequently aggravate the condition are peanuts, coffee, colas, beer, and spicy foods.[5,20] Highly acidic foods and foods that are responsible for an allergic reaction in the patient should be suspected and eliminated for several weeks.

Psoriasis, contact dermatitis, precancerous or cancerous lesions, Bowen's disease (interepithelial epithelioma), keratoacanthoma, melanoma, squamous cell carcinoma, and basal cell carcinoma can also cause pruritus ani.

Laboratory tests to consider are culture and sensitivity testing if bacterial infection is suspected, a potassium hydroxide and/or wet preparation to look for yeast or fungi, Wood's lamp examination for *Tinea cruris*, and a punch biopsy for suspicious lesions.[53]

TREATMENT OPTIONS

Treatment options in anorectal disorders include elimination of spicy or offending foods or of food allergies and improvement of the patient's digestion. If an infective agent is identified, a course of topical therapy to remove the yeast, fungi, or bacteria should be initiated. Initial washing with 3% hydrogen peroxide followed by application of a topical herbal formula containing *Usnea*, *Hydrastis*, *Spilanthes*, oregano, and tea tree oil, which is then allowed to dry, helps eliminate the infective agents. In order to reestablish the skin's defensive barrier, this step should be followed by a healing salve containing *Calendula*, comfrey, and vitamins E and A. Relief should be obtained within 7 to 10 days if the underlying cause has been eliminated.

For pinworms, numerous naturopathic treatments have proved to be effective. Additionally, all clothing and bedding should be washed in warm to hot water to eliminate the eggs that have been laid outside the rectum at night.

Various homeopathic medicines are also effective and may help prevent future episodes in chronic cases. Having the patient use moist cotton wipes after stool and eliminating excess moisture in the perineal area helps break the circle. Topical application of zinc oxide also has proved effective in the treatment of pruritus ani.

Botanicals

Botanical medicines have been used in the treatment of anorectal diseases throughout history by many different cultures. Many of the plants used by the various folk traditions are of the same genus, varying by species only, whereas others are unique to their locations. More recent examinations of the various botanical medicines have elicited their chemical properties and actions, but the eclectic and herbalist traditions have also placed an importance on the symptom specificity of the medicine. Doing so enhances its healing effect.

Aesculus hippocastanum is classified as a tonic, astringent, febrifuge, narcotic, and antiseptic. High in tannic acid and aesculin, this herbal medicine is good for pain relief of internal viscera and is indicated for hemorrhoids and rectal irritation when there is marked congestion and a sense of spasmodic closing of the rectum

as if there were a foreign body present. Additionally, it is effective for itching, a sensation of heat, aching, and rectal pains. It has also been found to be useful for rectal neuralgia and proctitis.[38]

Achillea millefolium (yarrow) possesses slightly astringent properties as well as being an alterative and diuretic. It acts as a tonic on mucous membranes to stem the flow of mild hemorrhage; thus is used for bleeding hemorrhoids, especially if they are accompanied by mucoid discharges.[38]

Althea officinalis (marsh mallow) is high in mucilage, which helps restore the electrical charge to inflamed rectal mucosa. It is often put into rectal suppositories because of its ability to decrease swelling, irritation, and inflammation.[38]

Cinnamomum (cinnamon) is commonly found in herbal rectal suppositories because of its ability to stem hemorrhaging.[38]

Collinsonia canadensis (stone root) is an alterative, tonic, stimulant, and diuretic. It is used primarily for its effects on the venous system because it tones vascular tissue. It is especially indicated for hemorrhoids due to chronic constipation and venous insufficiency. Patients so affected have a sense of constriction, weight, and heat in the rectum and pass very dry stools. It is also useful for proctitis, anal fistulas, and rectal ulcer.[38]

Hamamelis virginiana (witch hazel) is primarily a tonic and astringent. It affects the venous system by restoring vascular integrity; therefore it is an excellent medicine for varicose veins, hemorrhages, and hemorrhoids. Indications for its use are venous tissues that are pale and in varying states of flaccidity but may also possess a deep redness because of vascular engorgement and stagnation of blood flow. The hemorrhoidal tissues are usually very painful and may have a tendency to ulceration.[38]

Hydrastis canadensis (goldenseal) contains hydrastine, berberine, canadine, and acrid resins. It exerts its action upon the mucous membranes and affects the healing of ulcerations while controlling mild hemorrhages; it also has antibacterial properties. Additionally, it has an astringent effect upon hemorrhoids. Goldenseal is indicated for hemorrhoids due to constipation with a sinking feeling in the stomach and a dull headache and for anal fissures that are painful with severe burning before, during, and after stool.[9,54]

Ruscus aculeatus (butcher's broom) acts upon the venous system, where it reduces swelling and has a vasoconstrictive action, thus reducing bleeding.[55]

Homeopathic Medicines

Various homeopathic medicines have historically been used in the treatment of anorectal diseases. Often a few key symptoms manifesting during the initial consultation guide the practitioner to the correct medicine, thus decreasing the need to take a full constitutional case.

TREATMENT SUMMARY FOR HEMORRHOIDS

As with all diseases, the primary treatment for hemorrhoids is prevention. This goal involves reducing the factors that may be responsible for increasing pelvic congestion; straining during defecation, sitting or standing for prolonged periods of time, or underlying liver disease. A high-fiber diet is crucial for the maintenance of proper bowel activity. Fiber supplements, flavonoids, and various botanical medicines such as butcher's broom are appropriate supplementary measures.

Warm sitz baths and topical preparations are useful to ameliorate the discomfort, but have only temporary effects.

Diet

A high-complex-carbohydrate diet rich in dietary fiber is recommended. The diet should contain liberal amounts of flavonoid-rich foods, such as blackberries, citrus fruits, cherries, and blueberries to strengthen vein structures.

Nutritional Supplements

- Psyllium seed husks: 5 g at bedtime
- Vitamin C: 500-1000 mg three times a day
- Flavonoids (choose one of the following):
 - Citrus bioflavonoids, rutin, and/or hesperidin: 3000-6000 mg/ day
 - Micronized diosmin: 500 to 1000 mg/day
 - Grape seed extract: (95% procyanidolic oligomers) 150-300 mg/day
 - Pine bark extract: 150 to 300 mg /day

Botanical Medicine

- Butcher's broom (*Ruscus aculeatus*) extract (9%-11% ruscogenin content): 100 mg three times a day

Physical Medicine

- Hydrotherapy: warm sitz baths to relieve uncomplicated hemorrhoids

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CHAPTER 204

Psoriasis

Michael T. Murray, ND, and Michael Traub, ND, DHANP, FABNO

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- Circumscribed red, thickened plaques overlying silvery-white scale.
- Characteristically involves the scalp; the extensor surfaces of the wrists, elbows, knees, buttocks, and ankles; and sites of repeated trauma.
- Positive family history in 30% of cases.
- Nail involvement results in characteristic pitting. Other nail changes include onycholysis, discoloration, thickening, and dystrophy.
- Possible arthritis.

GENERAL CONSIDERATIONS

Psoriasis is a common skin disorder. Its rate of occurrence in the United States is between 2% and 4% of the population. Psoriasis affects few black people in tropical zones but is more common among those in temperate zones, though still lower than for whites. It appears commonly among Japanese but is rare in American Indians. Psoriasis occurs in men and women equally, and the mean onset is at 33 years of age,[1] although 2% of patients show onset by 2 years of age.

Psoriasis is a classic example of a hyperproliferative skin disorder. The rate of keratinocyte proliferation, assessed by proliferating cell nuclear antigen staining, is highest in verrucae (72.1%) and psoriasis (45%), followed by squamous cell carcinoma (28%), actinic keratosis (23%), and basal cell carcinoma (21.4%). The apoptosis inhibitor survivin is a recently described member of the "inhibitor of apoptosis" family expressed in most human cancers and also known to be a regulator of mitosis. Survivin has been detected in 88% of patients with psoriasis. It is likely that other factors are also involved in the development of a hyperplastic epidermis.[2]

The pathogenesis of psoriasis is incompletely understood; it is a complex, multifactorial disease with a genetic predisposition. The etiopathogenicity of psoriasis can be examined from several different viewpoints. It is a polygenic disorder. Oxidative stress has been linked to the inflammation in psoriasis.[3] It is an immune dysfunction. Angiogenesis plays a critical role. Neuropeptides are involved.[4] Research into each of these factors reveals increasing levels of sophisticated studies. At this time, it does not seem possible to combine them all under one unifying theory.

Nevertheless, recent genetic and immunologic advances have greatly increased the understanding of psoriasis as a chronic, immune-mediated inflammatory disorder. The primary immune defect in psoriasis appears to be an increase in cell signaling via chemokines and cytokines that act on upregulated gene expression and cause the hyperproliferation of keratinocytes. Current knowledge of psoriasis has catalyzed the development of targeted biological treatments.

HLA-Cw6, which lies in the major histocompatibility region on chromosome 6, is currently considered the major genetic determinant of psoriasis. Variants in or near genes that encode subunits of cytokines (IL12B, IL23A) or cytokine receptors (IL23R) are of interest. The gene product of IL12B, p40, is the target of a recently approved monoclonal antibody therapy for psoriasis (ustekinumab). Association with psoriasis has also been found in genes coding for tumor necrosis factor-alpha (TNF-α) and other cytokines. Many of these genetic variations are also associated with immune disorders considered psoriatic comorbidities, including Crohn's disease and diabetes.[5]

Although in the past psoriasis was considered a disorder of keratinocytes, it is now generally accepted that it is primarily an immune-mediated disorder. The cells of the

skin consist of cytokine-synthesizing keratinocytes, antigen presenting cells, epidermotrophic and circulating T lymphocytes, dermal capillary endothelial cells, mast cells, tissue macrophages, granulocytes, fibroblasts, and non-Langerhan cells. These cells all communicate by means of cytokine secretion and respond accordingly via stimulation by bacteria, chemical, ultraviolet light, and other irritating factors. The primary cytokine released in response to antigen presentation is TNF-α. Ordinarily this is a controlled process unless the insult to the skin is prolonged, in which case an imbalanced cytokine production in a susceptible host leads to a pathologic state such as psoriasis. Studies have shown that activated keratinocytes in psoriatic lesions not only undergo accelerated turnover but also are a major source of proangiogenic cytokines, such as vascular endothelial growth factor (VEGF), endothelial-cell stimulating angiogenesis factor, TNF-α, and platelet-derived growth factor (PDGF).[6] Other angiogenic mediators—such as hypoxia-inducible factors, angiopoietins, interleukin-8 (IL-8), and IL-17—are upregulated in psoriasis.[7] Patients with psoriasis receiving anti-VEGF treatment for cancer showed complete remission of their cutaneous symptoms.[8]

Initially, immature dendritic cells in the epidermis stimulate T cells from lymph nodes in response to antigen stimulation. The lymphocytic infiltrate in psoriasis comprises predominately CD4 and CD8 T cells. Adhesion molecules that promote leukocyte adherence are highly expressed in psoriatic lesions.[9] After T cells receive primary stimulation and activation, a resulting synthesis of mRNA for IL-2 occurs, resulting in a subsequent increase in IL-2 receptors. The increased IL-2 from activated T cells and IL-12 from Langerhans cells ultimately regulate genes that code for the transcription of cytokines, such as IFN-gamma, TNF- α, and IL-2, which are responsible for the differentiation, maturation, and proliferation of T cells into memory effector cells. Ultimately, T cells migrate to the skin, where they accumulate around dermal blood vessels, producing proangiogenic cytokines and other angiogenic factors as described above. These are the first in a series of immunologic changes that result in the formation of acute psoriatic lesions.[10] The above-described immune response is a somewhat normal response to antigen stimulation. It remains unclear why the T-cell activation that occurs, followed by subsequent migration of leukocytes into the epidermis and dermis, creates accelerated cellular proliferation. One factor that contributes to this is fibronectin (FN), a cell adhesion molecule that anchors cells to collagen or proteoglycan substrates and is involved in many cellular processes, including tissue repair, embryogenesis, blood clotting, and cell migration/adhesion. Transforming growth factor beta (TGF-β) stimulates extra domain A-FN (EDA-FN), a form of FN with an additional domain domain. EDA-FN in turn stimulates keratinocyte hyperproliferation, and through stimulation of Toll-like receptor (TLR) 4, produces proinflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-12. These FN loops contribute to the maintenance and progression of psoriatic lesions. Although the association between psoriasis and cardiovascular disease remains somewhat unclear, one plausible link may be the promotion of atherosclerosis and thrombotic heart disease by EDA-FN.[11]

In summary, it is now recognized that psoriasis is caused by abnormal reactivity of specific T cells in the skin. Alterations in the epidermal barrier, innate defenses, and processing of inflammatory signals may all contribute to the triggering of a nonspecific innate immune mechanism, which, in combination with IL-23 signaling, may lead to the dysregulation of T-cell–driven immune responses.

It is known that psoriasis develops in bone marrow transplant recipients from donors with psoriasis, clears in recipients from donors without psoriasis, and that immunosuppressive drugs are effective in reducing psoriasis.[12,13] Given the genetic predisposition to this disease, what can be done to reduce the phenotypic expression besides resorting to immunosuppressive and biological therapies with their attendant side-effect profiles?

It is interesting that researchers have recognized "unidentified antigens" as ostensibly the source of the psoriatic cascade. A clear relationship of psoriasis with conditions like celiac disease[14] and Crohn's disease[15] has been reported. Furthermore, the bowel mucosa of psoriatic patients without bowel symptoms have shown microscopic lesions and greater intestinal permeability, even when the mucosa appeared macroscopically normal.[16,17] Given information regarding bowel toxemias, food allergies, low proteolytic and bile enzymes, as well as suboptimal liver function and food allergies (see the following sections), a plausible naturopathic suggestion here would be to consider that factors leading to poor intestinal function most likely encourage greater intestinal permeability and inflammation, which ultimately allow these antigenic and endotoxic compounds to leave the intestinal confines, travel through the bloodstream, and initiate activated immune cascades in susceptible tissues.

THERAPEUTIC CONSIDERATIONS

Although psoriasis has a significant genetic component, a decrease in the source of blood-borne antigenic immune activators can be substantially achieved through natural medicine intervention. A number of controllable factors appear to cause or contribute to etiologic bases and pathogenesis of psoriasis, as follows:

- Incomplete protein digestion
- Bowel toxemia
- Impaired liver function
- Bile deficiencies
- Alcohol consumption
- Excessive consumption of animal fats
- Nutritional deficiencies
- Stress

Gastrointestinal Function

Incomplete Protein Digestion

Incomplete protein digestion or poor intestinal absorption of protein breakdown products can result in elevations of amino acids and polypeptides in the bowel. These are metabolized by bowel bacteria into several toxic compounds. The toxic metabolites of the amino acids arginine and ornithine are known as polyamines (e.g., putrescine, spermidine, and cadaverine) and have been shown to be higher in individuals with psoriasis. Polyamines inhibit the formation of cyclic adenosine monophosphate and therefore contribute to the excessive rate of cell proliferation (Figure 204-1).[18-20] Lowered skin and urinary levels of polyamines are associated with clinical improvement in psoriasis.[18]

A number of natural compounds can inhibit the formation of polyamines and may be of benefit in the treatment of psoriasis. For example, vitamin A and the alkaloids of *Hydrastis canadensis* (goldenseal) such as berberine inhibit bacterial decarboxylase, the enzyme that converts amino acids into polyamines.[21,22] However, the best way to prevent the excessive formation of polyamines is to evaluate digestive function with the aid of Heidelberg Gastric Analysis and/or a comprehensive digestive stool analysis and then take the action necessary (e.g., hydrochloric acid supplementation) to ensure complete protein digestion and absorption (these assessment methods can be found in Chapters 18 and 27).

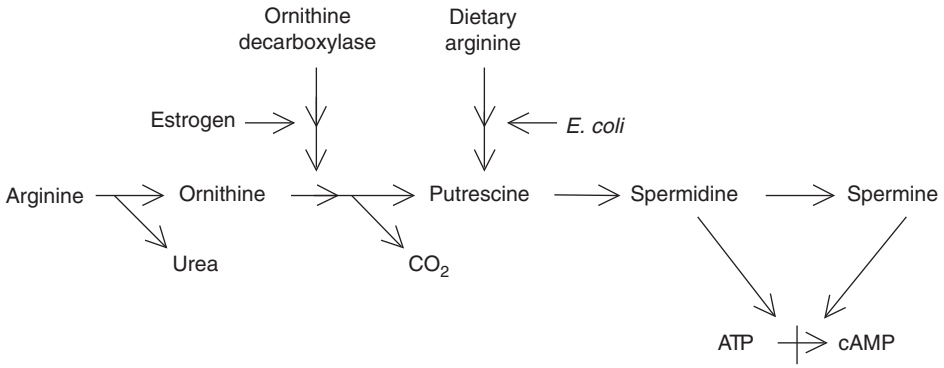


FIGURE 204-1 Amino acids, polyamines, and inhibition of adenylate cyclase.

Bowel Toxemia

A number of gut-derived toxins are implicated in the development of psoriasis, including endotoxins (cell-wall components of gram-negative bacteria), streptococcal products, *Candida albicans,* yeast compounds, and immunoglobulin (Ig) E and IgA immune complexes.[23-25] Endotoxins have been found in high levels in the blood of psoriatic patients,[26] and these compounds lead to increases in cyclic guanosine monophosphate (GMP) levels within skin cells, thereby increasing the rate of proliferation dramatically. Overgrowth of *C. albicans* in the intestines (chronic candidiasis) may play a role in some patients with psoriasis.

A diet low in dietary fiber is associated with increased levels of gut-derived toxins.[23] Dietary fiber is critical to maintaining a healthy colon. Many fiber components bind bowel toxins and promote their excretion in the feces. It is therefore essential that the diet of an individual with psoriasis be rich in beans, fruits, and vegetables. Natural compounds that bind endotoxins and promote their excretion may also be used. For example, an aqueous extract of the herb *Smilax sarsaparilla* was found in a 1942 study to be effective in psoriasis, particularly the more chronic, large plaque–forming variety.[27] In this controlled study of 92 patients, *S. sarsaparilla* greatly improved the psoriasis in 62% of the patients and resulted in complete clearance in another 18% (i.e., 80% of the subjects experienced significant benefits). This benefit is apparently due to *S. sarsaparilla*'s components' binding to and promoting the excretion of bacterial endotoxins.

Because clinical severity as well as therapeutic response have been shown to correlate well with the level of circulating endotoxins, control of gut-derived toxins is important in the treatment of psoriasis. An effort should be made to promote proper binding and elimination of these compounds through support of their excretion in the feces as well as proper handling of absorbed endotoxins by the liver.

Liver Function

The correction of abnormal liver function may be of benefit in the treatment of psoriasis.[28] The connection between the liver and psoriasis relates to one of the liver's basic tasks—filtering and detoxifying the blood returning through the portal circulation from the bowels. Structurally, the hepatic architecture may already be altered in psoriatic patients.[29] As mentioned previously, psoriasis has been linked to the presence of several microbial by-products in the blood. If hepatic function is compromised by excessive levels of these toxins from the bowel or if there is a decrease in the liver's detoxification ability, the systemic toxin level rises and the psoriasis worsens.

Alcohol consumption is known to significantly worsen psoriasis.[30] Alcohol has this effect because it both increases the absorption of toxins from the gut (by damaging the gut mucosa) and impairs liver function. Alcohol intake must be restricted in individuals with psoriasis.

Silymarin, the flavonoid component of *Silybum marianum*, has been reported to be of value in the treatment of psoriasis.[28] Presumably this is a result of its ability to improve liver function, inhibit inflammation, and reduce excessive cellular proliferation.[31,32]

Bile Deficiencies

In the psoriatic patient, endotoxins are able to translocate from the intestine into the bloodstream.[26] Bile acids normally present in the intestines act to detoxify bacterial endotoxins. In the absence of sufficient amounts of bile acids, endotoxins translocating into the bloodstream can produce pathologic conditions that vary in severity depending on their amount, including the release of inflammatory cytokines known to play a role in psoriasis.

A fascinating Hungarian study of 800 psoriatic patients was conducted in which 551 were treated with oral bile acid (dehydrocholic acid) supplementation for 1 to 6 weeks or 3 to 8 weeks for acute or chronic cases, respectively. Conventional therapies were administered to 249 patients as a comparison group. Both groups were advised to eat a diet high in vegetables and fruits and were instructed to avoid hot spices, alcohol, raw onion, garlic, and carbonated soft drinks. Of the 551 patients receiving bile acid, 434 (78.8%) became asymptomatic, whereas only 62 (24.9%) of the 249 patients receiving conventional therapies demonstrated clinical recovery during this treatment period. Additionally, the curative effect of bile acid supplementation was more pronounced in the acute form of psoriasis; 95.1% of the patients in this group became asymptomatic. In follow-up assessments 2 years later, 319 of the 551 patients with acute and chronic psoriasis who had been treated with bile acid (57.9%) were asymptomatic, compared with only 15 of the 249 patients (6%) who had received the conventional treatment.[26] The bile acid supplements used in the preceding study were either 2 or 3 dehydrocholate sodium (Suprachol) sugar-coated pills once a day or dehydrocholic acid powder (acidum dehydrocholicum pulvis) at two to three doses of 0.25 g/day.

Because there is a theoretical risk of malignant tumors in patients with sluggish intestinal function given long-term bile acid therapy, the investigators in this study recommended that their subjects not continue ingesting bile acids on a regular basis but to supplement with them only after a fatty meal once the initial treatment period had been completed. Two separate evaluations of bile acid effects on the proliferation of colonic mucosa report conflicting results.[33,34] Two other studies actually found a cancer-protective effect of ursodeoxycholic acid. One was an observational study of 114 patients with primary biliary cirrhosis in whom a reduction in the risk for colon adenoma was discovered. The prevalence of

colorectal adenomas was 13% in the treated group versus 24% in the untreated group. Additionally, the colon epithelial cell proliferation index was significantly lower in treated patients than in untreated patients.[35] A second randomized controlled clinical trial of 52 subjects found significant declines in the risk for developing colorectal dysplasia or cancer in patients with ulcerative colitis and primary sclerosing cholangitis.[36] More clinical research is needed to examine the different varieties of bile acids and their efficacy as well as their safety profile. Nevertheless, given the preceding information, it seems reasonable to consider the use of bile acids for the short-term treatment of psoriasis and to monitor the colon before and after treatment in patients at high risk for colon cancer.

Nutrition

Omega-3 Fatty Acids

The manipulation of dietary oils is extremely important in the management of psoriasis because serum levels of free fatty acids are typically abnormal in affected patients.[37] Of particular benefit are the omega-3 fatty acids. Most of the clinical research has utilized fish oils rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Several double-blind clinical studies have demonstrated that supplementing the diet with 10 to 12 g/day of fish oils (providing 1.8 g EPA and 1.2 g DHA) results in significant improvement.[38-40] This amount of EPA and DHA would be equivalent to the amount of EPA in about 150 g of salmon, mackerel, or herring.

The improvement in psoriasis from EPA is partly due to the competition of EPA for arachidonic acid binding sites, producing leukotriene B5 (LTB5), which is only one tenth as potent as the inflammatory mediator LTB4. Levels of LTB4 have been shown to be elevated in psoriatic plaques and to demonstrate chemotactic properties necessary for the infiltration of leukocytes and the proliferation of keratinocytes.[41] In the skin of individuals with psoriasis, the production of inflammatory leukotrienes from arachidonic acid is many times greater than normal.[42] Leukotrienes are potent inflammatory agents and promoters of guanylate cyclase activity.

In the psoriatic epidermis, the cellular contents of free arachidonic acid and 12-hydroxyeicosatetraenoic acid (12-HETE; a product of lipoxygenase metabolism of arachidonic acid) are 250 and 810 times greater, respectively, than in uninvolved epidermal tissue.[42]

Immunomodulatory effects of omega-3 fatty acids include the suppression of lymphocyte proliferation, CD4 cells, antigen presentation, adhesion molecule presentation, Th1 and Th2 responses, and proinflammatory cytokine production (such as IL-1, TNF-α, and PDGF), which prevents vascularization within the psoriatic plaque.[43]

Trauma also induces the release of free arachidonic acid and may account for the common clinical observation of plaques at the sites of repeated trauma. These observations are significant, because the increase in 12-HETE stimulates the 5-lipoxygenase pathway, promoting leukotriene formation. This pathway is inhibited by EPA and glutathione peroxidase, suggesting that a selenium deficiency may be a contributory factor (see later "Diet, Fasting, and Food Allergy Control")

As might be expected, cyclooxygenase inhibitors (e.g., aspirin and most other nonsteroidal antiinflammatory agents) may exacerbate psoriasis, whereas lipoxygenase inhibitors (e.g., benoxaprofen) may bring improvement.[44] Naturally occurring substances such as quercetin (the ubiquitous plant flavonoid), vitamin E, onion, and garlic are known to inhibit lipoxygenase and therefore may be of benefit. However, it is improbable that selective inhibition of one component or enzyme (e.g., a 5-lipoxygenase inhibitor) would do more than create an imbalance in this closely integrated network of mediators, which may not necessarily be beneficial.[45]

Because arachidonic acid is found only in animal tissues, patients with psoriasis must limit their intake of animal products, particularly animal fats and dairy products.

Diet, Fasting, and Food Allergy Control

An evaluation of 316 patients with psoriasis and 366 control subjects, both groups being in the age range of 16 to 65 years, found that psoriasis was positively associated with body mass index and inversely related to the intake of carrots, tomatoes, fresh fruits, and the index of beta-carotene intake.[46] Research at a Swedish hospital studying the effects of fasting and vegetarian regimens on chronic inflammatory disease found that such diets helped psoriatic patients.[47] The improvement was probably due to decreased levels of gut-derived toxins and polyamines. Patients have also benefited from gluten-free and elimination diets.[48,49] Several herbs used as seasonings—including turmeric, red pepper, cloves, ginger, cumin, anise, fennel, basil, rosemary, garlic and pomegranate—can block the activation of nuclear factor-kappa B of inflammatory cytokines.[50]

Individual Nutrients

Decreased levels of vitamin A and zinc are common in patients with psoriasis.[51-53] Given the critical roles of these nutrients in the health of the skin, supplementation might be warranted even without this association.

Chromium supplementation may be indicated to increase the sensitivity of insulin receptors, because psoriatic patients typically have increased serum levels of both insulin and glucose and carry an increased risk for type 2 diabetes mellitus and metabolic syndrome.[54]

Substantial evidence indicates that psoriasis is an independent risk factor for cardiovascular disease.[55] It remains difficult to conclude whether risk factors are caused by psoriasis or share a common pathogenesis. Inflammation, characterized by the presence of proinflammatory cytokines and endothelial activation, is a common theme underlying these conditions. Dyslipidemia, coronary calcification, increased highly sensitive C-reactive protein, decreased folate, and hyperhomocysteinemia are found significantly more often in psoriatic patients.[56]

The inflammatory processes underlying psoriasis suggest the possibility of omega-3 fatty acid, folate, and vitamin B_{12} deficiencies, which are also found in cardiovascular disease.[57] High homocysteine and decreased folate levels correlate with the psoriasis area and severity index (PASI). The rapid keratinocyte turnover rate in psoriasis may result in folate utilization and subsequent deficiency.[58] The authors of one study conclude that "Dietary supplementation of folic acid, B_6, and B_{12} appears reasonable in psoriasis patients, particularly those with elevated homocysteine, low folate and additional cardiovascular risk factors."[59] In supplementing with folic acid or its active form 5-methyltetrahydrofolate, the recommended dose is 1 to 5 mg/day.

Glutathione peroxidase (GP) levels are low in psoriatic patients, possibly because of such factors as alcohol abuse, malnutrition, and the excessive loss of skin due to the hyperproliferative disease. The depressed levels of GP normalize with oral selenium and vitamin E therapy.[60] One investigation found that patients with longer-term psoriasis (3 years or more) demonstrated low plasma selenium status.[61] Another study comparing 113 patients with moderate to severe psoriasis and 104 healthy controls found that male psoriatic patients between 20 and 49 years of age and women with the disease of longer than 20 years' duration had particularly low selenium concentrations. The lowest whole-blood selenium

values were found in the subgroup of male patients with widespread disease of long duration who also required treatment with methotrexate and retinoids.[62]

It has been established that patients with disseminated psoriasis have significantly decreased serum levels of the biologically active form of vitamin D, 1,25-dihydroxycholecalciferol (calcitriol) compared with age- and gender-matched controls and also compared with patients with moderate psoriasis.[63] Whether this is a contributing factor to psoriasis or a result of the disorder has not been elucidated.

Keratinocytes in the epidermis convert 7-dehydrocholesterol to vitamin D_3 in the presence of ultraviolet B. Sunlight, UVB phototherapy, oral calcitriol, and topical vitamin D and its analogs are effective therapy for psoriasis owing to vitamin D's antiproliferative and prodifferentiating actions on keratinocytes.[64] Vitamin D also encourages a shift toward type 2 helper T-cell cytokine expression, with an increase in IL-10 and a decrease in IL-8, which may be responsible for the improvements seen in psoriasis.[65]

Vitamin D analogs like calcipotriol have also been shown to mediate the expression proinflammatory antimicrobial peptides such as β-defensin and to decrease IL-17A, IL-17F, and IL-8 in lesional psoriatic skin.[66] Topical calcitriol has also been shown to reduce the number of dendritic cells in the skin.[67]

Calcitriol-binding to vitamin D receptors (VDRs) in the skin modulates the expression of a large number of genes including cell-cycle regulators, growth factors, and their receptors. Polymorphisms of the VDR gene are associated with psoriasis and may predispose to the development of psoriasis and resistance to calcipotriol therapy while also contributing to liver dysfunction in patients with psoriasis.[68]

Given the importance of vitamin D in psoriasis, cancer, inflammatory diseases, and other conditions, it has been suggested by some investigators that recommendations for sun protection and skin cancer prevention may need to be reevaluated to allow for sufficient vitamin D status. However, studies conducted in Honolulu, Miami, and southern Arizona showed that abundant sun exposure did not necessary ensure vitamin D adequacy, which points to the need for vitamin D supplementation to achieve optimal blood levels while also protecting the skin from sun damage and skin cancer.[69]

It has been demonstrated that oral vitamin D can be safely taken in daily doses of up to 5000 IU/day, with some experts recommending up to 10,000 IU/day to correct a deficiency.[70]

Fumaric Acid

Over the past three decades, fumaric acid therapy has become increasingly popular in western Europe for psoriasis. Therapy consists of the oral intake of dimethylfumaric acid (240 mg/day) or monoethylfumaric acid (720 mg/day) and the topical application of 1% to 3% of monoethylfumaric acid. Clinical studies have shown that it is useful in many patients with psoriasis,[71] but side effects such as flushing of the skin, nausea, diarrhea, general malaise, gastric pain, and mild liver and kidney disturbances can occur.[72] We recommend using fumaric acid therapy only after other natural therapies have proved ineffective.

Psychological Aspects

Research work concerning the role of stress in psoriatic exacerbations is mixed. One investigation revealed that a large proportion (39%) of patients with psoriasis report the occurrence of a specific stressful event within 1 month before their initial episode. Such patients have a better prognosis.[73] Yet other findings show a limited relationship between stress and vulnerability to psoriasis, whereby correlation seemed to occur mostly in patients with repeated stressors occurring four times or more in 1 year.[74] Stress management can benefit individuals with psoriasis.[75] As judged by two independent dermatologists, subjects who listened to a guided meditation tape while undergoing phototherapy cleared four times as quickly as those who received phototherapy only. Psoriasis status was assessed in three ways: direct inspection by unblinded clinic nurses, direct inspection by physicians blinded to the patient's study condition (tape or no-tape), and blinded physician evaluation of photographs of psoriatic lesions. Four sequential indicators of skin status were monitored during the study: a First Response Point, a Turning Point, a Halfway Point, and a Clearing Point. Subjects in the tape groups reached the Halfway Point ($P = 0.013$) and the Clearing Point ($P = 0.033$) significantly more rapidly than those in the no-tape condition for both UVB and PUVA treatments. Finally, psychotherapy can be an essential adjunct for individuals with persistent unresolved psychological issues such as anxiety, depression, and the psychosocial stress of this chronic skin disease. A few case histories have been reported that document the successful treatment of psoriasis with hypnosis and biofeedback alone.[76]

Physical Therapeutics

Sunlight and Ultraviolet Light

Sunlight (which contains ultraviolet light) is extremely beneficial for individuals with psoriasis.[77,78] Outdoor 4-week heliotherapy was shown to promote significant clearance of psoriatic symptoms in 84% of 373 subjects.[79] Studies employing nonprescription commercial tanning beds have shown that a majority of patients find them helpful[80]; they also objectively facilitate improvements in both psoriasis severity and health-related quality of life.[81] In addition, an open-label retrospective trial studied the combined use of the retinoid acitretin (a vitamin A derivative) along with a 4- to 5-day-per-week tanning regimen; 83% of 23 subjects experienced complete or near-complete recovery.[82]

Specific ultraviolet exposure may also be of benefit owing to its induction of vitamin D synthesis in the skin. The standard ultraviolet medical treatment of psoriasis typically involves the use of the drug psoralen and ultraviolet A (PUVA therapy; 320 to 340 nm). Ultraviolet B (UVB; 280 to 320 nm) exposure alone also leads to inhibition of cell proliferation; in certain studies, it has been shown to be as effective as PUVA therapy, with fewer side effects.[87] At the Dead Sea, where 80% to 85% of psoriatic conditions clear in 4 weeks, UVB wavelengths are known to be the dominant light.[83,84] In one investigation of 28 patients, UVB had a clear advantage over PUVA therapy.[18] Conversely, another report comparing UVB with PUVA in 100 patients demonstrated clearance of psoriasis in a significantly greater proportion of patients treated with PUVA (84%) than with UVB (63%), and with significantly fewer treatments.[85] Other studies have found both to be effective, with similar untoward side effects.[86,87] It is clear that more study is needed to clarify both the risks and benefits of these therapies and whether certain presentations of psoriasis may respond best to a specific ultraviolet therapy. As noted above, ultraviolet light deactivates vitamin D topical agents, Therefore, if they are used in conjunction, the topical agent should be applied only after ultraviolet treatment. Furthermore, any light therapy should be monitored carefully, especially in patients at risk for skin cancers.

Other Physical Therapeutics

The induction of localized elevation of temperature (42°C to 45°C) to the affected area by ultrasound and heating pads has been shown to be an effective treatment of psoriasis.[88,89] Italian

researchers have conducted small clinical trials using a hypotonic sulfate water (Leopoldine water) in a balneotherapeutic manner. These treatments have yielded favorable immunohistologic profiles of the affected tissues with significant decreases in the numbers of T lymphocytes, Langerhans cells, and markers of keratinocyte inflammatory expression.[90]

Topical Treatments

A number of natural proprietary formulas as well as over-the-counter preparations can be used to provide symptomatic relief in mild to moderate psoriasis.

Aloe vera

A very exciting, double-blind, placebo-controlled study found that topical application of an *A. vera* extract in a hydrophilic cream was highly effective in psoriasis vulgaris. Sixty patients with slight to moderate chronic plaque-type psoriasis and the PASI scores between 4.8 and 16.7 (mean 9.3) whose mean duration of disease averaged 8.5 years (range 1 to 21 years) applied either the aloe or a placebo gel three times a day. The treatment was well tolerated by all the patients, with no adverse drug-related symptoms and no dropouts. By the end of the study (4 to 12 months of treatment), the *A. vera* extract cream had cured 25 of 30 patients (83.3%) compared with the placebo cure rate of only 2 of 30 (6.6%), resulting in significant clearing of the psoriatic plaques (328 of 396 [82.8%] vs. placebo 28 of 366 [7.7%]) and a decrease in PASI score to a mean of 2.2.[91a]

Curcumin

Curcumin gel yielded 90% resolution of plaques in 50% of patients within 2 to 6 weeks; the remainder of the study subjects showed 50% to 85% improvement.[91] Curcumin was found to be twice as effective as calcipotriene cream (which generally takes 3 months to exert its full effect). Curcumin acts as a selective phosphorylase kinase inhibitor, thereby reducing inflammation through the inhibition of NFκB.

Mahonia aquifolium

Several open and placebo-controlled trials have supported the effectiveness of *Mahonia aquifolium* topical cream in the treatment of psoriasis. On the basis of physician and patient assessments, 71% to 81% of patients improved in these trials.[92] A randomized double-blind placebo-controlled trial of 200 patients also demonstrated statistically significant improvement when this agent was applied twice daily for 12 weeks.[93]

Topical Vitamin D

Topical corticosteroids are the most common treatment for psoriasis; however, their long-term use is associated with a potential risk for side effects. Topical vitamin D modulators have been developed as an option for use in place of or in addition to, topical corticosteroids. Topically, vitamin D inhibits keratinocyte proliferation, normalizes differentiation, and modulates immune cell activity with minimal effect on serum calcium.[94] Calcipotriene is the most widely used topical vitamin D. Although evidence suggests that in the long term it is approximately as effective as low- to medium-potency corticosteroids (response is not obtained as quickly as with corticosteroids), it is associated with cutaneous irritation, especially when used on sensitive skin. Calcitriol ointment was recently approved and contains the naturally occurring active form of vitamin D_3 and is associated with a low rate of cutaneous and systemic adverse effects.

By inhibiting proinflammatory cytokines such as IL-12, IL-23, and TNF-α, topical nicotinamide has been shown to enhance the efficacy of calcipotriene therapy when used in combination.[95]

Emollients

The scaliness of psoriasis benefits from the use of emollients. Intercellular lipids such as ceramides play an important role in regulating the homeostasis of the skin water barrier and the skin's water-holding capacity, and it has been shown that ceramides are decreased in the psoriatic epidermis. Newer ceramide-containing emollients (e.g., CeraVe, Mimyx, Aveeno Eczema Care) have shown benefit in psoriasis and may improve skin barrier function and decrease water loss.[96]

THERAPEUTIC APPROACH

Despite the complexity of this disease, the therapeutic approach is fairly straightforward: decrease bowel toxemia, rebalance fatty acid levels and inflammatory processes systemically and in the skin, and use the listed therapeutic regimen to further balance the abnormal cell proliferation.

Diet

- Limit sugar, meat, animal fats, and alcohol.
- Increase intake of dietary fiber and cold-water fish and, if indicated, bring weight to normal levels.
- Eliminate sources of gluten if patient is gluten-sensitive.
- Identify and address any food allergies.

Supplements

- High-potency multivitamin/multimineral formula.
- Fish Oils: 3000 mg EPA+DHA
- Vitamin D: 5000 to 10,000 IU/day based on serum 25(OH)D level.
- Consider vitamin E 400 IU/day, chromium 400 mcg/day, selenium 200 mcg/day, zinc 30 mg/day.
- Consider digestive enzymes and/or bile acids with meals.
- Water-soluble fiber (psyllium, pectin, guar gum, etc.): 5 g at bedtime.

Botanical Medicines

Consider the following if indicated by impaired digestion or liver function:

H. canadensis (goldenseal):
- The dose should be based on berberine content, because there is a wide range of quality in goldenseal preparations, standardized extracts are preferred three times a day.
- Dried root or as infusion (tea): 2 to 4 g three times a day.
- Fluid extract (1:1): 2 to 4 mL (0.5 to 1 tsp) three times a day.
- Solid (powdered dry) extract (4:1 or 8% to 12% alkaloid content): 250 to 500 mg three times a day.

S. sarsaparilla:
- Dried root or by decoction: 1 to 4 g three times a day
- Liquid extract (1:1): 8 to 16 mL (2-4 tsp) three times a day
- Solid extract (4:1): 250 to 500 mg three times a day

S. marianum (milk thistle):
- Silymarin: 70 to 210 mg three times a day

Psychological Considerations

- Evaluate stress levels and use stress reduction techniques as appropriate.

Physical Medicines

- Sunbathing—taking precautions not to become sunburned.
- UVB: 295 to 305 nm, 2 mW/cm^2, 3 minutes, three times a week

Topical Treatment

- *Aloe vera,* curcumin, *Mahonia aquifolium,* or vitamin D. Apply to affected areas of the skin two to three times/day.
- Ceramide-containing emollient two to three times a day.

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CHAPTER 205

Rheumatoid Arthritis

Gregory T. Yasuda, ND, LMP, Peter B. Bongiorno, ND, LAc, and Michael T. Murray, ND

DIAGNOSTIC SUMMARY

- Insidious onset of chronic, severe joint pain and inflammation.
- Polyarticular and symmetrical bilaterally.
- Begins in the small joints and progresses to affect other joints in the body.
- A systemic disease: fatigue, low-grade fever, weakness, weight loss, joint stiffness, and vague joint pain may precede the appearance of classic symptoms by weeks or months.
- Extra-articular manifestations include vasculitis, subcutaneous and systemic granulomas, pleurisy, pericarditis, pulmonary fibrosis, lymphadenopathy, splenomegaly, and anemia.
- Serum is usually positive for rheumatoid factor (RF) and/or anti–cyclic citrullinated peptide antibodies (anti-CCP), although no single laboratory test is diagnostic.

GENERAL CONSIDERATIONS

The most common form of inflammatory polyarthritis, rheumatoid arthritis (RA) is a chronic condition with a widely variable course that affects the entire body. Fatigue, low-grade fever, weakness, joint stiffness, and vague joint pain may precede the appearance of joint inflammation by weeks or months, sometimes making early diagnosis difficult.[1] Between 0.3% and 1% of most populations are affected and women outnumber males almost 3:1. Although RA may begin at any age, the usual age at onset is 40 to 50 years.[2]

The onset of RA is usually gradual but occasionally quite abrupt. The joints with the greatest ratio of synovium to articular cartilage are generally most affected: the knees, ankles, feet, wrists, and hands. Any joints may be affected eventually: however, the distal interphalangeal joints are generally spared.[1] Although joint involvement is confined to one or a few joints in about one third of persons, the initial presentation is generally polyarticular and bilaterally symmetrical—both hands, both wrists, or both ankles.[3]

Involved joints characteristically present with inflammation and prolonged morning stiffness. As the disease progresses, bony erosion, subluxations, dislocations, and contractures develop and lead to joint deformities, particularly in the hands and feet. Cervical spine involvement is common and instability of the atlantoaxial joint is a dangerous manifestation owing to the risk of spinal cord compression.[2] Because of joint destruction and commonly prescribed immunosuppressive drugs, rheumatoid arthritis patients are also predisposed to septic arthritis; with a mortality rate as high as 11.5%,[4] this must not be confused with a flare of RA.

Pathogenesis

Although the mechanism that produces the characteristic inflammatory joint destruction has not been elucidated completely, RA is considered an autoimmune condition because it features autoantibody production in most patients. Although the exact triggers of this autoimmune reaction are unknown, RA is far from idiopathic. This appears to be a multifactorial disease in which genetic, environmental, and immunologic factors contribute to the disease process.

Genetic Susceptibility

Female gender and positive family history are considered risk factors for developing RA, and studies of twins demonstrate other genetic risk factors.[1] There is a 15%

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concordance rate in monozygotic twins—four times that in dizygotic twins.[2] Genetic studies have isolated a "shared epitope" in HLA-DR1 and -DR4 subtypes that is expressed in 80% of whites with RA.[1]

In addition to susceptibility, genetics also play a role in the disease process. HLA-DRB1 and other factors may be associated with more aggressive disease by affecting antioxidant pathways, detoxification pathways, and other processes that likely contribute to the pathogenesis of RA. Patients with RA also have changes in fecal flora that are thought to contribute to the pathogenesis of the disease (see discussion below), and studies have shown that the flora of monozygotic twins is more similar than that of dizygotic twins independent of other contributing factors.[5]

Environmental Factors

The low penetrance in the genetic studies indicates that environmental factors are contributory. Toxins in cigarette smoke interact with the HLA-DRB1 shared epitope alleles, enhancing the inflammatory process and increasing the risk of seropositive RA.[6] Smokers' risk of developing RA is nearly eightfold for carriers of the shared epitope and nearly sixteenfold for homozygous individuals.[7] Smoking also increases RA risk in the general population, threefold for men, and quitting smoking results in a decreased risk of seropositve disease.[8]

Low socioeconomic status is associated with increased morbidity and mortality in RA.[9] Other factors such as poor diet, drinking more than three cups of coffee per day, silicate exposure, and psychological factors may also play a role in the development of the disease and affect the levels of pain and physical disability experienced by RA patients,[10] whereas oral contraceptives, tea intake, and increased vitamin D consumption have been found to be protective.[1] Other environmental factors such as low temperature, high atmospheric pressure, and high humidity have been correlated with increased RA pain.[11]

Oxidative Stress

Several studies have shown that the risk of RA is highest in people with the lowest levels of nutrient antioxidants. One study examined people who developed RA and systemic lupus erythematosus (SLE) 2 to 15 years after they donated blood in 1974.[12] For each case, four controls were selected from the serum bank donors matched for race, gender, and age. Stored serum samples from cases and controls were assayed for α-tocopherol, beta-carotene, and retinol. Patients with both diseases had lower serum concentrations of α-tocopherol, beta-carotene, and retinol in 1974 than their matched controls. Low antioxidant levels may be exacerbated by genetic factors; the shared epitope leads to increased nitrous oxide production and inhibition of antioxidative cellular pathways.[13] The resulting increase in oxidative stress could produce free radical damage of DNA and mutations that may contribute to the pathogenesis of RA.[14] Once disease is established, synovial concentrations of free radicals are elevated and concentrations of antioxidants are diminished,[15] accelerating inflammation and joint destruction.

Autoantibody Production

The serum of most individuals with RA contains rheumatoid factor (RF) and cyclic citrullinated peptide autoantibodies (anti-CCP); their presence is thought to contribute to the pathogenesis of RA. The serum titers often correlate well with the severity of arthritis symptoms and prognosis, but not in every case, and the antibodies are not directly responsible for joint destruction. Autoantibodies have been detected as long as 10 years prior to the onset of clinical disease, and inflammatory markers—such as soluble tumor necrosis factor receptor II—have been elevated for up to 12 years prior to diagnosis[16] and positively correlated with RA incidence. This suggests a "multiple hit" model[17] in which pathogenesis progresses in distinct stages, perhaps explaining why autoantibodies are present for years before clinical manifestations appear.

Microbial Influences: Infection and Cross-Reactivity

Microorganisms play important roles in states of health and disease, the most obvious being frank infections that facilitate the pathogenesis of RA. The onset of RA is preceded by a specific inciting event, such as an infection, in 8% to 15% of cases,[18] and antimicrobials such as metronidazole,[19] clotrimazole,[20] acyclovir,[21] roxithromycin,[22] tetracycline,[23] sulfasalazine,[24] and minocycline[25] have been associated with improvement in symptoms and, in some cases, complete remission. Many pathogens—such as Epstein-Barr virus, cytomegalovirus, parvovirus, rubella virus, *Mycoplasma,*[1] amebic organisms,[18] *E. coli*,[26] influenza AH2N2,[27] *Porphyromonas,* and *Proteus*—have been associated with RA. Although no single microbial agent has been consistently isolated in patients with the disease, it may be that a multitude of organisms can directly or indirectly contribute to the disease process by infection, antigen persistence, circulating immune complexes, or immune cross-reactivity. This is not unprecedented: reactive arthritis occurs secondary to an enteric, urogenital, or respiratory infection by any of over a dozen different microorganisms in a genetically susceptible individual and persists well beyond—or occurs even in the absence of—any clinically evident infection. The condition becomes chronic in 15% to 60% of cases.[1]

Some organisms, such as parvovirus B19, commonly produce an RA-like arthritis and autoantibodies, including RF and ANA, which may be positive in early infection. Although most patients clear the infection, chronic forms are known in up to 20% of cases, where viral DNA is recoverable from a variety of tissues for years postinfection, raising the possibility that RA development could be driven by chronic infection and/or persistence of parvovirus B19 antigens.[28] Other pathogens, such as *Proteus mirabilis,* stimulate production of cross-reactive antibodies, which were found to be elevated in over 90% of patients with active RA in one study; these antibody levels were positively correlated with markers of disease activity: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF).[29] These antibodies are homologous with type XI collagen found in hyaline cartilage, and their immune complexes have been recovered in the synovia of RA patients.[30] This mechanism of cross-reactivity has been demonstrated with other organisms as well. For example, antibodies to *Campylobacter, Salmonella,* and *Shigella* have been shown to cross-react with collagen, whereas antibodies to *Klebsiella pneumoniae, Proteus vulgaris,* and *Yersinia enterocolitica* cross-react with other joint tissues.[31,32]

Dysbiosis and Small Intestinal Bacterial Overgrowth

Perhaps more important than specific pathogenic organisms is the subtler influence of the commensal microflora on the internal gut environment. There are more microflora in the digestive tract than human cells in the body, and the composition of the hundreds of species of microorganisms is know to be affected by genetics, medical treatment, diet, and stress.[33] The flora have a profound influence on immune function, nutritional status, and stress response and can contribute to many diseases.[34] *Bacteroides thetaiotaomicron,* a member of the normal flora in mice and humans, was inoculated in the GI tracts of germ-free mice. Monitoring the host

transcriptional response to this single species, the researchers observed an unexpected breadth of influence on intestinal function, including improved nutrient absorption and processing by the host, mucosal barrier fortification, influx of IgA-producing B cells, and prevention of the inflammatory response or complement-mediated mucosal damage. Also affected were xenobiotic metabolism, neurotransmitter production, the enteric nervous system, gut motility, angiogenesis, and postnatal intestinal maturation.[35] Many of these intestinal functions are thought to be involved in the pathogenesis of RA.

Fecal flora is significantly altered in RA, including significantly less bifidobacteria and bacteria of the *Bacteroides-Porphyromonas-Prevotella* group[36]; randomized, clinical studies have demonstrated improvement with changes in microbial flora.[37,38] Likewise, many RA patients have small intestinal bacterial overgrowth (SIBO), 51% in one study,[39] and the degree of SIBO was associated with the severity of symptoms and disease activity. Vasquez[40] introduces the concept of multifocal dysbiosis, whereby alteration in normal flora is not confined to the gut and cumulatively can produce immune dysregulation typical of any autoimmune condition. Discussed above was the impact of a single species; the cumulative load of all microflora, the majority of which are uncultivated and novel organisms,[41] is difficult to predict. This concept of total pathogen burden does, however, appear to correlate with increased CRP and cardiovascular risk[42] and may also contribute to the pathogenesis of RA. Evidence to support this concept can be found in patients with concurrent RA and periodontal disease. One study found identical periodontal bacterial DNA in 100% of synovial fluid samples and 83.5% of serum samples of RA patients,[43] and another study found a correlation between the severity of periodontitis and the severity of RA symptoms.[44] Antibodies to *Porphyromonas gingivalis* are associated with elevated anti-CCP antibodies and may be involved in breaking immune tolerance to citrullinated antigens and promoting the autoimmune response in RA.[45]

Adverse Food Reactions

As many as 10% of the population have food allergies[46]; for patients who have tested positive for allergies on skin-prick testing, consumption of those allergenic foods is associated with increases in inflammatory markers such as tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), CRP, and ESR.[47] Outcomes of food allergy studies in RA have been conflicting. Two possible explanations for negative correlations include that the allergen challenges were too small in quantity, frequency, or both, and that serum antibody levels are not representative of the mucosal immune response in the intestine. Another confounding factor is that adverse food reactions such as food intolerance, sensitivity, and dietary lectins[48] are not antibody-mediated and therefore not apparent with antibody testing; yet, these reactions may be contributory.

One group analyzed the studies that considered the quantitative exposure to allergenic foods and found that studies using larger doses of food antigens tend to provide a positive correlation between RA and food allergies in 20% to 40% of patients.[49] These same authors examined the jejunal and serum antibody secretions of RA patients and compared them with those of controls. Although serum food antibodies were not correlated with RA, jejunal IgA, IgG, and especially IgM were significantly elevated against nearly all food antigens in RA patients compared with controls, and the antibodies were substantially cross-reactive. The investigators concluded that RA patients may have multiple modest hypersensitivity reactions and that the additive effect could lead to widespread antibody-mediated tissue destruction.

Xenobiotics and Autoantibody Production

Xenobiotics appear to intersect with genetics, pathogenic organisms, and other dietary and environmental factors to stimulate autoantibody production and autoimmunity. Certain xenobiotics may be particularly toxic to both RA patients and people at risk for RA owing to impaired metabolism in acetylation pathways. A single genetic risk factor, the N-acetyltransferase 2 polymorphism, affects both the acetylation of xenobiotics and individual susceptibility to RA.[50] It also predicts disease severity: the slow-acetylator genotype is associated with a 4.39 times greater risk of erosive RA than fast types.[51]

Other toxins also appear to induce similar autoimmune responses in genetically susceptible patients. Bacterial toxins, such as streptokinase and heat-shock proteins, can bind to mucosal tissue enzymes and stimulate autoantibody production against peptides and tissue antigens.[52] This same response was also stimulated by gliadin peptides, illustrating that food antigens can elicit responses similar to those caused by bacterial superantigens. Streptokinase, gliadin, casein (a milk protein), and ethyl mercury (the vaccine adjuvant in thimerosal) bind to different lymphocyte receptors and tissue antigens, producing neoantigens that can induce the production of cross-reactive autoantibodies.[53]

Abnormal Gut Permeability

Individuals with RA have greater intestinal permeability to dietary and bacterial antigens as well as alterations in bacterial flora.[54-56] Chronic inflammation in the gut can cause increased intestinal permeability and is associated with joint inflammation.[57] Adverse food reactions and bacterial endotoxins[58] may contribute greatly to chronic gut inflammation; moreover, the nonsteroidal antiinflammatory drugs (NSAIDs) that are commonly prescribed for RA can also exacerbate this.[59] However, increased gut inflammation and permeability also occur in RA independent of NSAID use.[60] This "leaky gut" facilitates the translocation of dietary and gut-derived antigens[9,57] and bacterial gut flora to blood, mesenteric lymph nodes, the spleen, and the kidneys.[61] In conjunction with dysbiosis and bacterial overgrowth, increased gut permeability to bacterial endotoxins and food antigens can produce immune activation and circulating immune complexes, many of which have been recovered in synovial fluid and could contribute to joint inflammation and degeneration.

Decreased Androgen Levels

Androgens and progesterone are natural immune suppressors and appear to be involved in the apoptosis of activated immune cells.[62] Chronically low levels of testosterone and dehydroepiandrosterone (DHEA), a known inhibitor of cytokines owing to nuclear factor-kappa B inhibition, have been found in early-stage and established RA.[63-65] A small study showed positive effects of testosterone replacement therapy in male RA patients, decreasing RF titers, the number of affected joints, and NSAID use.[66] Although DHEA at 200 mg/day was found to be effective for SLE in a randomized, controlled trial,[67] another small open-label trial involving 11 elderly patients with RA who were taking antirheumatic drugs found little benefit from supplementing with DHEA at the same dose.[68] DHEA and testosterone may have to be modulated in concert with estrogens to be optimally effective in RA. Chronic inflammation and elevated TNF-α promote conversion of testosterone to estrogen by stimulating aromatase activity,[69] and a reduced androgen:estrogen ratio has been identified in both male and female RA patients.[70]

Abnormal Estrogen Levels

Unlike androgens, estrogens may be involved in sustaining the inflammatory activity of activated T cells[62] and humoral immunity.[71] Estradiol levels have been found to be higher in RA patients than controls and strongly and positively associated with indices of inflammation.[63] A large 5-year study comprising 689 patients with similar disease duration and severity found that gender is a major predictor of remission in early RA. Women have a lower androgen:estrogen ratio and, at 2 and 5 years, had more severe disease as well as 16% to 22% fewer remissions than men. This effect could not be explained by any other differences between the groups, including disease duration, age, and treatments used.[71]

DIAGNOSIS

The most commonly used criteria in the diagnosis of RA have been those issued by the American College of Rheumatology (ACR) in 1987; however, the sensitivity and specificity of these criteria are low, especially in early disease.[72] Because earlier diagnosis allows for earlier and more aggressive treatment, which may lead to better outcomes,[73] the ACR engaged in a joint initiative with the European League Against Rheumatism to create new guidelines that classify definite RA based upon the presence of synovitis in at least one joint, with no alternative explanation, and a score of 6 or greater in a four-tier rubric (see Table 205-1).[74]

Laboratory Findings

Rheumatoid Factor

RF is made up of a group of antibodies, usually IgM, that bind the Fc fragment of IgG. Although it is present in 70% to 80% of RA patients, a variety of conditions can cause elevations of RF, and 4% of apparently healthy individuals test positive as well.[2] Despite the relatively low sensitivity and specificity of the RF test, its presence is a confirmatory finding in the diagnosis of RA and seropositivity is associated with worse outcomes.[75]

TABLE 205-1 **Classification Criteria for Rheumatoid Arthritis**

Joint Involvement: Select the One with Highest Point Value	
1 medium-large joint	0 points
2-10 medium-large joints	1 point
1-3 small joints	2 points
4-10 small joints	3 points
10+ small joints	5 points
Serology	
Seronegative for RF and anti-CCP	0 points
Low-titer of RF and/or anti-CCP	2 points
High-titer of RF and/or anti-CCP (more than three times the upper limit of normal)	3 points
Duration of synovitis	
Less than 6 weeks	0 points
6+ weeks	1 point
Acute phase reactants	
Normal ESR and CRP	0 points
Elevated CRP or ESR	1 point

Data from Aletaha D, Neigi T, Silman A, et al. 2010 Rheumatoid arthritis classification criteria: An American college of pheumatology/European league against rheumatism collaborative initiative 62, no 9 (Sept 2010): 2569-81.

Anti–Cyclic Citrullinated Peptide Antibodies

Anti-CCP antibodies have emerged as a much more specific indicator of RA than RF as well as a better predictor of clinical course. Whereas the sensitivity of anti-CCP antibodies testing is similar to that of RF (70%-80%), its specificity is greater than 95%.[2] These autoantibodies, as well as RF, have been identified as much as 10 years prior to diagnosis,[76] and their presence heralds more aggressive disease and poorer prognosis.[1] No single laboratory test is definitive for the diagnosis of RA, and patients may be seropositive for anti-CCP, RF, both, or neither.

Erythrocyte Sedimentation Rate and C-Reactive Protein

The ESR and CRP are acute-phase reactants that become elevated during active inflammation. Although not specific to RA, they are useful in confirming the diagnosis and monitoring disease activity and response to treatment. Because RA patients are at increased risk for cardiovascular disease,[77] CRP in particular is a useful marker of cardiovascular risk as well.

Other Laboratory Abnormalities

Anemia, usually normocytic and normochromic or hypochromic, is quite common in RA and in chronic inflammatory diseases in general. Although the serum iron level and total iron-binding capacity are usually low, supplemental iron is of no value and may actually promote further damage due to free radicals. Because serum ferritin is an acute-phase reactant, iron stores may appear falsely elevated in RA when ESR and/or CRP are elevated.[78] Antinuclear antibodies may be present but at lower levels than in SLE.[2] Joint aspiration is not necessary to diagnose RA but may be necessary to rule out crystalline arthropathies or septic arthritis.

Other Diagnostic Testing

It is important to keep in mind that some other conditions can mimic RA and should be ruled out before a diagnosis is made. These include vitamin D deficiency, hemochromatosis, hypothyroidism, and infections such as Lyme disease and hepatitis B and C. Other tests to consider include the following:

- Hormone profiles: DHEA-S, testosterone, and estradiol
- Food allergies: see Chapter 15
- Lactulose-mannitol test: see Chapter 20
- Hydrogen-methane breath test: see Chapter 10
- Stool testing for digestive function and intestinal flora: see Chapter 27
- Urine testing: see Chapter 28
- Toxicity assessment: see Chapter 53

STANDARD MEDICAL THERAPY

Standard medical therapy is limited by its over reliance on pharmacologic therapies and focus on suppressing the disease process and its symptoms, most notably controlling the inflammation and free radicals that mediate joint damage[79] while failing to address the complex underlying causes of this disease. The effects and side effects of these drugs exacerbate many contributing factors to the disease process and possess significant morbidity and mortality risks of their own. Pharmacologic therapies generally fall into three categories: NSAIDs, disease modifying antirheumatic drugs (DMARDs), and biological therapies. Nonpharmacologic approaches include reduction of joint stress, physical and occupational therapy, and surgery.[2]

Nonsteroidal Antiinflammatory Drugs and Cyclooxygenase Inhibitors

Usually implemented before formal diagnosis,[1] NSAIDs are first-line antiinflammatory and analgesic medications that suppress symptoms while also accelerating factors that promote the disease process. NSAIDs can inhibit chondrocytes and cartilage formation[80] and promote chondrolysis and joint destruction.[81] Furthermore, they promote several factors thought to contribute to the pathogenesis of RA by increasing hyperpermeability of the GI tract,[82] dysbiosis,[83] free radicals in synovial fluid,[84] enteric inflammation, bacterial overgrowth, and bacterial translocation.[85] NSAIDs also cause serious GI side effects—including ulcers, hemorrhage and perforation—that led, according to one study, to 107,000 hospitalizations and 16,500 deaths in 1 year among arthritis patients alone.[86]

To mitigate this massive GI toxicity, NSAIDs are sometimes coadministered with acid-blocking medications. These drugs help alleviate the upper GI damage but do not protect from the ensuing iatrogenic hypochlorhydria, which is a causative factor in SIBO,[87] still another contributing factor to the pathogenesis of RA. Another way to protect the GI tract is to use selective cyclooxygenase-2 inhibitors. Although they have a much-improved GI safety profile compared with non-selective NSAIDs, they may not completely protect the lower GI tract from injury[88] and are associated with adverse cardiovascular events.[89] Because RA patients are already at increased risk for cardiovascular disease, these drugs may not be appropriate for general use in this population.[90] Finally, all drugs in this class also pose the risk of renal toxicity, and chronic use of high doses in arthritis patients increases the risk for renal failure.[91]

Corticosteroids

Corticosteroid medications are generally reserved for patients who do not respond to NSAID therapy. By blocking the inflammatory response, including the production and secretion of inflammatory mediators such as histamine, prostaglandins, and leukotrienes, they suppress not only inflammation but the normal immune response as well. These may be of great benefit in acute symptom management, but they become problematic with long-term use. Corticosteroids are associated with more frequent serious infections (those requiring hospitalization)[92] and increased mortality. Even small doses (up to 7.5 mg prednisone or equivalent) carry an increased risk for infection and death when used long-term. One study found the risk of mortality increased by 14% after 1 year and 49% after more than 10 years of use compared with the status of RA patients who had not been treated with low-dose corticosteroids.[93]

Common side effects of long-term corticosteroids at higher doses bring their use further into question because they exacerbate the manifestations of RA itself. Side effects include chondrotoxicity,[94] osteoporosis,[95] increased intestinal permeability,[96] and cardiovascular disease[97] as well as an increased risk of myocardial infarction. Furthermore, the risk of peptic ulcers and GI bleeding in patients already using NSAIDs is exacerbated by corticosteroids.[3] Insomnia is also a side effect, and patients with RA are more susceptible to insomnia than the general population.[98] In fact, one study concluded that the fatigue experienced by RA patients may be more due to sleep fragmentation than a constitutional symptom of the disease itself.[99] Finally, depression is a common side effect of prednisone and is also common among patients experiencing chronic pain from diseases such as RA. Patients with RA who experience depression have worse outcomes[100] than those who are not depressed, thus further contraindicating the use of corticosteroids.

Synthetic Disease-Modifying Antirheumatic Drugs

Once reserved for severe cases, disease-modifying antirheumatic drugs (DMARDs) are now used as first-line therapies according to conventional treatment guidelines. Methotrexate is the most common drug used, with the best balance of efficacy and toxicity.[101] Originally used as a chemotherapeutic agent, this agent exerts an immunosuppressive effect by decreasing white blood cell production. The more severe side effects of methotrexate include gastrointestinal ulceration, severe bone marrow suppression, frequent infections, elevated risk of cancer, and damage to the lungs, liver, and kidneys. Other drugs in this class—including hydroxychloroquine (Plaquenil), azathioprine, cyclophosphamide, and leflunomide—have similar, and sometimes more severe side effects. Many patients may not actually continue long-term therapy with any DMARD beyond the first few years owing to adverse effects or lack of efficacy. However, there is evidence that beginning a DMARD within the first 3 months of diagnosis is associated with a decreased risk of joint erosion. Therefore, patients presenting with a diagnosis of RA will most often be on DMARDs, individually or increasingly in combination, and perhaps additional drugs to manage their side effects.

Biological Disease-Modifying Antirheumatic Drugs

Newer biological agents include TNF-α antagonists such as infliximab, etanercept, and adalimumab. Other members of this class include tocilizumab, an interleukin inhibitor, and abatacept, a drug acting on T lymphocytes. According to a recent review article,[102] these medications are no more effective than methotrexate when used as monotherapy. However, in about 10 comparative trials analyzed, the combination of TNF-α antagonists with methotrexate was more effective than methotrexate alone, especially in initially severe RA. The investigators found no firm evidence that other drug combinations were more effective than these. Unfortunately, drug-free remission is still very rarely achieved and most patients experience higher disease activity upon discontinuation of therapy.[103]

Many patients will experience significant improvement within a few weeks. However, blocking TNF-α without addressing the conditions that created the imbalance leads to long-term consequences, such as sepsis and pneumonia and an increased risk of reactivating tuberculosis.[104] A potent inflammatory mediator, TNF-α is also a critical part of the host defense against certain pathogens. For all patients using TNF-α inhibitors, vigilance for hypersensitivities, anemias, infections, and malignancy is required. Another study also showed accelerated atherosclerotic activity.[105] Long-term follow-up studies do not exceed 2 years; however, the risk of severe adverse effects is likely higher with drug combinations.[105]

THERAPEUTIC CONSIDERATIONS

RA is a multifactorial condition that requires a comprehensive therapeutic approach addressing all the factors known to be involved in the inflammatory disease process. Foremost in this approach is the use of diet.

Diet

Population studies have demonstrated that RA is less common in societies that favor a more "primitive" diet and is found at higher rates in societies consuming the so-called Western diet.[106] A diet

of organic whole foods, rich in vegetables and fiber and low in sugar, meat, refined carbohydrates, saturated fat, and additives appears to offer some protection against the development of RA as well as promise in its treatment.[107-110]

Adverse Food Reactions

The elimination of reactive foods has been shown to offer significant benefit to some individuals with RA.[111-114] The most common triggers in one study included corn (56%), wheat (54%); bacon/pork (39%); oranges (39%); milk and oats (37%); rye (34%); egg, beef, and coffee (32%); malt (27%); cheese and grapefruit (24%); tomato (22%); peanuts and cane sugar (20%); butter, lamb, soy, and lemon (17%). Nineteen percent of participants who continued to avoid their reactive foods remained well without medications for follow-up periods of up to 5 years.[115] Dietary elimination and challenge is one method of identifying triggering foods, which can be different for each patient. Some studies that fail to show any benefit from dietary intervention provide the entire experimental group with the same "hypoallergenic" diet, not one customized to each participant's particular sensitivity or sensitivities. One such group of investigators concluded that, "our data are not inconsistent with the possibility that individualized dietary manipulations might be beneficial for select patients with rheumatic disease."[116]

Therapeutic Fasting

Patients with RA have historically benefited from fasting. Short-term fasts of 3 to 5 days' duration are recommended during acute flares so as to induce a substantial reduction of joint pain, swelling, morning stiffness, and other symptoms of RA.[117] It is an obvious method for eliminating reactive foods but has effects that extend beyond allergen avoidance. Fasting increases serum DHEA-S and decreases serum IL-6, CRP, ESR, and disease activity[118]; it also has a favorable effect on intestinal permeability.[119] Juice, broth, and water fasts of longer duration, up to 10 days, have been shown to be effective as well. Strict water fasting should be done only under direct medical supervision. (For a full discussion, see Chapter 37.)

Vegetarian Diet

One 13-month controlled study began with a 7- to 10-day fast before transitioning to a vegetarian diet.[120] The fast consisted of herbal teas, garlic, vegetable broth, a decoction of potatoes and parsley, and carrot, beet, and celery juices. The diet was followed by a systematic reintroduction of a single food item every 2 days with elimination of foods that aggravated RA symptoms. The treatment group showed significant improvements compared with controls, and these improvements were maintained at 1-year follow-up in those patients still maintaining the diet. This study supported the positive results noted in prior studies of short-term fasting followed by a vegetarian diet,[121-123] and the pooling of these data in a systematic review showed statistically and clinically significant beneficial long-term effects.[124] Beyond allergy elimination, vegetarian diets are also associated with higher fiber intake and improved gut flora,[37,38] including decreased antibodies to *Proteus mirabilis*,[125] less SIBO, and an improvement in RA symptomatology.[40] Other changes included increased potassium intake, which may lead to improved biosynthesis and the release of cortisol[126] as well as a favorable fatty acid profile and increased antioxidant intake.

The Mediterranean Diet

Patients with established RA in one study obtained a reduction in inflammatory activity, an increase in physical function and improved vitality in 12 weeks on a Mediterranean diet.[127] Rich in seasonally fresh plant-derived foods, the Mediterranean diet is similar to the vegetarian diet with the addition of fish and poultry, low to moderate red meat, dairy and red wine, and olive oil as the main source of lipids.[128] Different types of dietary fats can either alleviate or aggravate RA[129] by influencing eicosanoid metabolism. Both vegetarian and Mediterranean diets are inherently low in saturated fats and arachidonic acid, the precursor to the inflammatory series-2 prostaglandins and leukotrienes, and rich in gamma-linolenic acid (GLA) and α-linolenic acid (ALA), the precursors to antiinflammatory series-1 and series-3 prostaglandins. The consumption of cold-water fish such as mackerel, herring, sardines, and salmon, which are rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), further promotes antiinflammatory eicosanoids. A population-based case-control study of women living in the Seattle area compared fish consumption in 324 cases of RA with 1245 control cases.[130] Consumption of broiled or baked fish was associated with a dose-dependent decreased risk of RA. This may explain some of the antiinflammatory effects of the Mediterranean diet, which includes fish but relatively little meat. By excluding meats, not only preformed, proinflammatory arachidonic acid is removed from the diet but also a potential food allergen: several studies have found that RA patients are commonly allergic to meats, especially beef and pork.[115,131,132] Furthermore, the inclusion of olive oil produces additional benefits in RA, including antioxidant and antiinflammatory effects, competitive inhibition of omega-6 fatty acids, pain reduction, reduced morning stiffness, and improved patient evaluation of global disease.[133] Additionally, these effects seem to be synergistic with fish oils.

Dietary Antioxidants

The continuous production of free radicals within arthritic joints promotes joint degeneration, exhausts antioxidant systems, and may cause the low antioxidant levels commonly seen in RA patients.[134] The importance of consuming a diet rich in fresh fruits and vegetables in the dietary treatment of RA cannot be overstated. These are the best sources of antioxidants such as vitamin C, beta-carotene, vitamin E, selenium, and bioflavonoids, all of which promote healthy joints by neutralizing inflammation and supporting collagen structures. Antioxidants work together synergistically, such as needing vitamin C to regenerate vitamin E, and this may explain why systematic reviews have not found single antioxidant supplements to be effective but have documented benefit for antioxidant-rich diets.[135] The antioxidant content of vegetarian and Mediterranean diets almost certainly contributes to their effectiveness in treating RA. (For more information, see Chapter 108.)

Nutritional Supplements

Gamma-Linolenic Acid

Evening primrose, black currant, and borage oils contain GLA, an omega-6 fatty acid that acts as a precursor to the antiinflammatory prostaglandins of the 1-series. Although one study showed that the long-term supplementation with GLA produced a paradoxical increase in tissue arachidonic acid levels while decreasing tissue levels of EPA,[136] GLA nevertheless appears to provide antiinflammatory support in RA. In one double-blind study, 37 patients with RA were given either GLA (1.4 g/day) or placebo for 24 weeks. GLA supplementation reduced the number of tender joints by 36%, the tender joint score by 45%, the swollen joint count by 28%, and the swollen joint score by 41%.[137] In contrast, no patients in the placebo group showed significant improvement

on any measure. The subjects in the study did, however, continue to take antiinflammatory drugs, which may have masked a change in arachidonic acid and EPA levels or acted synergistically with the GLA. In any case, two recent reviews[138,139] found statistically significant improvements in pain and global function for GLA from data pooled from three randomized controlled trials. Although the investigators emphasized the need for more trials, their conclusions in favor of GLA were even stronger than those for fish oil.

Omega-3 Fatty Acids

The richest sources of omega-3 oils are cold-water fish and flaxseed oil. The ALA in flaxseed oil must be enzymatically converted to EPA and DHA to exert an antiinflammatory effect. Although several studies have shown that flaxseed oil is not as effective as fish oil, these studies failed to address zinc (a cofactor for delta-6-desaturase), and omega-6 fatty acids.[140,141] A study incorporating a low-omega-6 diet while supplementing with 13 g (approximately 1 tbsp) of flaxseed oil a day found that such supplementation, along with the restriction of linoleic acid and addressing underlying zinc deficiency, raises tissue EPA levels to an extent comparable with the effects of fish oil supplementation.[142] Several human and animal studies have demonstrated that flaxseed oil supplementation can inhibit the autoimmune reaction as well as fish oil.[143]

Supplementing with fish oils bypasses the metabolism of α-linolenic acid by directly supplying preformed EPA and DHA. Many published studies have documented the efficacy of fish oil.[144-149] Because it competitively inhibits COX-2, which is overexpressed in the RA synovium, supplementation has been shown in randomized trials to decrease long-term use of NSAIDs.[150] A recent review that included three meta-analyses of fish oil concluded that there is convincing evidence of benefit in RA, including briefer morning stiffness, fewer tender or swollen joints, less joint pain, less fatigue, and reduced serum markers of inflammation, such as CRP, IL-1β, TNF-α and LTB_4.[151] Supplements may have to be consumed for at least 12 weeks at a minimum daily dose of 3 g of combined EPA and DHA before effects become apparent.[152] Furthermore, fish oil may further benefit RA patients by decreasing cardiovascular risk. It is important to select a product that has been rigorously tested for contaminants such as heavy metals, polychlorinated biphenyls, dioxins, and lipid peroxides, or one may rely on cold-water fish and flaxseed oil for the omega-3 oils rather than fish oil capsules to help avoid these toxins.[153-155] (For more information about fish oils, see Chapter 91.)

Multivitamin/Multimineral Supplementation

Blood and/or tissue samples from RA patients indicate that such patients are deficient in many nutrients, including magnesium, folate, vitamin B_{12},[156] vitamin B_6,[157] zinc,[158] and selenium.[159,160] Many factors may contribute to this, including decreased dietary nutrient intake among RA patients,[161] decreased absorption due to impaired gut function, increased utilization of antioxidant nutrients due to elevated oxidative stress, and increased excretion of nutrients due to stress and medications. Studies are few in number and have produced conflicting results, and systematic reviews have failed to demonstrate benefit from supplementation of individual nutrients, but it is almost certainly the case that a multifactorial condition such as RA requires a multifaceted approach to treatment rather than a nutrient monotherapy. It appears reasonable, safe, and—at least hypothetically—efficacious to address deficiencies of multiple nutrients simultaneously. Following are specific nutrients to consider that have been found to be deficient and/or beneficial in some clinical trials with RA.

Selenium and Vitamin E

An important mineral cofactor for glutathione peroxidase and thioredoxin reductase, selenium is especially important for reducing the production of inflammatory prostaglandins and leukotrienes and controlling tissue damage due to free radicals. Clinical studies have not demonstrated improvement from selenium supplementation in RA; however, one clinical study did indicate that selenium combined with vitamin E had a positive effect.[162] In another randomized controlled trial, patients already diagnosed with RA who received 600 mg vitamin E twice a day showed significant pain reduction but no changes in clinical and biochemical indices of inflammation.[163] However, a review of five studies found no conclusive evidence of benefit from vitamin E or selenium supplementation alone.[164]

Zinc

A cofactor for delta-6-desaturase, the rate-limiting enzyme in omega-3 fatty acid metabolism, zinc deficiency is associated with poor conversion of ALA from flaxseed oil to EPA and DHA. Deficiency is common in RA patients, which may predispose them to increased inflammation due to impaired eicosanoid metabolism. Plasma zinc levels are inversely correlated with ESR, CRP, IL-1β, and TNF-α.[165] Zinc also has antioxidant effects and is a cofactor to the enzyme superoxide dismutase (copper-zinc SOD). Patients using corticosteroids may be at increased risk for zinc deficiency because these medications have been shown to decrease plasma zinc and increase urinary zinc.[166] Several studies have demonstrated a slight therapeutic effect from zinc supplementation in RA patients.[167-169]

Manganese and Superoxide Dismutase

Manganese functions in a different form of the antioxidant enzyme superoxide dismutase (manganese SOD). Manganese-containing SOD is deficient in patients with RA.[170] The injectable form of this enzyme has been shown to be effective in the treatment of RA[171]; however, it has not been demonstrated that oral supplementation affects SOD levels in tissue.[172] What has been established is that oral manganese supplementation increases SOD activity.[173] Although no clinical studies have been conducted to determine the effectiveness of manganese in the treatment of RA, it appears to be indicated on the basis of the low levels seen in patients with RA as well as its biochemical functions.

Vitamin C

An important antioxidant, vitamin C concentrations in white blood cells and plasma are significantly decreased in patients with RA.[174] Supplementation with vitamin C increases SOD activity, reduces histamine levels, and provides antiinflammatory action.[175,176] One intervention study with a Mediterranean diet showed a negative correlation between plasma vitamin C levels and RA disease activity[177]; this was corroborated by another study that found an inverse correlation between vitamin C levels and CRP.[178]

Pantothenic Acid

Whole-blood levels of pantothenic acid have been reported to be lower in patients with RA than in normal controls and inversely correlated with disease activity.[179] Correction of these low levels brings about some alleviation of RA symptoms. In one

double-blind study, a subjective improvement of RA symptoms was noted in patients receiving 2 g/day of calcium pantothenate.[180] Patients noted improvements in duration of morning stiffness, degree of disability, and severity of pain.

Pyridoxine (Vitamin B_6)

There is a clear relationship between low serum levels of pyridoxal 5'-phosphate and inflammatory indicators of RA. One cross-sectional study found that vitamin B_6 levels in plasma were lower in patients with high ESR and CRP levels, who also had more disability, pain, fatigue, and swollen joints.[181] This circumstance was not attributed to deficiency of intake but rather to ongoing chronic inflammatory processes. In a separate study,[182] higher levels of homocysteine were also noted and correlated with low vitamin B_6 status in RA patients, consistent with the increased risk of cardiovascular disease seen in these patients.

Copper

The wearing of copper bracelets has been a long-time folk remedy that appears to have some scientific support, as described in a double-blind study performed in Australia. Presumably copper is absorbed through the skin and is chelated to another compound that can exert antiinflammatory action.[183] Copper salicylate is a form of aspirin that yields better results in reducing pain and inflammation than standard aspirin preparations in patients with RA.[184,185]

Copper is also used in copper-zinc SOD. Deficiency may result in significant susceptibility to free radical damage as a result of decreased SOD levels. However, an excess intake of copper may be detrimental because of its ability to combine with peroxides and damage joint tissues.[186]

Vitamin D

Vitamin D is a steroid hormone that displays immunoregulatory and antiinflammatory properties. Epidemiologic evidence indicates a significant association between vitamin D deficiency and an increased incidence of several autoimmune diseases, including RA.[187] One study identified lower vitamin D levels and a higher incidence of RA in northern European countries compared with southern European countries. In both parts of Europe, however, low 25(OH)D3 levels were significantly correlated with worse RA symptomatology.[188] Furthermore, a high intake of vitamin D is associated with a decreased risk of RA.[189]

Vitamin D also plays an important role in normal calcium metabolism. One study involving 147 women, mean age of 50.9 years, found that 13% had vitamin D levels below the threshold for vitamin D–deficiency osteomalacia.[190] In the winter, 73% had serum concentrations below the normal range. The authors suggest that there is a disturbance in vitamin D metabolism in RA that might play a role in RA-associated osteoporosis.

Pancreatic Enzymes and Hydrochloric Acid

Impaired digestion from inadequate secretion of pancreatic enzymes and/or hydrochloric acid, which is common in RA patients, can be a major contributor to the disease process.[191,192] In addition to poor assimilation of ingested nutrients, incompletely digested food molecules can be inappropriately absorbed, stimulating an immune response. In one study, 80% of untreated RA patients had reduced maximal gastric acid output.[193] Gastric acid also plays a role in passive immunity, and hypochlorhydric or achlorhydric patients may be predisposed to SIBO. Half of RA patients in one study who had inadequate hydrochloric acid secretion also had SIBO, and restoration of gastric pH can help to resolve the overgrowth.[39]

Beyond their physiologic role in digestion, pancreatic enzymes may offer additional benefits when taken between meals. Specifically, the proteases in pancreatin have been shown to reduce circulating levels of immune complexes in RA and other autoimmune diseases.[194,195] Because clinical improvements usually correspond with decreases in levels of immune complexes, proteolytic enzyme supplementation is often warranted. (For more information, see Chapter 111.)

Probiotics

Probiotic supplementation is immunomodulatory. Commensal organisms interact with Toll-like receptors in the intestinal mucosa to promote immune tolerance and regulatory T-cell formation while blocking NF-kappaB, inflammation, and allergies. These effects in RA patients may be strain-specific.[196] One small-scale human trial on *Lactobacillus rhamnosus* GG did not show a clinical benefit,[197] however, a recent study on *Bacillus coagulans* GBI-30, 6080, produced statistically significant improvement in pain scale compared with placebo. Treatment also resulted in greater improvement in patient global assessment, self-assessed disability, CRP, ability to walk 2 miles and participation in daily activities.[198] Probiotics, prebiotics, and/or antimicrobial compounds may be indicated in cases of dysbiosis and SIBO in addition to dietary modification. (For more information, see Chapters 115 and 116.)

Botanical Medicines

Many botanicals possess significant antiinflammatory action and are useful in the treatment of RA. The suggestions made here represent some of the more popular and better researched of these botanical medicines.

Curcuma longa

Curcumin, the yellow pigment of *Curcuma longa* (turmeric), exerts excellent antiinflammatory and antioxidant effects[199-204] and has been found to be as effective as cortisone or phenylbutazone in models of acute inflammation. Molecular targets include transcription factors (e.g., NF-kappaB, PPAR-gamma), enzymes (e.g., COX-2, 5-LOX), and cytokines (e.g., TNF-α, IL-1, IL-6).[205] Animals models also indicate that curcumin may enhance endogenous corticosteroid activity, perhaps through increased synthesis and/or release, potentiation of receptor sites, or slowing of catabolic pathways.

One double-blind clinical trial compared curcumin (1200 mg/day) with phenylbutazone (300 mg/day) in RA patients.[206] The improvements in the duration of morning stiffness, walking time, and joint swelling were comparable in both groups. Furthermore, although phenylbutazone is associated with significant adverse effects, curcumin has not been shown to produce any side effects. It is noteworthy that curcumin also lacks any direct analgesic action.

One concern regarding curcumin has been absorption. There now exist a number of methods and products that enhance the absorption. One of the first methods was using piperine, a compound found in black pepper.[207] A more recent method is complexing the curcumin with soy phospholipids to produce the product Meriva.[208] Absorption studies in animals indicate that peak plasma levels of curcumin after administration of Meriva were fivefold higher than those after administration of regular curcumin. Studies with another advanced form of curcumin, Theracurmin, shows even greater absorption (e.g., 27 times greater than regular curcumin).[209]

Bromelain

Bromelain is a mixture of enzymes found in pineapple. Since 1957, more than 200 scientific papers have appeared in the research literature documenting a wide variety of beneficial effects,[210] including reduced inflammation in RA.[211] Much of its effects are due to activation of compounds that break down the inflammation-induced fibrin matrix that leads to inadequate tissue drainage and edema. Bromelain also blocks the production of kinins, compounds produced during inflammation that increase swelling and cause pain. A proteolytic enzyme product containing bromelain, papain (an enzyme from papaya), trypsin, and chymotrypsin (pancreatic enzymes) was shown to decrease excessive levels of transforming growth factor beta in human blood,[212] and polymorphisms of this transforming growth factor have been linked with the progression of joint destruction in rheumatoid arthritis.[213]

Zingiber officinalis

Ginger *(Z. officinalis)* contains antioxidants and exerts antiinflammatory effects by inhibiting the synthesis of prostaglandins, thromboxanes, and leukotrienes. A preliminary clinical study was conducted with seven RA patients in whom conventional drugs had provided only temporary or partial relief.[214] All patients were treated with ginger. One patient took 50 g/day of lightly cooked ginger and the other six took either 5 g/day of fresh ginger or 0.1 to 1 g/day of powdered ginger. Despite the difference in dose, all patients reported a substantial improvement, including pain relief, better joint mobility, and a decrease in swelling and morning stiffness.

In the follow-up to this study, 28 patients with RA (18 with osteoarthritis and 10 with muscular discomfort) who had been taking 500 to 4000 mg of powdered ginger for periods ranging from 3 months to 2.5 years were evaluated.[215] On the basis of clinical observations, it was reported that 75% of the patients with arthritis and 100% of those with muscular discomfort experienced relief in pain or swelling and that the effects were dose dependent.

Fresh ginger contains higher levels of gingerols as well as a protease that may act on inflammation much like bromelain and therefore may be more effective in the treatment of RA than dried preparations.[216] Most studies have used 1 g of dry powdered ginger root, which is a relatively small dose compared with the daily average of 8 to 10 g consumed in India. A daily dose of 2 to 4 g of dry powdered ginger is safe and may be effective in RA. This is roughly equivalent to 20 g of fresh ginger root, or a 0.5-inch slice. These amounts of ginger can easily be incorporated into the diet in fresh fruit and vegetable juices.

Tripterygium wilfordii Hook F

In Chinese medicine, *Tripterygium wilfordii Hook F* or thunder god vine, has a long history of use in RA and other autoimmune diseases. Although studies have focused almost exclusively on the root, both the folium and the radix of the plant appear to have antiinflammatory, analgesic, and immunosuppressive effects that may be effective in treating RA.[217] In a double-blind placebo-controlled study involving patients with long-standing RA in whom conventional therapy had failed, 80% of those who received a high dose (380 mg/day) of ethanol/ethyl acetate root extract had a positive response, defined as at least 20% improvement according to the American College of Rheumatology criteria. Forty percent of the low-dose (180 mg/day) group also responded positively, compared with none in the placebo group.[218] Another recent randomized, controlled trial demonstrated that 180 mg/day of *Tripterygium* extract was more effective than sulfasalazine 1 g twice a day.[219] Two other review articles have documented the efficacy of this herb in the treatment of RA.[220,221]

Side effects reported for this herb include GI upset, diarrhea, headache, hair loss, menstrual abnormalities, and hypertension. Randomized controlled trials have demonstrated efficacy and decreased advere reactions from sustained-release table,[222] topical applications,[223] and coadministration with *Glycyrrhiza glabra* (licorice) root.[224] Coadministration of *Tripterygium* with methotrexate may improve efficacy and decrease side effects compared with methotrexate alone.[225]

Valeriana officinalis

Between 54% and 70% of RA patients report sleep disruptions. *V. officinalis*, or valerian, has long been used as a sleep aid and has been shown to decrease the time between going to bed and the first cycle of deep sleep compared with placebo in RA patients.[226] Valerian is a sedative and anxiolytic that sensitizes GABA receptors and may also affect the actions of serotonin and adenosine. Even if they were unaware of it, one study found that all RA patients had marked sleep disturbances; it was therefore concluded that the fatigue experienced commonly in RA might be a sign of undiagnosed sleep disturbance rather than a product of the disease process itself.[99] This fatigue is frequently perceived by RA patients as overwhelming, uncontrollable, and ignored by their doctors.[227] Addressing an underlying sleep disorder may provide profound relief on many levels.

Another study found that the morning symptoms of RA were correlated with a nonrestorative sleep disorder.[228] Inadequate sleep can lead to inflammation, as measured by increased CRP,[229] and both CRP and sleep problems are inversely related to pain thresholds in RA patients.[230] Therefore, using valerian to improve the quality of sleep may also improve fatigue, pain threshold, and psychological measures of quality of life.

Physical Medicine

Exercises

Exercise can improve strength and performance while maintaining range of motion in RA patients. Furthermore, it decreases cardiovascular risk, RA disease activity, and systemic inflammation as evidenced by reduced ESR.[231] Patients with well-developed disease should begin with progressive, passive range-of-motion and isometric exercises, gradually introducing active range-of-motion and isotonic exercises as appropriate. One randomized controlled multicenter trial studied the effects of high-intensity exercise in over 300 patients with RA. Participants were given either standard physical therapy or a high-intensity exercise program for 2 years. Whereas radiographic damage of the large joints was not increased except possibly in those patients who had considerable baseline damage, high-intensity exercise improved functionality and mood and provided a sense of well-being.[232]

Hydrotherapy

Heat is typically used to help relieve stiffness and pain, relax muscles, and increase range of motion. Moist heat (e.g., moist packs, hot baths) is more effective than dry heat (e.g., heating pad); paraffin baths are used if skin irritation from regular water immersion develops. Cold packs are of value during acute inflammatory flare-ups or following hot applications.

Constitutional hydrotherapy is a classic naturopathic technique utilizing alternating hot and cold applications to the torso and back in combination with electrical stimulation. As with contrast hydrotherapy in other parts of the body, this creates an alternating vasodilation and vasoconstriction—a sort of vascular pump—intended to improve the circulation of blood through the viscera, promote detoxification, and tone the nervous system. Rather than treating the symptomatic joints, this therapy is focused on the causative factors underlying the disease: healing impaired gut function and eliminating metabolic wastes and xenobiotic toxins.

Psychological Aspects

Optimistic patients with RA report better psychosocial and physical functioning than pessimistic patients, who adopt passive coping strategies like staying in bed for many hours a day.[233] Patients who believe they have the ability to control and decrease pain by using spiritual/religious coping methods tend to have less joint pain and negative moods and are much more likely to have higher levels of general social support. Positive support from a spouse[234] or other family member is inversely related to depression and can significantly enhance quality of life. Patients who lack support or experience other challenges—including histories of abuse, somatization disorders, and obsessive-compulsive disorders—often rely on their health care providers for these needs. Rheumatic patients want to be seen as individuals and not as mere diagnoses, to be believed as far as pain and suffering are concerned, and to have their subjective experience acknowledged.[235] A supportive and validating doctor–patient relationship is vital in diseases like RA. Counseling is often appropriate to explore common themes experienced by RA patients, such as coping with severe pain, self-esteem issues, negative feelings, reflections on the past, concentration on recovery from disease, support, and others.[236]

THERAPEUTIC APPROACH

RA is often an aggressive disease that requires aggressive treatment. In mild to moderate RA, the measures below are extremely effective. Foremost is the use of diet to reduce the causes and ameliorate the symptoms of RA. Symptom relief can also be attained through the use of physical medicine techniques, botanicals, and nutrients. In severe cases, NSAIDs and other drugs may be necessary, at least in the acute phase. However, the physician should encourage patients not to abandon natural measures, because they will actually enhance the effectiveness of the drugs, allowing for lower doses when drugs are necessary while providing a foundation for healing by addressing the underlying causative factors and using modalities that are both safe and beneficial in long-term use.

Diet

The first step is a therapeutic fast or elimination diet, followed by careful reintroduction of individual foods to detect those that trigger symptoms. Although any food can cause a reaction, the most common are wheat, corn, dairy products, beef, nightshade family foods (tomato, potato, eggplant, peppers), pork, citrus, oats, rye, egg, coffee, peanuts, cane sugar, lamb, and soy.

After all allergens have been isolated and eliminated, a vegetarian or Mediterranean-style diet rich in organic whole foods, vegetables, cold-water fish (mackerel, herring, sardines, and salmon), olive oil, and berries and low in sugar, meat, refined carbohydrates, and animal fats is indicated.

Supplements

- High-potency multiple-vitamin-and-mineral formula, as described in Chapter 6, Supplementary Measures
- Fish oils: 3000 mg EPA+DHA a day
- Vitamin C: 500 to 1000 mg/day
- Selenium: 200 to 400 mcg/day
- Vitamin E (mixed tocopherols): 200 to 400 IU/day
- Vitamin D_3: 2000 to 4000 IU/day
- Choose one of the following:
 - Grape seed extract (>95% procyanidolic oligomers): 100 to 300 mg/day
 - Pine bark extract (>95% procyanidolic oligomers): 100 to 300 mg/day
 - Or, some other flavonoid-rich extract with a similar flavonoid content, "super greens formula" or other plant based antioxidant that can provide an oxygen radical absorption capacity (ORAC) of 3000 to 6000 units or higher per day
- Probiotic *(Lactobacillus* and *Bifidobacter sp.):* minimum of 5 to 10 billion colony forming units daily
- Pancreatin (10× USP): 350 to 750 mg between meals three times daily; or Bromelain: 250 to 750 mg (1800 to 2000 MCU) between meals three times a day

Botanical Medicines

The following botanicals may be used alone or in combination with others. Severe inflammation and joint destruction require more aggressive therapy.

- Curcumin: Choose one of the following:
 - Curcumin: 400 mg three times a day between meals
 - Meriva: 1000 to 2000 mg/day
 - Theracurmin: 600-1200mg/day
- Ginger: 8 to 10 g of dried ginger or ginger extracts standardized to contain 20% gingerol and shogaol at a dosage of 100 to 200 mg three times a day
- *Tripterygium wilfordii Hook F*: 360 to 570 mg/day of ethyl acetate extract
- *Valeriana officinalis*: 1.5 to 3 g/day of dried herb

Physical Medicine

- Heat (moist packs, hot baths, etc.): 20 to 30 minutes, one to three times daily
- Cold packs for acute flareups or following heat
- Active or passive range-of-motion exercises: 3 to 10 repetitions once or twice a day
- Progressive isometric (and isotonic as the joints improve) exercise: 3 to 10 repetitions several times a day with generous periods of rest

Counseling/Psychological Therapy

A supportive and validating doctor–patient relationship should be established. Priorities include stress management and evaluation for depression and of the patient's support network. Attempts should be made to work with spouses and family members if possible.

OTHER CONSIDERATIONS

Positive results from other testing may indicate DHEA, testosterone, vitamin D, and therapeutics for intestinal permeability, SIBO, dysbiosis, and environmental toxicity.

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CHAPTER 206

Rosacea

Michael T. Murray, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- Chronic acneiform eruption on the face of middle-aged and older adults associated with facial flushing and telangiectasia.
- The acneiform component is characterized by papules, pustules, and seborrhea; the vascular component by erythema and telangiectasia; and the glandular component by hyperplasia of the soft tissue of the nose (rhinophyma).
- The primary involvement occurs over the flush areas of the cheeks and nose.
- More common in women (3:1) but more severe in men.

GENERAL CONSIDERATIONS

Rosacea is a common, chronic, progressive inflammatory skin disorder in which the nose and cheeks are abnormally red and may be covered with pimples similar to those seen in acne (see Chapter 141). Rosacea was originally called "acne rosacea" because its inflammatory papules and pustules so closely mimic those of acne vulgaris. Unlike acne vulgaris, whose etiology is based on the interaction of abnormal keratinization, increased sebum production, and bacterially induced inflammation, rosacea's inflammation is vascular in nature. Rosacea generally occurs in patients between the ages of 25 and 70 years, and it is much more common in people with fair complexions. Women are three times more likely than men to have rosacea, although the disease is generally more severe in men. At least 13 million Americans are known to be affected.[1,2]

Rosacea is divided into three stages, but because progression does not necessarily occur, rosacea is also often divided into four specific subtypes (erythematous telangiectatic, papulopustular, phymatous, and ocular)[1,3,4]:

- *Stage I:* In this stage, or erythematous telangiectatic rosacea, erythema triggered by hot beverages, spicy foods, and alcohol may persist for hours; telangiectasias are noticeable on the central third of the face; and burning, stinging, and itching after the application of cosmetics, fragrances, and sunscreens become a major complaint.
- *Stage II:* In this stage, or papulopustular rosacea, the hallmarks are inflammatory papules and pustules. Flushing, telangiectasias, and seborrhea increase, and minimal enlargement of facial pores becomes obvious.
- *Stage III:* A small number of patients progress to this stage, or phymatous rosacea, which exhibits deep inflammatory nodules, large telangiectatic vessels, markedly dilated facial pores, sebaceous gland hyperplasia, and tissue hyperplasia, especially of the nose (rhinophyma).

Ocular rosacea describes the spectrum of eye findings associated with the skin involvement. Ocular rosacea can cause the eyes to have a watery or bloodshot appearance, the sensation of a foreign body, burning or stinging, dryness, itching, light sensitivity, and a host of other signs and symptoms. Sties are a common sign of rosacea-related ocular disease, and some individuals may have decreased visual acuity owing to corneal complications.

It is important to point out that what differentiates the flushing that rosacea patients experience is its prolonged nature and intensity. Many people without rosacea experience evanescent flushing in response to embarrassment, exercise, or hot environments. However, although evanescent flushing episodes last from several seconds to few minutes, the flushing that the typical rosacea patient describes lasts longer than 10 minutes and is more red than pink, with an accompanying burning or stinging sensation.

The stimuli that bring on such flushing in rosacea patients may be acutely felt emotional stress, hot drinks, alcohol, spicy foods, exercise, cold or hot weather, or hot baths or showers. However, many times the episodes are without known stimuli.

Etiology

The cause of rosacea is poorly understood, although numerous theories have been offered. Included in the factors that have been suspected of causing acne rosacea are the following:

- The mite *Demodex folliculorum*
- Alcoholism
- Menopausal flushing
- Vasomotor neurosis
- Seborrheic diathesis
- Local infection
- Food allergies
- B-vitamin deficiencies
- Gastrointestinal disorders

Most cases of rosacea are associated with moderate to severe seborrhea, although sebum production is not increased in many. Vasomotor lability is prevalent, and migraine headaches are three times more common in persons with rosacea than in age- and gender-matched controls.

There is also emerging evidence for a role for *Helicobacter pylori* in rosacea (discussed below as well). It is known that *H. pylori* infection increases several vasoactive substances, such as histamines, prostaglandins, and leukotrienes, and various cytokines. However, these vascular mediators are found only with *H. pylori* strains that also produce a specific cytotoxin, cytotoxin-associated gene A (CagA). The presence of *H. pylori* capable of producing this cytotoxin may be more important in the etiology of rosacea than other strains. When the presence of CagA was assessed in 60 rosacea patients and compared with age- and gender-matched control subjects with nonulcer dyspepsia, researchers found that when infected with *H. pylori,* 67% of rosacea patients versus only 32% of controls had positive findings for CagA. In addition, these patients had elevated systemic levels of tumor necrosis factor-α and interleukin 8. After the eradication of *H. pylori* infection in the rosacea patients, symptoms disappeared in almost all of them (51 of 53) and tumor necrosis factor-α and interleukin 8 levels normalized.[7,8]

In regard to the etiology of rosacea, the bottom line is that because many of the implicated triggers of rosacea are experienced by healthy persons who never go on to develop the symptoms or signs of rosacea, it is believed that rosacea-prone individuals must have an inherent sensitivity to these triggers.

THERAPEUTIC CONSIDERATIONS

One of the first recommendations to the patient with rosacea is to avoid those stimuli that tend to exacerbate the disease—exposure to extremes of heat and cold, excessive sunlight, and ingestion of hot liquids, alcohol, and spicy foods. The conventional medical treatment of rosacea is usually oral tetracycline, especially for the papular or pustular lesions, although this treatment usually only controls rather than eradicates the disease. Topical therapy for rosacea with antibiotics or synthetic retinoids is generally less successful than systemic antibiotic treatment. Also, although topical corticosteroids may initially improve signs and symptoms, long-term corticosteroid therapy is not advisable because it may actually lead to rosacea. The treatment of chronic skin changes and severe rhinophyma may require laser treatments and surgical intervention respectively.

The natural approach to rosacea is to try to identify and eliminate contributing factors if possible. Key factors to address are hypochlorhydria, eradication of *H. pylori,* elimination of food allergies, and optimal intake of B vitamins.

Hypochlorhydria

Gastric analysis of patients with rosacea has led to the postulate that it is the result of hypochlorhydria.[1] Psychological factors—such as worry, depression, and stress—often reduce gastric acidity.[2] Hydrochloric acid supplementation results in marked improvement in those patients with rosacea who have achlorhydria or hypochlorhydria.[6,7] Patients with rosacea have also been shown to have diminished secretion of lipase (although bicarbonate and chymotrypsin secretion were normal) and to benefit from pancreatic supplementation.[8]

Helicobacter pylori

Given the high incidence of hypochlorhydria, it is perhaps not surprising that a high incidence of *H. pylori* infection in the stomach has also been found in patients with rosacea.[9] In a pilot study, *H. pylori* was found in 46 of 94 patients with rosacea, 38 of 88 patients with other inflammatory diseases, and 5 of 14 patients without an inflammatory disease. The researchers believed that the flushing reaction in rosacea is caused by gastrin or vasoactive intestinal peptides. They also quoted an Irish study that found that 19 of 20 patients with acne rosacea tested positive for *H. pylori.*

Another study that evaluated histologic sections of the stomach mucosa found that 84% of 31 patients were *H. pylori*–positive.[10] Interestingly, 20% of the patients who tested histologically positive also tested serologically negative for the organism. The consistency between clinical success in the treatment of rosacea with metronidazole and the abatement of *H. pylori* isolates and serologic results after treatment provides additional evidence suggesting an etiologic relationship between rosacea and *H. pylori* infection. However, it is also possible that *H. pylori* is simply associated with rosacea and is not a causative factor per se, because patients with rosacea may have rates of *H. pylori* infection similar to those in healthy subjects.[11] Interestingly, patients with rosacea complain significantly more frequently of "indigestion" and use more antacids than the general population.[11]

A large number of studies have now confirmed a strong association between *H. pylori* and rosacea, with a 2003 study showing a correlation between the severity of rosacea and the level of infection.[12]

Food Allergy

The statistically significant incidence of indigestion and migraine headaches accompanying rosacea points to food intolerance, as does the reflex flushing caused by vasodilating substances. Some of the later studies seem to support the concept of rosacea as a hypersensitivity disorder. Although these studies have focused on local factors, it is possible that given the known association of rosacea with dietary factors exacerbating the skin flushing, food hypersensitivity plays a significant role.

B Vitamins

The administration of large doses of B vitamins has been shown to be quite effective,[13] with riboflavin appearing to be the key factor. For example, researchers on B vitamins were able to infect the skin

of riboflavin-deficient rats with the mite *Demodex folliculorum* but not the skin of normal rats.[14] This mite was once considered a causative factor in rosacea and may still be a factor in some patients, especially those with more granulomatous lesions. Evidence suggests that a delayed hypersensitivity reaction in follicles is triggered by *D. folliculorum* antigens, stimulating the progression of the affection to the papulopustular stage.[15]

Although B vitamins are important for patients with rosacea, care must be exercised because some patients' rosacea may be aggravated by large doses of these common nutrients. There is a case report of a 53-year-old woman who presented to a dermatology clinic with a 9-month history of a facial eruption resembling acne rosacea. Treatment with oral hydroxychloroquine, ibuprofen, terfenadine, prednisone, erythromycin, and tetracycline had been tried during the 9 months without success. Topical desoximetasone, hydrocortisone, and cosmetic elimination also yielded no benefit. A patch test showed a positive reaction to nickel. The eruption began at the time of a personal stress as the patient was going through a marital separation. To help with her stress, the patient began taking 100 mg/day of pyridoxine and 100 mg/day of vitamin B_{12}. Discontinuation of the vitamins resulted in a dramatic improvement; with rechallenge, the condition reappeared. The investigators noted that inflammation and exacerbations of acne related to vitamins B_2, B_6, and B_{12} have been reported in the European literature.[16]

Zinc

Zinc supplementation has been shown to be helpful in acne vulgaris and may also be effective in acne rosacea. To test this hypothesis, 25 patients with rosacea were evaluated and given a clinical score, then randomly allocated to receive either zinc (23 mg from zinc sulfate) or identical placebo capsules three times daily. After 3 months, the patients crossed over. A total of 19 patients completed the study. In the group started on zinc, the scores before therapy ranged from 5 to 11. The mean started to decrease directly after the first month of therapy with zinc sulfate to a significantly lower level. After shifting to placebo treatment, the mean started to rise gradually in the fifth month but remained significantly lower than the levels before therapy. In the group started on placebo, the score before therapy ranged from 5 to 9. The mean remained high in the first 3 months of therapy while the patients were on placebo. After shifting to zinc sulfate, the mean started to decrease after the fourth month to significantly low levels. No important side effects were reported apart from mild gastric upset in 3 (12%) patients on zinc sulfate. The authors concluded that zinc is a good option in the treatment of rosacea because it was found to be safe and effective and had no significant side effects.[17]

Topical Azelaic Acid

Topical application of azelaic acid (AzA) appears to be extremely effective in papulopustular rosacea. Initially, AzA was released in a 20% cream formulation and was shown in this vehicle to be effective in the treatment of mild to moderate rosacea. A 15% gel formulation of AzA vastly improved the delivery of AzA and has been proved to be superior in head-to-head studies to the 20% AzA cream. It is and equally as effective as metronidazole cream or gel.[18-20] In a meta-analysis of five double-blind trials involving topical azelaic acid (cream or gel) for the treatment of rosacea compared with placebo or other topical treatments, four of five studies demonstrated significant decreases in mean inflammatory lesion count and erythema severity after treatment with AzA compared with placebo, and AzA was found to be equal to metronidazole in papulopustular rosacea. However, no significant decrease in the severity of telangiectasia occurred in any treatment group.[19]

THERAPEUTIC APPROACH

Although the causes of rosacea have not yet been determined, sufficient information is available to treat most affected patients adequately. Eradication of *H. pylori* infection (when present) and control of hypochlorhydria and food intolerance form the basis of therapy. This approach is supported with supplementation of B-complex vitamins and the avoidance of vasodilating foods.

General Recommendations

See Chapter 141 for general recommendations for acne.

Diet

The patient should avoid coffee, alcohol, hot beverages, spicy foods, and any other food or drink that causes a flush. Also to be eliminated from the diet are all refined and/or concentrated sugars, foods containing *trans* fatty acids such as milk, milk products, margarine, shortening and other synthetically hydrogenated vegetable oils, as well as fried foods and foods high in iodized salt.

Supplements

- Vitamin B complex: 100 mg/day (avoid niacin)
- Pancreatin (8-10× USP): 350 to 500 mg before meals
- Hydrochloric acid: follow guide provided in Appendix 7
- Zinc: 60 to 75 mg/day for no more than 3 months, followed by 15 to 20 mg/day thereafter
- Topical zinc: application of 15% azelaic acid gel

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CHAPTER 207

Seborrheic Dermatitis

Michael Traub, ND, DHANP, FABNO, and Michael T. Murray, ND

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DIAGNOSTIC SUMMARY

- Branny or greasy scaling over erythematous skin patterned on the sebum-rich areas of the scalp, face, and trunk. Facial areas include the forehead, eyebrows, eyelashes, nasolabial folds, and beard. Truncal involvement includes the presternal region, umbilicus, axillae, inframammary and inguinal folds, and perineum.
- The scalp appearance varies from mild, patchy dandruff to widespread, thick, adherent crusts; it may involve the anterior and posterior hairline and the periauricular skin. In infants it occurs as "cradle cap."
- Usually nonpruritic, although active phases can manifest with burning and itching.
- Seasonal; worse in winter.

GENERAL CONSIDERATIONS

Seborrheic dermatitis is a common papulosquamous condition similar in appearance to psoriasis. Clinically it may be associated with excessive oiliness (seborrhea) and dandruff. The scale may be yellowish and either dry or greasy. The erythematous, follicular, scaly papules may coalesce to form large plaques or circinate patches. Flexural involvement is often complicated by candidal infection. The condition occurs either in infancy (usually between 2 and 12 weeks of age) or in the middle-aged or elderly and has a prognosis of lifelong recurrence.

Malassezia yeast organisms are probably not the cause but a cofactor linked to depressed helper T cells (seborrheic dermatitis is very common in AIDS); increased natural killer cells, which increase inflammatory cytokines; increased sebum levels; activation of the alternate complement pathway; and genetic susceptibility to a skin barrier dysfunction.[1] *Malassezia* species have lipase activity, which releases inflammatory arachidonic acid. Seborrheic dermatitis is aggravated by changes in humidity, scratching, emotional stress, diet, various medications, and androgen excess.

THERAPEUTIC CONSIDERATIONS

Nutrition

Food Allergy

Seborrheic dermatitis usually begins as cradle cap and, although not primarily an allergic disease, has been associated with food allergy (67% of patients exhibit some form of allergy by 10 years of age).[2]

Biotin

The underlying factor in infants may be a biotin deficiency.[3] A syndrome clinically similar to seborrheic dermatitis has been produced by feeding rats a diet high in raw egg white (high in avidin, a glycoprotein that binds biotin, making it unavailable for absorption). Because a large portion of the human biotin supply is provided by intestinal bacteria, it has been postulated that the absence of normal intestinal flora may be responsible for biotin deficiency in infants.[2] A number of articles have demonstrated successful treatment of seborrheic dermatitis with biotin in both the nursing mother and the infant.[3,4]

In adults, treatment with biotin alone is usually of no value.

Pyridoxine

Both the administration of desopyridoxine, which induces pyridoxine deficiency in humans, and the placing of rats on a pyridoxine-deficient diet cause dermatologic lesions indistinguishable from seborrheic dermatitis.[5] Despite these results, oral and parenteral applications of pyridoxine have shown little success. However, in the sicca form of the disorder (involvement of the scalp [dandruff], brow, nasolabial folds, and bearded area with varying degrees of greasy adherent scales on an erythematous base), all cases cleared completely within 10 days of local application of a water-soluble ointment containing 50 mg/g of pyridoxine. Other types of seborrheic dermatitis, particularly flexural and infected, did not respond to this mode of therapy.

In one study of patients with elevated levels of urinary xanthurenic acid, oral, parenteral, and local applications of pyridoxine all returned excretion levels to normal, implying transcutaneous absorption of pyridoxine.[5,6] These results are clouded, however, by those of another study indicating that the improvement from topical application may be due more to reduction in sebaceous secretion rate by the ointment itself, the added pyridoxine having no effect.[7]

The patient should be checked for exposure to pyridoxine antimetabolites. Examples are the hydrazine dyes (U.S. Food Drug and Cosmetic Act [FD&C] yellow no. 5) and drugs (isoniazid and hydralazine), dopamine, penicillamine, oral contraceptives, and excessive protein intake.[8]

Botanical Medicines

Aloe vera

Aloe vera gel can be quite helpful when applied topically. In one double-blind trial in people with seborrheic dermatitis, the application of a 30% crude aloe emulsion cream twice a day for 4 to 6 weeks produced improvements in scaling and itching in 62% of subjects compared with improvements in only 25% of the placebo group.[9]

Melaleuca alternifolia

M. alternifolia (tea tree) oil has demonstrated activity against *Malassezia* species, which may be of benefit in the treatment of seborrheic dermatitis. Honey and cinnamic acid have similar activity.[10] A study of 126 patients using 5% tea tree oil shampoo showed 41% improvement in severity versus 11% in the placebo group.[11] Tea tree oil may be added to the patient's favorite shampoo as a way of increasing compliance.

Homeopathic Therapy

A 2002 study evaluated the efficacy of a homeopathic combination remedy in the control of seborrheic dermatitis and chronic dandruff. The homeopathic therapy of Kali brom 1x, Natrum brom 2x, Niccolum sulf 3x, and Natrum mur 6x (potassium bromide, sodium bromide nickel sulfate, and sodium chloride) was studied in a placebo crossover trial in 41 patients with seborrheic dermatitis and/or chronic dandruff. At the end of 10 weeks, all patients crossed over to the active medication under a different label for an additional 10 weeks in an open-study format. Twenty-nine patients completed the 10-week blinded portion of the study. After 10 weeks of treatment, the disease state of the patients receiving active medication showed significant improvement compared with that of the patients receiving placebo ($P < 0.04$). Ten weeks after crossover, the placebo patients experienced improvement as well ($P < 0.01$).[12]

THERAPEUTIC APPROACH

Although the optimal approach to treating all patients with seborrheic dermatitis is not clear at this time, effective therapy is available for most patients. In infants, alleviation of the biotin deficiency and control of the food allergies are key. For adults, using *Aloe vera* and *M. alternifolia*oil is the primary therapy.

Diet

The physician should detect and treat food allergens. In nursing infants, the food allergies of the mother should be considered.

Supplements

- Biotin: 1 mg daily for infants[13]
- Homeopathic combination remedy once a day

Topical Treatments

- Pyridoxine ointment: 50 mg/g (in water-soluble base)
- *Aloe vera* gel: Apply twice a day to affected areas.
- Melaleuca oil: 5% solution (may be added to patient's shampoo of choice)

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CHAPTER 208

Senile Cataracts

Michael T. Murray, ND

DIAGNOSTIC SUMMARY

- Clouding or opacity in the crystalline lens of the eye
- Absence or alteration of red reflex (small cataracts stand out as dark defects)
- Gradual loss of vision

GENERAL CONSIDERATIONS

Cataracts are the leading cause of impaired vision and blindness in the United States. Approximately 4 million people have some degree of vision-impairing cataract, and at least 40,000 people in the United States are blind because of cataracts. Cataracts are a source of a tremendous financial burden on our society; cataract surgery is the most common major surgical procedure performed in the United States each year (600,000 per year) for persons receiving Medicare benefits.

Cataracts may be classified by location and appearance of the lens opacities, by cause or significant contributing factor, and by age at onset. Many factors may cause or contribute to the progression of lens opacity, including ocular disease, injury, surgery, systemic diseases (e.g., diabetes mellitus, galactosemia), toxins, ultraviolet and near-ultraviolet light, radiation exposure, and hereditary disease.

Aging-related (or senile) cataracts are discussed in this chapter; diabetes- and galactose-induced cataracts (sugar cataracts) are discussed in Chapter 161.

The crystalline lens is obviously a vital component of the optical system owing to its ability to focus light (via changes in shape) while maintaining optical transparency. Unfortunately, this transparency diminishes with age. The majority of the geriatric population displays some degree of cataract formation. In the normal aging eye there is a progressive increase in size, weight, and density of the lens throughout life.

Cataract formation is characterized histopathologically by the following features:

- Fibrous metaplasia of the epithelium
- Liquefaction of fibers, resulting in morgagnian globule formation (drops of fluid beneath the capsule and between the lens fibers)
- Sclerosis (melding of fibers)
- Posterior migration and swelling of the epithelium

According to a topoanatomic classification, these basic alterations result in the following five types of cataracts:

- *Anterior subcapsular cataract:* Fibrous metaplasia of lens epithelium (usually follows iritis and adherence of the iris to the lens—posterior synechiae)
- *Anterior cortical cataract:* Liquefaction of lens fibers occurs and morgagnian globules form in the cortex anteriorly
- *Nuclear cataract:* An exaggeration of the normal aging-related melding of fibers in the nucleus
- *Posterior cortical cataract:* Liquefaction and globular degeneration of the posterior lens cortex
- *Posterior subcapsular cataract:* Epithelial cells migrate posteriorly under the capsule and form large irregular nucleated cells

About 75% of senile cataracts are cortical; the rest are nuclear. Clinically cortical cataracts take three forms:

- Spoke wheel, beginning in the periphery and coursing anteriorly and posteriorly to the nucleus

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- Perinuclear punctate opacities
- Granular opacities under the posterior capsule (subcapsular cataracts)

THERAPEUTIC CONSIDERATIONS

The etiology of cataract formation is ultimately related to an inability to maintain normal homeostatic concentrations of Na^+, K^+, and Ca^{2+} within the lens. These abnormalities are apparently the result of decreased Na^+,K^+-ATPase activity,[1-6] a defect usually due to free radical damage to some of the sulfhydryl proteins in the lens, including Na^+,K^+-ATPase, which contains a sulfhydryl component.

In cataract formation, the normal protective mechanisms are unable to prevent free radical damage. The lens, like many other tissues of the body, depends on adequate levels and activities of superoxide dismutase (SOD), catalase, and glutathione (GSH) as well as adequate levels of accessory antioxidants such as lutein, vitamins E and C, and selenium to help prevent damage by free radicals. Individuals with higher dietary intakes of vitamin C and E, selenium, and carotenes (especially lutein) have a much lower risk of developing cataracts.[7] Several studies have shown that various nutritional supplements—multiple vitamin formulas, vitamins C and E, B vitamins (especially vitamin B_{12} and folic acid), and vitamin A—also offer significant protection against both nuclear and cortical cataracts.[8-11] Studies conducted by the Age-Related Eye Disease Study Research Group and others indicate that a combination of these nutrients will likely produce better results than any single nutrient alone or even limited combinations of three or less nutrients in the prevention of both age-related macular degeneration and cataracts (see Chapter 187 for more information).

Antioxidants

Lutein

Lutein, the yellow-orange carotene that offers significant protection against macular degeneration, also exerts protection against cataract formation.[12] Like the macula, the human lens concentrates lutein. In 1992, a prospective cohort study showed that consumption of spinach (high in lutein) was inversely related to the risk of cataracts severe enough to require extraction.[13] This initial investigation was followed by three prospective studies showing that intake of lutein was inversely associated with cataract extraction (20% to 50% risk reduction).[14-16] In a double-blind intervention trial, 17 patients clinically diagnosed with age-related cataracts were randomly assigned to receive dietary supplementation with lutein (15 mg), α-tocopherol (100 mg), or placebo three times a week for up to 2 years.[17] Visual performance (visual acuity and glare sensitivity) improved in the lutein group, whereas there was a trend toward the maintenance of visual acuity with α-tocopherol and a decrease with placebo supplementation.

Vitamin C

A high dietary intake of vitamin C from either dietary sources or supplements has been shown to protect against cataract formation.[8-11,18] In addition to preventing cataracts, antioxidant nutrients like vitamin C may offer some therapeutic benefits. Several clinical studies have demonstrated that vitamin C supplementation can halt cataract progression and in some cases significantly improve vision. For example, in a study conducted in 1939, a total of 450 patients with cataracts were started on a nutritional program that included 1 g/day of vitamin C, resulting in a significant reduction in cataract development.[1] Similar patients had previously required surgery within 4 years, but in the vitamin C–treated patients only a small handful needed surgery, and in most there was no evidence that the cataracts had progressed over the 11-year study period.

It appears that the daily dose of vitamin C necessary to increase the vitamin C content of the lens is 1000 mg.[2] The lens of the eye and active tissue of the body require higher concentrations of vitamin C. The level of vitamin C in the blood is about 0.5 mg/dL, whereas that in the adrenal and pituitary glands is 100 times that. In the liver, spleen, and lens of the eye, the vitamin C level is increased by at least a factor of 20. In order for these concentrations to be maintained, the body must generate enormous amounts of energy to pull vitamin C out of blood against this tremendous gradient. Keeping blood vitamin C concentrations elevated helps the body concentrate vitamin C into active tissue by reducing the gradient. That is probably why such a high dose is required to raise the vitamin C content of the lens.

In another study, 450 patients with incipient cataracts were started on a nutritional program including 1 g/day of vitamin C, which led to a significant reduction in cataract development.[3]

In a large double-blind trial, 11,545 apparently healthy U.S. male physicians 50 years or older without a diagnosis of cataract at baseline were randomly assigned to receive 400 IU of vitamin E or placebo on alternate days and 500 mg of vitamin C or placebo daily.[19] After 8 years of treatment and follow-up, there was no significant difference in cataract formation in the groups. This study may have failed to show benefit because it was below the threshold of 1 g/day of vitamin C.

Glutathione

A tripeptide composed of glycine, glutamic acid, and cysteine, GSH is found at very high concentrations in the lens. GSH plays a vital role in maintaining a healthy lens and has been postulated as a key protective factor against toxins of both intralenticular and extralenticular origin. It functions as an antioxidant, maintains reduced sulfhydryl bonds within the lens proteins, acts as a coenzyme of various enzyme systems, participates in amino acid transport with gamma-glutamyl transpeptidase, and is involved in cation transport.[4] GSH levels are diminished in virtually all forms of cataracts.

Ascorbic Acid and Glutathione Interactions. The antioxidants ascorbic acid (AA) and GSH work in close conjunction and are the most important of all the host-protective factors against the induction of cataracts. The reactions between them are as follows:

$$\text{AA} + \text{superoxide} \rightarrow \text{dehydroascorbate} + H_2O_2$$

Light may also cause oxidation of AA, leading to hydrogen peroxide formation as follows:

$$\text{AA} + \text{light} \rightarrow \text{dehydroascorbate} + H_2O_2$$

An interesting cycle is then set into motion. The dehydroascorbate and hydrogen peroxide produced are reduced by selenium-containing glutathione peroxidase, as follows:

$$2\text{GSH} + \text{dehydroascorbate} \rightarrow \text{GSSG} + \text{AA}$$

$$2\text{GSH} + H_2O_2 \rightarrow \text{GSSG} + 2H_2O$$

The oxidized glutathione (GSSG) serves as an inducer of the hexose monophosphate shunt, which provides the NADPH (nicotinamide adenine dinucleotide phosphate, reduced form)

necessary for reducing GSSG via riboflavin-dependent glutathione reductase, as follows:

$$GSSG + 2NADPH \rightarrow 2GSH + 2NADP$$

The NADP is reduced by hexose monophosphate dehydrogenase as follows:

$$NADP + \text{glucose-6-(P)} \rightarrow NADPH + \text{ribulose 5-(P)} + CO_2$$

This combination of enzymatic and nonenzymatic scavenging of free radicals is a key mechanism for the protection of the lens from photochemical and other forms of oxidative damage.

Selenium and Vitamin E

Selenium and vitamin E, both antioxidants, are known to function synergistically. The maintenance of proper selenium levels appears to be especially important because human lens glutathione peroxidase is selenium-dependent. Low selenium levels strongly promote cataract formation. Previous studies have shown that the selenium content in the cataractous human lens is only 15% of normal.[5]

A later study was conducted to better examine the role of selenium in cataract formation.[6] Selenium levels in the serum, lens, and aqueous humor were determined in 48 patients with cataracts and compared with levels in matched controls. Selenium levels in the serum and aqueous humor were found to be significantly lower in the patients with cataracts (serum, 0.28 mg/mL; aqueous humor, 0.19 mg/mL) than in normal controls (serum, 0.32 mg/mL; aqueous humor, 0.31 mg/mL). However, the selenium level in the lens itself did not significantly differ between the patients with cataracts and the controls.

The most important finding of the study was the decreased level of selenium in the aqueous humor in patients with cataracts. Excess hydrogen peroxide levels, up to 25 times normal, are found in the aqueous humor in patients with cataracts. An excess of hydrogen peroxide is associated with higher lipid peroxidation and altered lens permeability as a result of damage to the sodium-potassium pump. These changes ultimately leave the lens unprotected against free radical and sun damage. As a result, a cataract is formed. Because selenium-dependent glutathione peroxidase is responsible for the breakdown of hydrogen peroxide, it is obvious that low levels of selenium are a major factor in the development of a cataract.

As previously described, vitamin E supplementation alone does not slow the progression of cataract formation.[17] A double-blind study in which vitamin E was given at a dose of 500 IU daily also found that supplementation did not slow cataract formation.[20] In a 7-year trial, supplementation with vitamin E (400 IU) combined with vitamin C (500 mg) and beta-carotene (15 mg) had no effect on the development or progression of cataracts.[21]

Superoxide Dismutase

The activity of SOD is lower in the human lens than in other tissues owing to the higher levels of ascorbate and glutathione in the lens, and a progressive decrease in SOD is encountered in cataract progression. Oral supplementation is probably of little value because it does not affect tissue SOD activity.[22] Of greater value is supplementation with the trace mineral cofactors of SOD, the levels of which are greatly reduced in the cataractous lens (copper by > 90%; manganese by 50%; and zinc by > 90%).[23]

Catalase

Catalase is concentrated in the epithelial portion of the lens (anterior surface), with very low levels found in the rest of the lens. Its primary function is to reduce (to water and oxygen) the hydrogen peroxide formed from the oxidation of ascorbate.

Tetrahydrobiopterin

Pteridine compounds are believed to play a protective role against cataract formation via the prevention of oxidation and damage by ultraviolet light. This action prevents the formation of high-molecular-weight proteins in the lens. Tetrahydrobiopterin functions as an essential coenzyme in the hydroxylation of monoamines such as phenylalanine hydroxylase, tyrosine hydroxylase, and tryptophan hydroxylase. Studies of human senile cataracts have demonstrated decreased levels of pteridine-synthesizing enzymes and tetrahydrobiopterin.[24] Supplemental folic acid may help to compensate for this deficiency.

Other Nutritional Factors

Riboflavin

Lenticular GSH requires flavin adenine dinucleotide (FAD) as a coenzyme for GSH.[25,26] Deficiency of riboflavin, the precursor of FAD, is believed to enhance cataract formation by depressing GSH activity. Although riboflavin deficiency is fairly common in the geriatric population (33%), original studies demonstrating an association between riboflavin deficiency and cataract formation were followed by studies demonstrating no such association. The patient's riboflavin status can be determined by measuring GSH activity in red blood cells before and after stimulation with FAD.[26]

Although correction of the deficiency is warranted, no more than 10 mg/day of riboflavin should be prescribed for patients with cataracts, because it is a photosensitizing substance—superoxide radicals are generated by the interaction of light, ambient oxygen, and riboflavin/FAD. Riboflavin and light (at physiologic levels) have been used experimentally to induce cataracts. The evidence appears to suggest that excess riboflavin does more harm than good in patients with cataracts.

Amino Acids

Methionine is a component of the lenticular antioxidant enzyme methionine sulfoxide reductase and a precursor of cysteine, a component of GSH. Cysteine, along with the other amino acid precursors of GSH, has been shown to be of some aid in cataract treatment.[27]

Zinc, Vitamin A, and Beta-Carotene

The antioxidants zinc, vitamin A, and beta-carotene are known to be essential to normal epithelial integrity. Adequate amounts of these nutrients are vitally important to the health of the epithelial portion of the lens. In particular, beta-carotene may act as a filter, protecting against light-induced damage to the fibrous portion of the lens. Beta-carotene is the most significant of the singlet oxygen free radical scavengers and is used in treating photosensitive disorders.[28] However, in long-term studies, beta-carotene supplementation (50 mg on alternate days) on its own has been found to have no impact on cataract prevention in either women or men.[29,30]

Melatonin

Melatonin is a very efficient free radical scavenger and antioxidant that can neutralize hydroxyl and peroxyl radicals as well as enhance endogenous and exogenous antioxidant efficiency. In animal models, melatonin has been an effective inhibitor of DNA damage, lipid peroxidation, and cataract formation. Melatonin is present at significant levels in the cell nucleus, aqueous cytosol, and lipid-rich cellular membranes.[31]

Dairy Products

Cataracts often develop in infants with a homozygous deficiency of either galactokinase or galactose-1-phosphate uridyl transferase and in laboratory animals fed a high-galactose diet. Abnormalities of galactose metabolism can be identified by measurements of the activity of these enzymes in red blood cells. It has been suggested that such abnormalities are an important mechanism in approximately 30% of cataracts.[26] However, this mechanism of cataract formation appears to be significant only in diabetic cataract formation and is probably not relevant to senile cataract formation (for further discussion, see Chapter 161).

Heavy Metals

A number of heavy metals have been shown to have higher concentrations in both the aging lens and the cataractous lens. Although the levels are higher in the latter, the significance of this finding is unknown.[23]

The cadmium concentration is two to three times higher in cataractous lenses than in lenses of age-matched controls. Because cadmium displaces zinc from binding in enzymatic proteins by binding to the sulfhydryl groups, it may contribute to deactivation of free radical quenching and other protective/repair mechanisms.

Other elevated elements of unknown significance are bromine, cobalt, iridium, and nickel.[23]

Botanical Medicines

A number of excellent choices from the botanical world are available to help with antioxidant mechanisms. They are discussed here.

Flavonoid-Rich Extracts

Among the best may be flavonoid-rich extracts from *Vaccinium myrtillus* (bilberry), *Vitis vinifera* (grape seed), and *Pinus maritima* (pine bark). The occurrence of cataracts in rats can be retarded by changing their diet from a commercial laboratory chow to a "well-defined diet."[32] Preliminary research suggests that flavonoid components in the well-defined diets may be responsible for the protective effects.[33]

Of the flavonoid-rich extracts, bilberry anthocyanosides may offer the greatest protection. In one human study, bilberry extract plus vitamin E stopped progression of cataract formation in 97% of 50 patients with senile cortical cataracts.[34]

Hachimijiogan

An ancient Chinese herbal formula, Hachimijiogan, has been shown to raise the antioxidant level of the lens of the eye.[35] This activity may explain its use in treatment of cataracts for hundreds of years. According to clinical research, its therapeutic effect is quite impressive in the early stages of cataract formation. In one study, 60% of the subjects receiving Hachimijiogan noted significant improvement, 20% of the group showed no progression, and only the remaining 20% displayed progression. Hachimijiogan contains the following eight herbs (per 24 g):

- *Rehmania glutinosa:* 6000 mg
- *Poria cocos sclerotium:* 3000 mg
- *Dioscorea opposita:* 3000 mg
- *Cormus officinalis:* 3000 mg
- *Epimedium grandiflorum:* 3000 mg
- *Alisma plantago:* 3000 mg
- *Astragalus membranaceus:* 2000 mg
- *Cinnamonum cassia:* 1000 mg

THERAPEUTIC APPROACH

In cases of marked visual impairment, cataract removal and lens implantation may be the only alternative. As with most diseases, prevention or treatment at an early stage is most effective. Free radical damage appears to be the primary factor in the induction of senile cataracts, so avoidance of oxidizing agents and promotion of free radical scavenging are critical to successful treatment. The patient should avoid direct ultraviolet light, bright light, and photosensitizing substances; wear protective lenses when outdoors; and greatly increase intake of antioxidant nutrients. Progression of the pathologic process can be stopped and early lesions can be reversed. However, significant reversal of well-developed cataracts does not appear to be possible at this time. Because the geriatric population is especially susceptible to nutrient deficiencies, every effort should be made to ensure that the patient is ingesting and assimilating adequate macronutrients and micronutrients.

Diet

Patients should avoid rancid foods and other sources of free radicals and increase consumption of legumes (high in sulfur-containing amino acids), yellow vegetables (carotenes), and foods rich in vitamins E and C.

Supplements

- High-potency multivitamin/multimineral formula
- Lutein: 5 to 15 mg/day
- Vitamin C: 1 g one to three times a day
- Vitamin E: 600 to 800 IU/day
- Selenium: 400 mcg/day
- L-Cysteine or *N*-acetylcysteine: 400 mg/day
- L-Glutamine: 200 mg/day
- L-Glycine: 200 mg/day

Botanical Medicines

- Bilberry extract (25% anthocyanidin content): 80 mg three times a day
- Hachimijiogan formula: 1000 mg three times a day

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CHAPTER 209

Streptococcal Pharyngitis

Michael T. Murray, ND

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DIAGNOSTIC SUMMARY

- Abrupt onset of sore throat, fever, malaise, nausea, and headache
- Throat red and edematous, with or without exudate
- Tender cervical lymph nodes
- Positive rapid detection of streptococcal antigen
- Group A streptococci on throat culture

GENERAL CONSIDERATIONS

Signs and symptoms of streptococcal pharyngitis ("strep throat") resemble those of viral pharyngitis. Of children with sore throat, 15% to 36% have pharyngitis caused by group A beta-hemolytic streptococci (GABHS). Slightly lower percentages occur in adults as throat cultures yield GABHS in less than 20% of adult patients presenting clinically with a sore throat. However, it must be kept in mind that 10% to 25% of the general, asymptomatic population are carriers for group A streptococci; therefore, the true number of cases of pharyngitis due to GABHS is probably lower than reported.

Rapid "strep" screens that detect the presence of group A streptococcal antigens are a major clinical advancement. Because definitive diagnosis with a positive culture usually takes 2 days, antibiotic therapy during this period for presumed group A strep throat leads to unnecessary exposure to antibiotics and a greater likelihood of the development of antibiotic-resistant organisms. Rapid strep screens, such as the Strep A OIA test, have now shown excellent sensitivity and specificity and will soon replace throat culture as the diagnostic gold standard.[1] In addition, the hope is that the use of these rapid strep screens will eliminate the unnecessary use of antibiotics. That said, these tests remain underutilized, because one analysis found that they were performed on only 53% of cases of acute pharyngitis where an antibiotic was prescribed.[2] Many physicians continue to rely on antibiotics as a precaution against the sequelae of streptococcal pharyngitis even in the absence of a positive diagnosis, resulting in unnecessary prescriptions for antibiotics. Even in positive cases, antibiotics may not be necessary, because strep throat is usually a self-limited disease and most research has shown that clinical recovery is similar in cases where antibiotics are prescribed and those where they are not.[3-5]

The primary concern about not using antibiotics is the development of the "nonsuppurative poststreptococcal syndromes" (rheumatic fever, poststreptococcal glomerulonephritis, etc.). However, antibiotic administration does not significantly reduce the incidence of these sequelae. In developed countries, most cases of rheumatic fever and glomerulonephritis due to group A beta-hemolytic strep throat occur because the affected persons do not consult a physician.[6] It is also important to point out that, although the dogma holds that acute rheumatic fever can be caused only by group A streptococcal infection of the upper respiratory tract, epidemiology indicates that streptococcal pyoderma is a major cause in the Aboriginal people of Northern Australia and perhaps other high-incidence communities. In contrast, in settings where rheumatic fever has become rare, the group A streptococcal strains causing pharyngitis are of relatively low virulence in terms of causing rheumatic fever.[6]

At present it appears that the use of antibiotics should be reserved those patients who are suffering from severe infection or whose sore throats are unresponsive to therapy

(i.e., no response after 1 week of immune supportive therapy) and those with a prior history of rheumatic fever or glomerulonephritis. Penicillin, amoxicillin, erythromycin, and first-generation cephalosporins are the recommended antibiotics for the treatment of sore throat due to GABHS. Amoxicillin tends to be the most common prescription to children primarily for compliance reasons, whereas macrolides like erythromycin and cephalosporins have been recommended as the best first-line antibiotics, because penicillin fails to eradicate the streptococci in more than 20% of patients.[7] The primary reason for this is the presence of beta-lactamase–positive organisms (*Staphylococcus aureus* and *Bacteroides* species), which shield streptococci by deactivating the penicillin. In these instances, stronger antibiotics, such as a cephalosporin, may be required.[8] Nonetheless, because of the low cost and absence of resistance, penicillin is still regarded as an acceptable first choice.[9]

Antibiotics are often praised for their role in effectively eliminating rheumatic fever as a serious concern. However, the dramatic decrease in the incidence of rheumatic fever began before the advent of effective antibiotics.[10] As for the eradication of most infectious diseases, improvements in socioeconomic, hygienic, and nutritional conditions were more important than the liberal use of penicillin. The present attack rates after a streptococcal infection are 0.4% to 2.8% for rheumatic fever and 0.2% to 20% for glomerulonephritis. Obviously such a wide range of reported sequelae makes accurate evaluation of the risk difficult.

THERAPEUTIC CONSIDERATIONS

The primary therapeutic consideration is the status of the patient's immune system. If the patient's immune system is functioning well, the illness will be short-lived. Enhancing general immune function, as described in Chapter 56, may shorten the course. In cases of poor immune function, every effort should be made to strengthen the immune system by following the recommendations given in that chapter.

Vitamin C

During the 1930s there was considerable interest in the relationship between malnutrition and the development of the sequelae of streptococcal pharyngitis. Both experimental animal work and epidemiologic surveys demonstrated a correlation between vitamin C deficiency and the development of sequelae. Rheumatic fever is virtually nonexistent in the tropics, where vitamin C intake is higher. Elsewhere, as many as 18% of children in high-risk groups have subnormal serum levels of vitamin C.

When streptococcus-infected, vitamin C–deficient, rheumatic fever–susceptible guinea pigs are supplemented with vitamin C, the development of rheumatic fever is totally prevented.[11,12] Uncontrolled clinical studies have demonstrated very positive results when children were given orange juice supplementation. Unfortunately, this promising line of research appears to have been dropped, probably owing to the advent of supposedly effective antibiotics.

Hydrastis canadensis and *Echinacea*

The guidelines for enhancing the immune system, as presented in Chapter 56 are particularly strongly indicated for streptococcal pharyngitis. In addition, the botanicals *H. canadensis* and *Echinacea* species are well respected as supports for the immune system during GABHS infections. The berberine alkaloid of *Hydrastis* exerts antibiotic activity against streptococci and, perhaps more importantly, has been shown to inhibit the attachment of group A streptococci to pharyngeal epithelial cells. *Echinacea* also exerts action against streptococcal infection. To promote the spread of colonies, streptococci secrete large amounts of hyaluronidase. This enzyme is inhibited by *Echinacea* as well as by many bioflavonoids. *Echinacea* also inactivates group A streptococci and reduces the proinflammatory response to strep infection[13] as well as promoting greater phagocytosis, natural killer cell activity, and properdin levels. See Chapters 86 and 97 for further discussion.

Pelargonium sidoides (South African Geranium)

Extracts from the rhizomes and tubers of *P. sidoides* have been shown to exert a number of effects that are beneficial in upper respiratory tract infections, particularly acute bronchitis, an indication for which it is an approved drug in Germany (see Chapter 153). *P. sidoides* has demonstrated immune-enhancing effects as well as antibacterial effects and the ability to prevent adhesion of bacteria to epithelial cells.[14] In a double-blind study, an extract of *P. sidoides* (EPs 7630) was shown to be superior to placebo for the treatment of non-GABHS tonsillopharyngitis in children.[15] A total of 143 children, aged 6 to 10 years, with non-GABHS tonsillopharyngitis were given either EPs 7630 or placebo (20 drops three times daily) for 6 days. The decrease in the Tonsillopharyngitis Severity Score from baseline (day 0) to day 4 was 7.1 points with EPs 7630, and 2.5 points in the placebo group. Treatment with EPs 7630 reduced the severity of symptoms and shortened the duration of illness by at least 2 days, consistent with the results seen in acute bronchitis. Although this study was in non-GABHS, it does raise the possibility that *P. sidoides* may have benefit in GABHS.

Bacteriotherapy

Colonizing the throat with group A non–beta-hemolytic streptococci may prove to be an effective treatment for recurrent group A beta-hemolytic streptococcal pharyngitis. In a double-blind study, 130 patients with recurrence of group A beta-hemolytic streptococcal pharyngotonsillitis received antibiotic treatment for 10 days, followed by 10 days of spray treatment with either placebo or group A non–beta-hemolytic streptococcal alpha-streptococci.[16] The clinical recurrences (bacteriologically verified) in the alpha-streptococci- and placebo-treated patient groups were 2% and 23%, respectively, in patients given spray for at least 5 days. No side effects were reported.

In another double-blind study, a total of 342 patients with verified GABHS pharyngitis by the rapid strep test and culture received antibiotic treatment for 10 days, followed by 10 days of alpha-streptococcal or placebo spray treatment. Pharyngeal status, throat culture, and adverse events were investigated up to 75 days after treatment. The frequencies of bacteriologically verified clinical recurrence at the last valid visit after 45 to 75 days were 19% and 30%, respectively—a statistically significant difference. Recolonization with alpha-streptococci seemed to hinder late recurrences of GABHS pharyngotonsillitis.[17]

Lactoferrin

Low concentrations of bovine lactoferrin have significantly hindered the in vitro invasion of cultured epithelial cells by group A streptococci isolated from patients with pharyngitis. The ability of lactoferrin to decrease streptococcal invasion was confirmed in a trial carried out in 12 children with pharyngitis and already scheduled for tonsillectomy. A lower number of intracellular group A streptococci were

found in tonsil specimens from children treated for 15 days before tonsillectomy with both oral erythromycin (500 mg three times daily) and lactoferrin gargles (100 mg three times daily) than in those from children treated with erythromycin alone (500 mg three times daily).[18]

THERAPEUTIC APPROACH

For further information, consult Chapter 56. If antibiotics are used, follow the recommendations for supplementation with *Lactobacillus acidophilus* given in Chapter 116.

Supplements

- Vitamin C: 500 mg every 2 hours
- Bioflavonoids: 1000 mg/day
- Zinc: 30 mg/day

Botanical Medicines

Echinacea species:
- Dried root (or as tea): 0.5 to 1 g/day
- Freeze-dried plant: 325 to 650 mg/day
- Juice of aerial portion of *E. purpurea* stabilized in 22% ethanol: 2 to 3 mL/day
- Tincture (1:5): 2 to 4 mL (0.5 to 1 tsp)/day
- Fluid extract (1:1): 2 to 4 mL (0.5 to 1 tsp)/day
- Solid (dry powdered) extract (6.5:1 or 3.5% echinacoside): 150 to 300 mg/day

Hydrastis canadensis

The dosage of *H. canadensis* should be based on berberine content. Because there is a wide range of quality in goldenseal preparations, standardized extracts are recommended.
- Dried root or as infusion (tea): 2 to 4 g three times a day
- Tincture (1:5): 6 to 12 mL (1.5 to 3 tsp) three times a day
- Fluid extract (1:1): 2 to 4 mL (0.5 to 1 tsp) three times a day
- Solid (powdered dry) extract (4:1 or 8% to 12% alkaloid content): 250 to 500 mg three times a day

Pelargonium sidoides

Dosage recommendations for EPs 7630 or equivalent preparation:

Adults: 1.5 mL three times a day or a 20-mg tablet three times a day for up to 14 days

Children: age 7 to 12 years, 20 drops (1 mL) three times a day; age 6 years or less, 10 drops (0.5 mL) three times a day

Local Treatment

The patient should gargle with lactoferrin (100 mg) dissolved in water three times a day. An alternative recommendation is a saltwater gargle consisting of 1 tablespoon of salt per 240 mL of warm water.

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CHAPTER 210

Trichomoniasis

Michael T. Murray, ND

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DIAGNOSTIC SUMMARY

- Profuse malodorous white to green discharge from the vagina.
- Discharge usually has a pH greater than 4.5, a weak amine odor, and large numbers of white blood cells and trichomonads on wet mount.
- Vulvovaginal pruritus, burning, and/or irritation.
- Vulva and introitus usually show erythema.
- Cervix may or may not have a mottled erythema—"strawberry cervix" (less than 5%).
- Dysuria and/or dyspareunia may be present.
- Rule out trichomoniasis in males exhibiting signs of prostatitis, urethritis, or epididymitis.

GENERAL CONSIDERATIONS

Trichomonas vaginalis infection is a common cause of vaginal irritation in women and is the most common nonviral sexually transmitted disease in the world. It is estimated to affect 5 million women in the United States each year alone. One in five women in the United States will have trichomoniasis at some time in her life. Aside from these alarming statistics, there are other reasons for taking trichomonal infections seriously, as follows[1,2]:

- Gonorrhea and trichomoniasis are common coexisting infections, with up to 40% of women with trichomoniasis having gonorrhea and vice versa.
- Trichomoniasis is a common cause (90%) of cervical erosion and therefore may be a factor in malignant transformation.
- Trichomoniasis may complicate interpretation of Papanicolaou smears, increasing the number of false-positive results.
- Trichomoniasis raises the rate of sterility among males and females, in the latter as a result of salpingitis and in the former because of toxic products that decrease the motility of spermatozoa.
- The rate of postpartum fever and discharge is higher in women in whom *T. vaginalis* infection occurs at delivery.
- Neonates infected via the birth canal may manifest serious illness (rare).
- Prostatitis and epididymitis are common in infected males.
- Trichomoniasis increases transmission and infectivity of human immunodeficiency virus (HIV), such that HIV-seropositive men with concomitant trichomoniasis may have a sixfold higher concentration of HIV RNA in their seminal plasma.
- Infection may confuse and/or complicate other urinary or genital tract problems.

DIAGNOSIS

T. vaginalis is a flagellate 15 to 18 micrometers in length. It is shaped like a turnip, with three to four anterior flagella and one posterior flagellum mounted in an undulating membrane. It is transmitted via sexual intercourse. Although women in the past have been thought to be the primary reservoir for *Trichomonas* and men merely the vector, the medical literature now suggests that men are also reservoirs.[3,4]

Diagnosis is made from clinical signs and symptoms (see the diagnostic summary), saline wet mount, and culture. Trichomonal cultures (using the Feinberg

Trichomonas medium) have recently been advocated to improve diagnostic sensitivity. Although the wet mount is one of the most commonly used and quickest methods to achieve a diagnosis, multiple studies have demonstrated that, compared with culture, the sensitivity of a wet mount ranges from only 45% to 60%.[1,2] In men, a reliable culture site has not been established, and cultures from urine and seminal samples have consistently afforded a low yield. Among patients with trichomonal vaginitis, the organism can be cultured from the vagina and paraurethral glands in 98%, from the urethra in 82%, and from the endocervix in 13%. In only 56% to 65% of patients is *T. vaginalis* seen on a Papanicolaou smear, thus making the smear an unreliable form of diagnosis.[1,2] However, recent data suggest that the positive predictive value of this test is acceptable for a diagnosis of trichomoniasis when it is found incidentally on Papanicolaou smear. A meta-analysis found a sensitivity of 57% and a specificity of 97%.[5]

Rapid point-of-care tests for trichomonal vaginitis are now available; they include the OSOM Trichomonas Rapid Test (Genzyme Diagnostics, Cambridge, Mass), an immunochromatographic capillary-flow dipstick technology, and the Affirm VP III (Becton Dickinson, Franklin Lakes, NJ), a nucleic acid probe test that evaluates for trichomonal vaginitis, *Gardnerella vaginalis*, and *Candida albicans*.[1] Both of these tests are performed on vaginal secretions and have a sensitivity greater than 83% and a specificity greater than 97%. The results of the OSOM Trichomonas Rapid Test are available in about 10 minutes, and the results of the Affirm VP III are available within 45 minutes. These tests tend to greatly assist physicians in the accurate and timely diagnosis of trichomoniasis.

Trichomonal Vaginitis

Sexual transmission is the clear route of *Trichomonas* infection. Prevalence is highest among women with multiple sex partners and in those with other sexually transmitted infections. Transmission rates from men to women seem to be high, because an 80% to 100% prevalence rate is found in the female partners of infected men.[4] In the female, *T. vaginalis* usually infests the vagina and urethra. However, infection may involve the endocervix, Bartholin glands, Skene glands, or bladder. The vagina appears to be a good reservoir for the organism. Under stimulation of estrogen, the vaginal walls are well glycogenated—essential for *T. vaginalis* to thrive. Prepubescent and postmenopausal women seldom have symptomatic trichomonal infections.

In addition to estrogen, an elevated pH increases susceptibility to *Trichomonas*. The normal adult vagina maintains a pH of 3.5 to 4.5 owing to the metabolism of free glucose into lactic acid by vaginal *Lactobacillus acidophilus*. A decrease in the number of lactobacilli raises pH. *Trichomonas* organisms grow optimally at a vaginal pH of 5.5 to 5.8. Other conditions that increase vaginal pH are as follows:

- Progesterone, which rises in the latter half of the menstrual cycle and during pregnancy
- Excess intravaginal secretions (i.e., cervical mucus)
- Overgrowth of certain bacteria, such as *Streptococcus* and *Proteus*

Trichomonas in the Male

Although the incidence is lower in men, 5% to 15% of cases of nongonococcal urethritis are estimated to be caused by trichomonal infections.[1,2] The estimated transmission rate is 70% for men who have had sexual contact with infected women in the previous 48 hours.[2] Men with *T. vaginalis* are most often asymptomatic, yet mild cases of urethritis, prostatitis, and epididymitis have been reported. As might be expected, trichomoniasis is a factor in male infertility.[4] Trichomonads have been identified in semen, urethral discharge, urine, and prostatic fluid and have been found in the prostatic secretions and semen in up to 23% of men with chronic nongonococcal prostatitis.[6]

Although men were thought to be the only vectors for *Trichomonas*, the parasite is now known to persist in the male reproductive tract. The reinfection of treated females who are sexually active is well documented.[4] Therefore, treatment of both sex partners is necessary. Furthermore, among both women and men, the association of *T. vaginalis* with enhanced HIV acquisition and transmission has been well documented.[2]

THERAPEUTIC CONSIDERATIONS

Conventional Treatment

Conventional therapy of trichomoniasis involves metronidazole[7] and tinidazole, a second-generation nitroimidazole used to treat metronidazole-resistant infection. Randomized controlled trials comparing tinidazole (2-g single oral dose) and either metronidazole (2-g single oral dose) or short-course metronidazole have demonstrated parasitologic cure rates of 86% to 100% for all treatments, although tinidazole is slightly more effective but also more expensive. In a Cochrane Database meta-analysis of randomized trials comparing short-course therapy with tinidazole and short-course therapy with metronidazole for trichomoniasis, metronidazole had significantly higher rates of parasitologic failure, clinical failure, and adverse effects.[8] Again, in order to reduce recurrence rates, sex partners should be treated at the same time.

Common side effects of metronidazole and tinidazole are nausea, vomiting, metallic taste, and gastrointestinal upset. With long-term high-dose use, rare occurrences of peripheral neuropathy have been reported.

If metronidazole or inidazole treatment is chosen, probiotic supplementation should accompany it. In the treatment of bacterial vaginosis, administration of vaginal insertion with *L. acidophilus* has led to cure rates superior to those with metronidazole.[9,10] This suggests some benefit in vaginal trichomoniasis, given the frequent disruption of proper vaginal flora in these women.

Diet

Dietary factors affect the body's ability to defend itself against foreign invaders and substances both directly and indirectly. As with any infection, it is not the pathogenicity of the organism but rather the "fertility of the soil" that allows the organism to grow and flourish. A well-balanced diet high in natural fiber (vegetable, fruits) and low in fat, sugar, and refined carbohydrates aids immune function (see Chapter 56 for more discussion) and may discourage any concomitant overgrowth of *Candida.*

Lifestyle

Depression and anxiety have been associated with exacerbations of trichomonal infections. Therefore, efforts to reduce stress are definitely indicated. Reduction may be achieved by a variety of means, including exercise and meditation.

The practice of safe sex or abstinence (during infection) also lowers the incidence of infection and reinfection.

Nutritional Supplements

In addition to the basic supplements for immune support described in Chapter 56, zinc supplementation appears to be an important consideration in the treatment of trichomonal infections in both men and women. The antimicrobial spectrum of zinc is broad and comprises many potential genitourinary pathogens, including *T. vaginalis* as well as *Candida albicans* and *Chlamydia trachomatis* and many viruses.[11] Trichomonads are readily killed by zinc at a concentration of 0.042% (6.4 mmol/L), a concentration that can occur in the prostatic fluid of men. The zinc concentration of prostatic fluid ranges from 0.015% to 0.10% (2.3 to 15.3 mmol/L).[11] This finding suggests that persistent trichomonal infections in men may be due to a low-level zinc deficiency. Zinc sulfate (220 mg twice daily for 3 weeks) has been recommended as a possible treatment for trichomonal infections that are refractory to metronidazole.[12]

For women with drug-resistant trichomoniasis, zinc douches in combination with metronidazole may provide welcome relief. In a small study, the women with recalcitrant trichomoniasis (4 months to 4 years culture-positive despite conventional treatment), all became culture-negative through the use of a combination of 1% zinc sulfate douching (for 3 days after each menstrual period) and 1.6 to 2.2 g/day of metronidazole (suppositories plus oral administration).[13]

Topical Trichomonacides

Povidone-Iodine

Iodine has long been recognized as a highly potent trichomonacide. Povidone-iodine (PVP) has a broad therapeutic effect in killing a large number of different microorganisms that cause vaginitis, including *T. vaginalis.*[14,15] PVP (iodine, which is absorbed into polyvinyl pyrrolidine) has several advantages over iodine in that it has little sensitizing potential, does not sting, is water-soluble, and washes out of clothing.

A success rate of 98.1% has been reported in patients with intractable trichomonal, monilial, nonspecific, and mixed vaginitis for a 2-week treatment regimen using PVP (Betadine) preparations.[16,17] Other studies suggest a 28-day course of povidone-iodine pessaries, particularly if the patient is using oral contraceptives.[18]

Propolis

An ethanol extract of propolis (150 mg/mL) has been shown to have a 100% lethal effect in vitro on the protozoans *T. vaginalis* and *Toxoplasma gondii* after 24 hours of contact.[19] This extract has also been shown to diminish the inflammation associated with trichomonal vaginitis.

Essential Oils

The diverse antimicrobial action of essential oils has been well demonstrated. Many possess strong antitrichomonal properties. In a study of 40 essential oils tested for their ability to kill *Trichomonas, Mentha piperita* (peppermint) and *Lavandula angustifolia* (lavender) had the fastest killing effects (20 and 15 minutes, respectively).[20]

Melaleuca alternifolia

M. alternifolia (tea tree) oil is a powerful cidal agent (see Chapter 102). Commonly used as a germicidal agent in Great Britain and Australia, a 40% solution of tea tree oil has been found to be a highly effective treatment.[21] The 40% solution of the oil produced no irritation, burning, or other side effects. Daily vaginal douches with a 0.4% solution of *Melaleuca* oil in 1 L of water was also found to be effective.[22]

Berberine-Containing Botanicals

The plant alkaloid berberine sulfate has been shown in vitro to inhibit the growth of several protozoa, including *Entamoeba histolytica*, *Giardia lamblia*, and *T. vaginalis*.[23,24] No clinical trials of this agent have been reported in trichomonas vaginalis (see Chapter 97 for further discussion).

THERAPEUTIC APPROACH

Given the risk of serious sequelae of trichomoniasis and the high success rate of conventional pharmaceutical intervention, systemic metronidazole should be carefully considered as a possible first-line treatment along with simultaneous and subsequent naturopathic therapies to decrease the risk of future recurrence and to treat some of the contributing underlying susceptibilities. Naturopathic therapies may be used as first-line therapy in patients who are allergic to metronidazole or are pregnant. The use of metronidazole in pregnancy remains somewhat of a controversy despite its apparent lack of teratogenic action, because data have accumulated that despite the role of *T. vaginalis* in perinatal morbidity, metronidazole treatment may actually increase the risk of preterm birth.[25,26] Discussion with the patient of such factors as diet, sexual habits, and lifestyle is a must. The clinician should inform the patient that *Trichomonas* infection is a sexually transmitted disease and that treatment of the sex partners is necessary to prevent reinfection. During the treatment, sexual intercourse should be avoided. If intercourse does occur, a condom must be used.

Diet

The patient should decrease the consumption of refined carbohydrates, alcohol, and fats and increase intake of fiber.

Nutritional Supplements

- Zinc (picolinate): 10 to 15 mg/day
- Vitamin E: 200 IU/day
- *L. acidophilus:* 5 to 10 billion live bacteria twice a day orally as well as the intravaginal application in vaginal trichomoniasis. See Chapter 116 for further discussion.

Topical Treatments

- Betadine douche, pessary, or saturated tampon: twice a day for 14 days
- *M. alternifolia* oil (40% solution): swabbed on affected area two times/day *or* used as a douche, 1 L of a 0.4% solution twice a day or a suppository, one at night
- Zinc sulfate douche: 1% solution twice a day
- *Lactobacillus* insertions or douches a day, preferably in the morning

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CHAPTER 211

Urticaria

Michael Traub, ND, DHANP, FABNO, and Michael T. Murray, ND

DIAGNOSTIC SUMMARY

- Urticaria (hives): Well-circumscribed erythematous wheals with raised serpiginous borders and blanched centers that may coalesce to become giant wheals; limited to the superficial portion of the dermis.
- Angioedema: Eruptions similar to those of urticaria but with larger well-demarcated edematous areas that involve subcutaneous structures as well as the dermis.
- Chronic versus acute: Recurrent episodes of urticaria and/or angioedema of less than 6 weeks' duration are considered acute, whereas attacks persisting beyond this period are designated chronic. When no underlying cause is found, chronic urticaria is referred to as chronic idiopathic urticaria.
- Special forms: Special forms have characteristic features—dermographism, cholinergic urticaria, solar urticaria, cold urticaria.

INTRODUCTION

Urticaria is named for the stinging nettle plant *Urtica dioica,* which is known to contain histaminic acid. Urticaria is a localized pruritic edema of the skin characterized by white or pink papules or plaques. The lesions are consistent with lesions of histamine-induced wheals. The lesions may develop variable erythema and coalesce to form plaques. About 50% of patients with urticaria experience angioedema—a deeper, less well-defined edema of the subcutaneous and soft tissues.

Urticaria and angioedema are relatively common conditions: It is estimated that they occur in 15% to 25% of the general population.[1] Although persons in any age group may experience acute or chronic urticaria and/or angioedema, young adults (postadolescence through the third decade of life) are most often affected.[2,3]

The basic pathophysiology of urticaria involves the release of inflammatory mediators from mast cells or basophilic leukocytes, both of which have high-affinity receptors for immunoglobulin E (Ig E).[4] Although this inflammation classically occurs as a result of IgE–antigen complexes interacting with these cells, other non–IgE-mediated mechanisms are probably also critical in many patients with urticaria, including prostaglandins, leukotrienes, cytokines and chemokines. A growing body of evidence shows that at least 40% of patients with chronic idiopathic urticaria have clinically relevant functional autoantibodies to the high-affinity IgE receptor on basophils and mast cells. The term *autoimmune urticaria* is used for this subgroup of patients presenting with continuous ordinary urticaria.[5]

PATHOPHYSIOLOGY

The signs and symptoms of acute and chronic urticaria show consistent patterns despite the many diverse etiologic and initiating factors (see later) that have been found, yet the pathogenesis cannot be entirely ascribed to any one mechanism. However, at present, it appears that mast cells and mast cell–dependent mediators play the most prominent role in the pathogenesis of urticaria.[6]

Mast cells are widely distributed throughout the body and are found primarily near small blood vessels, particularly in the skin. The granule-containing mast cell is a secretory cell capable of releasing both preformed and newly synthesized molecules, termed *mediators*. These mediators (listed in Box 211-1) play key roles in

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Thyroid, *1811*
Traditional Chinese Medicine/Acupuncture Therapy, *1811*
Supplements, *1811*
Diagnosis, *1812*
Physical Evaluation and History, *1812*
Laboratory Testing, *1812*
Therapeutic Approach, *1812*
Diet, *1812*
Supplements, *1812*
Psychological, *1812*
Physical Medicine, *1813*
Traditional Chinese Medicine/Acupuncture, *1813*

BOX 211-1 Mast Cell–Derived Mediators

Preformed, rapidly released:
- Histamine
- Eosinophil chemotactic factors of anaphylaxis (ECF-A)
- Eosinophil chemotactic oligopeptides
- Neutrophil chemotactic factor
- Superoxide anions
- Exoglycosidases (β-hexosaminidase, β-δ-galactosidase,* β-glucuronidase)
- Serotonin*
- Arylsulfatase A

Secondary or newly generated:
- Slow-reacting substances (SRS-A): leukotrienes (LT) C, LTD, LTE
- Prostaglandins
- Monohydroxyeicosatetraenoic acids (HETEs)
- Hydroperoxyeicosatetraenoic acids (HPETEs)
- Thromboxanes
- Platelet-activating factor (PAF)*
- Prostaglandin-generating factor of anaphylaxis (PGF-A)

Preformed, granule-associated:
- Heparin
- Proteases (chymotrypsin/trypsin)
- Peroxidase*
- Superoxide dismutase*
- Arylsulfatase B
- Inflammatory factors of anaphylaxis (IFA)*

*Found in mast cells of species other than human.
Data from Keahey TM. The pathogenesis of urticaria. Dermatol Clin 1985;3:13-28.

the pathogenesis of both immunologic and nonimmunologic inflammatory reactions. The three distinct sources of mediators are as follows:
- Preformed mediators, which are contained in the granules and are released immediately
- Secondarily formed mediators, which are generated immediately or within minutes by the interaction of the primary mediators and nearby cells and tissues
- Granule matrix–derived mediators, which are preformed but slowly dissociate from the granule after discharge and remain in the tissues for hours

The most common immunologic mechanism is mediated by IgE.

The early vascular changes appear to be the result of mast cell–dependent vasoactive mediators, particularly histamine and some secondarily generated end products of arachidonic acid metabolism. The wheal-and-flare reactions occur within minutes of initiation and last 30 to 60 minutes.

Histamine and other mediators can be released by other nonallergic mechanisms as well. Neuropeptides are known to cause mast cell degranulation and may well be involved in dermographism and emotional exacerbation of urticaria. The more prolonged and delayed reactions reflect leukocytic infiltration in response to the release of mast cell granule–derived chemotactic factors. These late-phase reactions develop over time and are characterized by erythema, edema, and induration beginning within 2 hours and lasting 12 to 24 hours. Leukocyte infiltration may contribute to the urticarial tissue response by inducing a second wave of mast cell activation or by releasing toxic lysosomal enzymes and mediators characteristic of the type of infiltrating cell.

The actual events initiated by the mediators also depend on the tissues into which they are released. For example, the release of histamine into the skin primarily produces pruritus and vascular permeability, whereas histamine release into the lungs may induce bronchospasm.

Helicobacter pylori has been implicated as a causative agent in chronic urticaria. However, two reviews of the trials showing the benefit of *H. pylori* eradication in patients with chronic urticaria have arrived at conflicting conclusions, one saying the benefit is weak and another that it is statistically significant.[7,8] Including testing for *H. pylori* seems reasonable; if positive, a decision to proceed with this management should be considered carefully in the context of relative harms/burdens and benefits as well as patient values and preferences.



CAUSES OF URTICARIA

Fundamental to the treatment of urticaria is the recognition and control of causative factors.

Physical Urticarias

Urticaria can be produced as a result of reactions to various physical stimuli. The most common forms of physical urticarias are dermographic, cholinergic, and cold urticarias (Table 211-1). These are briefly described here. Less common types of physical urticarias or angioedema are as follows[2]:
- Contact
- Solar
- Pressure
- Heat contact
- Aquagenic
- Vibratory
- Exercise-induced

Dermographism

Dermographism or dermographic urticaria is a readily elicited whealing of the skin that evolves rapidly when moderate amounts of pressure are applied. It may occur as a result of simple contact with furniture, garters, bracelets, watch bands, towels, or bedding.

The incidence of dermographic urticaria has been estimated at 1.5% to 5% in the general population. The most common type of physical urticaria, it is found twice as frequently in women as in men, with the average age at onset being in the third decade. The incidence is much greater among the obese, especially those who wear tight clothing.

Dermographic lesions usually start within 1 to 2 minutes of contact as an erythema, which is replaced within 3 to 5 minutes by edema and surrounding reflex urticaria. Maximal edema is usually produced within 10 to 15 minutes. Although the erythema generally regresses within an hour, the edema can persist up to 3 hours.

Dermographism may be associated with other diseases, including[2]:
- Parasitosis
- Insect bites
- Neuropsychiatric disorders
- Hormonal changes
- Thyroid disorders
- Pregnancy
- Menopause
- Diabetes
- Immunologic alterations

TABLE 211-1 **Clinical Aspects of Physical Urticarias**

TYPE	ELICITING STIMULUS	TIME OF ONSET	DURATION OF LESION	DIAGNOSTIC TEST	ASSOCIATED SYMPTOMS
Dermographic urticaria (tarda)	Stroking, scratching (rubbing for red dermographism)	2-5 min (0.5-5 hr)	1-5 hr (48 hr)	Firm stroking of skin	Headache, malaise
Cholinergic urticaria	Physical exercise + overheating; mental stress	2-20 min	30-60 min	Bicycling, running, sauna	Headache, gastrointestinal upset, wheezing, salivation, lacrimation, syncope
Cold urticaria	Cold contact	2-5 min	1-2 hr	Ice cube, cold arm bath, cold air	Wheezing, syncope
Solar urticaria	Light of varying wavelengths	2-15 min	0.25-3 hr	Phototest	Wheezing, dizziness, syncope
Pressure urticaria	Pressure	3-8 hr	8-24 hr	Locally applied weights	Flulike syndrome, fever, leukocytosis, arthralgias
Heat contact urticaria	Contact with heat	2-15 min	30-60 min	Hot arm bath	Gastrointestinal upset, dizziness, fatigue, wheezing, dyspnea
Aquagenic urticaria	Contact with water	2-30 min	30-60 min	Bath, compresses	None
Vibratory angioedema	Vibration	0.5-4 min	1 hr	Vibrating motor	Faintness, headache
Exercise-induced anaphylaxis	Exercise after a heavy meal	2-5 min	10-30 min	Exercise	Flushing, headache, disorientation, glottis edema, dyspnea, collapse
Familial cold urticaria	Cold wind, change from cold to warm air	0.5-3 hr	48 hr	Cold wind and subsequent rewarming	Tremor, headache, arthralgias, fever

Data from Czarnetzki BM. Urticaria. New York: Springer-Verlag, 1986.

- Other urticarias
- During or following drug therapy
- Infection with *Candida albicans*
- Angioedema
- Hypereosinophilia

Cholinergic Urticaria

Cholinergic, or heat-reflex, urticaria is the second most common physical urticaria. These lesions, which depend on the stimulation of the sweat gland via cholinergic afferent fibers, consist of pinpoint wheals surrounded by reflex erythema. The wheals arise at or between follicles and develop preferentially on the upper trunk and arms.

The three basic types of stimuli that may produce cholinergic urticaria are passive overheating, physical exercise, and emotional stress. Typical eliciting activities, in addition to physical exercise, may include taking a warm bath or sauna, eating hot spices, and drinking alcoholic beverages. The lesions usually arise within 2 to 10 minutes after provocation and last for 30 to 50 minutes.

A variety of systemic symptoms may also occur, suggesting a more generalized mast cell release of the mediators than in the skin. Headache, periorbital edema, lacrimation, and burning of the eyes are common symptoms. Less common symptoms are nausea, vomiting, abdominal cramps, diarrhea, dizziness, hypotension, and asthma attacks.[2]

Cold Urticaria

Cold urticaria is an urticarial and/or angioedematous reaction of the skin when it comes into contact with cold objects, water, or air. Lesions are usually restricted to the area of exposure and develop within a few seconds to minutes after the removal of the cold object and rewarming of the skin. The lower the object's or element's temperature, the faster the reaction. Children with cold urticaria have a higher risk of anaphylaxis, especially triggered by swimming.[9]

Widespread local exposure and generalized urticaria can be accompanied by the following symptoms:

- Flushing
- Headaches
- Chills
- Dizziness
- Tachycardia
- Abdominal pain
- Nausea
- Vomiting
- Muscle pain
- Shortness of breath
- Wheezing
- Unconsciousness

Cold urticaria has been observed to accompany a variety of clinical conditions, including the following[1]:

- Viral infections
- Parasitic infestations
- Syphilis
- Multiple insect bites
- Penicillin injections
- Dietary changes
- Stress

The association of cold urticaria with infectious mononucleosis is well established. Other conditions associated with cold urticaria

are cryoglobulinemia and myeloma, in which cold urticaria may precede the diagnosis by several years.[2]

Autoimmune Urticaria

Although much remains unknown regarding the specific pathophysiologic mechanisms underlying most cases of chronic urticaria, a minority seem to have an autoimmune basis. Research has discovered that a significant percentage of patients previously categorized as having idiopathic urticaria have autoantibodies to IgE or the FcεRIα subunit of the high-affinity IgE mast cell receptor.[10] Studies have identified these autoantibodies in 24% to 76% of patients with chronic urticaria. From a clinical perspective, these patients tend to have a somewhat more severe, prolonged course of disease. Middle-aged women are disproportionately represented in the population of patients with urticaria, and higher rates of autoimmunity in this group, particularly for thyroid disease, may account for this preponderance. Thyroid autoantibodies are found more frequently in patients with these IgE receptor autoantibodies (see later discussion of thyroid).

Autoimmune diseases are well known to be associated with bowel permeabilities.[11-14] Because subclinical impairments of small bowel enterocyte function have been postulated to induce a higher sensitivity to histamine in the digestive tract,[15] it makes sense from a naturopathic standpoint to treat overt and subclinical digestive system permeabilities to decrease systemic inflammatory responses to endotoxins in these autoimmune conditions.

Drugs

Drugs make up the leading cause of urticarial reactions in adults. In children, the reactions are usually due to foods, food additives, or infections.[2]

Most drugs are composed of small molecules incapable of inducing antigenic/allergenic activity on their own. Typically, they act as haptens that bind to endogenous macromolecules, ultimately causing the production of hapten-specific antibodies. Alternatively, drugs can interact directly with mast cells to induce degranulation. Many drugs have been shown to produce urticaria. Box 211-2 provides a condensed list.[16] The two most common urticaria-inducing drugs, penicillin and aspirin, are briefly discussed here.

Penicillin

Antibiotics, including penicillin and related compounds, are the most common cause of drug-induced urticaria. The allergenicity of penicillin in the general population is thought to be at least 10%. Nearly 25% of these individuals display urticaria, angioedema, or anaphylaxis on ingestion of penicillin.[2,17]

An important characteristic of penicillin is that it cannot be destroyed by boiling or steam distillation. This is a problem because penicillin and related contaminants can exist undetected in foods. To what degree penicillin in the food supply contributes to urticarial reactions is not known. However, urticaria and anaphylactic symptoms have been traced to penicillin in milk,[18] soft drinks,[19] and frozen dinners.[20] In one study of 245 patients with chronic urticaria, 24% had positive skin test results and 12% had positive results on the radioallergosorbent test for penicillin sensitivity.[21] Of those 42 patients sensitive to penicillin, 22 experienced clinical improvement with a dairy-free diet, whereas only 2 out of 40 patients with negative skin test results experienced improvement with the same diet. This study would seem to provide indirect evidence of the importance of penicillin in the food supply in urticaria.

In an attempt to provide direct evidence, penicillin-contaminated pork was given to penicillin-allergic volunteers. No significant reactions were noted other than transient pruritus in two volunteers.[22] Penicillin in milk appears to be more allergenic than penicillin in meat.[18] Presumably the reason is that penicillin can be degraded into more allergenic compounds in the presence of carbohydrate and metals, suggesting that penicillin in milk may be more allergenic than artificially contaminated meat.[18]

BOX 211-2 Drugs That Can Cause Urticaria

- Acetylsalicylic acid
- Allopurinol
- Antimony
- Antipyrines
- Barbiturates
- Bismuth
- Chlorhydrate
- Chlorpromazine
- Corticotropin (adrenocorticotropic hormone)
- Eucalyptus
- Fluorides
- Gold
- Griseofulvin (cold urticaria)
- Insulin
- Iodines
- Liver extract
- Menthol
- Meprobamate
- Mercury
- Morphine, opium
- Paraaminosalicylic acid
- Penicillin
- Phenacetin
- Phenobarbital
- Pilocarpine
- Poliomyelitis vaccine
- Potassium sulfocyanate
- Procaine
- Promethazine
- Quinine
- Reserpine
- Saccharin
- Thiamine chloride
- Thiouracil

Data from Andrews GC. Andrews' diseases of the skin, ed 7. Philadelphia: WB Saunders, 1982:131.

Aspirin and Nonsteroidal Antiinflammatory Drugs

Urticaria is a more common indicator of aspirin sensitivity than is asthma (see Chapter 147). The incidence of aspirin sensitivity in patients with chronic urticaria is at least 20 times greater than that in normal controls.[23-27] Studies (summarized in Table 211-2)[28-57] have demonstrated that 2% to 67% of patients with chronic urticaria are sensitive to aspirin.

Aspirin inhibition of cyclooxygenase apparently shunts eicosanoid metabolism toward leukotriene synthesis, thereby increasing smooth muscle contraction and vascular permeability. In addition, aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) have been shown to increase gut permeability dramatically and may alter the normal handling of antigens.[53,58] NSAIDs are also known be associated with prolonged and more pronounced autoreactivity in urticaria.[57] The daily administration of 650 mg of aspirin for 3 weeks has been shown to desensitize patients with urticaria and aspirin sensitivity. While taking the aspirin, patients also became nonresponsive to foods to which they usually reacted, such as pineapple, milk, egg, cheese, fish, chocolate, pork, strawberries, and plums.[59] Others have noted this effect in patients with asthma, but they have also found that the effect disappears within 9 days after the treatment is stopped, suggesting the loss of effect or a possible placebo response.[60]

Food-Related Causes

Food Allergy

IgE-mediated urticaria can occur on the ingestion of a specific reaginic antigen. Although any food can be the agent, the most common offenders are milk, fish, meat, eggs, beans, and nuts.[2,17,61-67] Other allergens are citrus, kiwis, peanuts, and apples.[61]

TABLE 211-2 **Provocation Tests with Food Additives in Chronic Urticaria**

STUDY	YEAR	NO. OF PATIENTS	Percent Positive Tests					
			TARTRAZINE	OTHER AZO DYES	ANNATTO	BENZOATES	BHA/BHT	ASPIRIN
Samter and Beers[28]	1969	40	8	—	—	—	—	—
Michaelsson and Juhlin[29]	1973	52	36	20	—	44	—	67
Thune and Granholt[30]	1975	100	21	14	—	10	14	33
Doeglas[31]	1975	23	30	—	—	23	—	24
Warin and Smith[32]	1976	108	12	—	—	16	—	—
Settipane et al.[33]	1976	38	8	—	—	—	—	—
Kaaber[34]	1978	65	5	5	8	3	—	—
Fujita et al.[35]	1978	57	—	—	—	23	—	—
Neuman et al.[36]	1978	30	23	—	—	—	—	—
August[37]	1979	86	23	—	—	22	—	—
Meynadier et al.[38]	1979	24	24	46	—	25	—	—
Lindemayr and Schmidt[39]	1979	90	19	16	—	29	—	—
Mikkelsen et al.[38]	1979	24	24	46	26	—	—	—
Wutrich and Hacki-Herrmann[41]	1980	81	21	—	—	18	11	—
Gibson and Clancy[42]	1980	76	28	—	—	34	—	54
Juhlin[43]	1981	330	—	18	11	11	15	10
Wutrich and Fabro[44]	1981	306	6	—	—	6	—	—
Kirchoff et al.[45]	1981	100	15	10	—	8	—	—
Egyedi and Torok[46]	1982	40	37	7	—	17	—	37
Merk and Gorez[47]	1983	25	24	—	—	—	—	—
Hannuksela[48]	1983	137	1	—	—	4	—	18
Ortolani et al.[49]	1984	75	13	—	—	21	10	43
Simon[50]	1984	25	0	—	—	—	—	—
Genton et al.[51]	1985	17	59	—	—	30	—	—
Pigatto et al.[52]	1985	61	10	—	—	—	15	—
Kemp and Schembri[53]	1985	23	7	—	—	7	—	36
Zieger and Hamstein[54]	1986	100	10	—	—	—	—	—
Supramaniam and Warnor[55]	1986	43	26	—	—	15	—	2

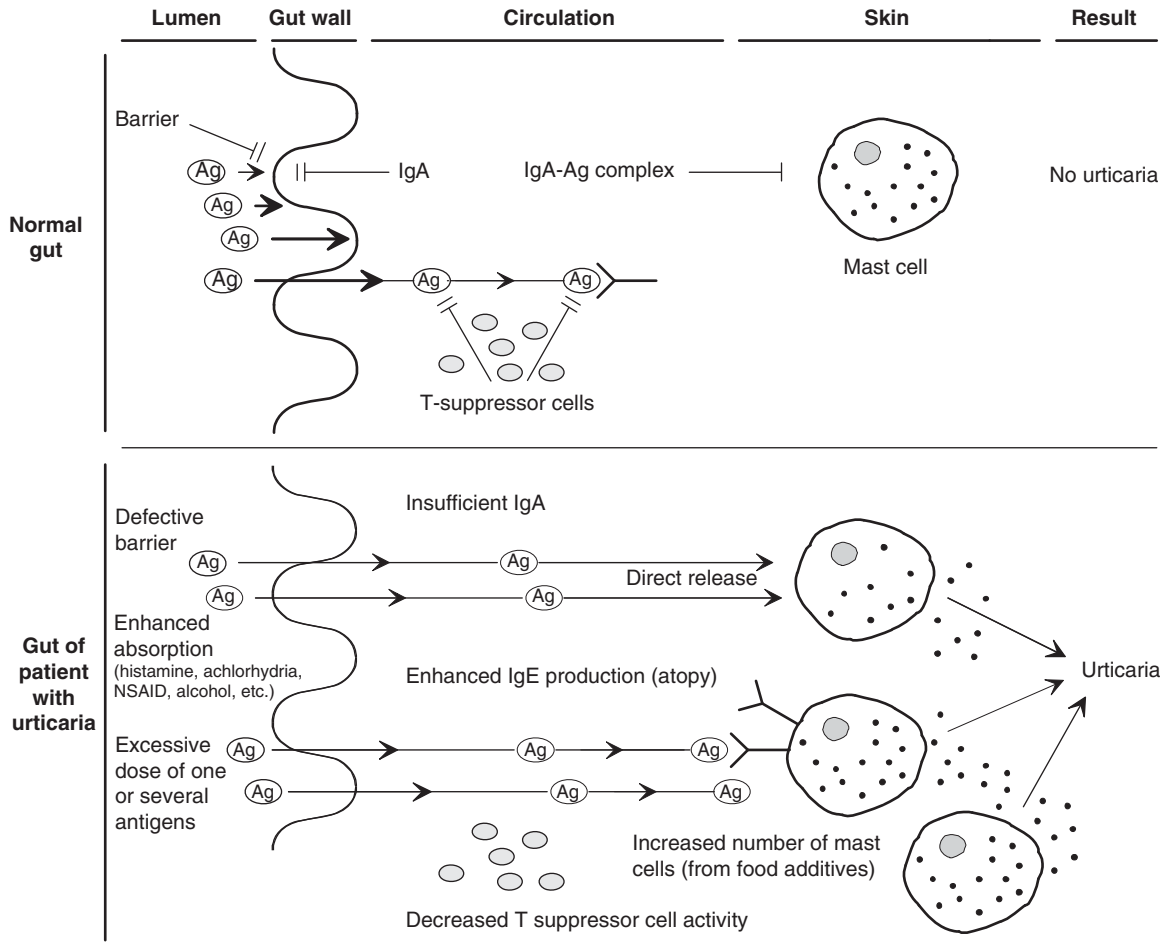


FIGURE 211-1 Hypothetical model of immune defense in the normal and urticarial gut.

Individuals with atopy are most likely to experience urticaria as a result of IgE-related mechanisms, although reports confirm the presence of pseudoallergic reactions, whereby direct mast cell histamine release is involved in this reactivity. Aromatic volatile ingredients in tomatoes, wine, and culinary herbs (basil, fenugreek, cumin, dill, ginger, coriander, caraway, turmeric, parsley, pepper, rosemary, and thyme) have been considered the initiating factors in some of these non-IgE events.[68,69]

Food allergies may contribute greatly to the increased permeability of the gut in urticaria. A basic requirement for the development of a food allergy is the absorption of the allergen through the intestinal barrier. Several factors are known to significantly increase gut permeability, including alcohol, NSAIDs, vasoactive amines ingested in foods or produced by bacterial action on essential amino acids, and possibly many food additives (see Chapter 20 for a full discussion). Gut permeabilities are also associated with autoimmune conditions.[11-14] Because chronic urticaria is now known to be at least partially related to an autoimmune process (see earlier discussion of autoimmune urticaria), it is possible that, depending on the genetic susceptibility of individual, these bowel permeabilities may play a key role in the instigation of immune activity and its prolongation, leading to chronic urticaria.

In addition, several investigators have reported alterations in gastric acidity, intestinal motility, and the function of the small intestine and biliary tract in up to 85% of patients with chronic urticaria.[70-74] Selective IgA deficiency, gastroenteritis, hypochlorhydria or achlorhydria, and other disruptive factors reported in patients with chronic urticaria may temporarily or permanently alter the barrier and immune function of the gut wall, predisposing an individual to allergic sensitization.

In one study of 77 patients with chronic urticaria, 24 (31%) were diagnosed as achlorhydric and 41 (53%) were shown to be hypochlorhydric.[72] Treatment with hydrochloric acid and a vitamin B complex gave impressive clinical results, highlighting the importance of correcting any underlying factor in the treatment of chronic urticaria (see Chapter 24).

Although IgE-mediated reactions are thought to predominate in immunologic urticaria, it has been suggested that IgG-mediated reactions are probably responsible for the majority of adverse reactions to foods, as seen in general practice (see Chapter 54). IgG antigen-antibody complexes are capable of promoting complement activation and the subsequent generation of anaphylatoxins that promote mast cell degranulation. This could be a significant factor in some cases of urticaria.

Figure 211-1 summarizes the basic aspects of a hypothetical model of immune defense in the normal gut and the urticarial gut.

Food Colorants

Food additives are a major factor in many cases of chronic urticaria in children. Colorants (azo dyes), flavorings (salicylates, aspartame), preservatives (benzoates, nitrites, sorbic acid), antioxidants (hydroxytoluene, sulfite, gallate), and emulsifiers/stabilizers (polysorbates, vegetable gums) have all been shown to produce urticarial reactions in sensitive individuals.*

*References 2, 17, 28-57, 66, 69, 81,115-118.

TABLE 211-3 **Response to a Diet Free of Added Dyes and Benzoates**

STUDY	YEAR	NO. OF PATIENTS	Percentage FREE OF URTICARIA	BETTER	SAME
Michaelsson and Juhlin[29]	1973	16	81	6	13
Thune and Granholt[30]	1975	100	12	50	38
Ros et al.[73]	1976	75	24	57	19
Warin and Smith[30]	1976	58	75	75	25
Douglas[74]	1977	18	67	67	33
Kaaber[34]	1978	23	44	30	26
August[37]	1979	22	45	23	32
Meynadier et al.[38]	1979	98	80	12	8
Lindemayr and Schmidt[39]	1979	90	20	55	25
Gibson and Clancy[42]	1980	65	75	15	10
Valverde et al.[115]	1980	258	62	22	16
Wutrich and Fabro[44]	1981	51	31	57	12
Kirchoff et al.[45]	1981	41	44	29	27
Verschave et al.[116]	1983	67	73	73	37
Kemp and Schembri[53]	1985	18	39	39	22

The importance of the control of food additives was well demonstrated in a study of 64 patients with common urticaria. After 2 weeks on an additive-free diet, 73% of the patients had a significant reduction in symptoms. The diet strictly forbade preservatives, dyes, and antioxidants. No fruits or refined sugars were allowed except honey. Rice, potatoes, and unprocessed cereals were allowed, as well as fresh milk.[75]

Tartrazine. In 1959, the azo dye tartrazine (Food, Drug and Cosmetic Act [FD&C] Yellow no. 5) was the first food dye reported to induce urticaria.[76] Tartrazine is one of the most widely used colorants. It is added to almost every packaged food as well as many drugs, including some antihistamines, antibiotics, steroids, and sedatives.[77] Reactions to this food additive are so common that its use has been banned in Sweden.[78]

In the United States, the average daily per capita consumption of certified dyes is 15 mg, of which 85% is tartrazine. Among children, consumption is usually much higher. Tartrazine sensitivity has been calculated as occurring in 0.1% of the population.[79]

Tartrazine sensitivity is extremely common (20% to 50%) in individuals sensitive to aspirin.[17,77] Like aspirin, tartrazine is a cyclooxygenase inhibitor and a known inducer of asthma, urticaria, and other allergic conditions, particularly in children. Inhibition of cyclooxygenase by tartrazine or aspirin apparently shunts eicosanoid metabolism toward leukotriene synthesis, thereby increasing smooth muscle contraction and vascular permeability.

In addition, tartrazine, as well as benzoate and aspirin, increases the production of the lymphokine leukocyte inhibitory factor.[79] This results in an increase in perivascular mast cells and mononuclear cells. Histologic examination of patients with urticaria shows that more than 95% have an increase in perivascular mast cells and mononuclear cells.[80]

Table 211-2 summarizes the findings in studies using provocation tests to determine sensitivity to tartrazine and other food additives in patients with urticaria. Rates have varied from 5% to 46%. Diets eliminating tartrazine as well as other azo dyes and food additives in sensitive individuals have in many cases been shown to be of great benefit. These studies are summarized in Table 211-3. Table 211-4 shows a recommended test battery.[81]

TABLE 211-4 **Test Battery for Patients With Recurrent Urticaria**

DAY	SUBSTANCE(S) TESTED	AMOUNT (MG)
1	Control (lactose)	100,000
2	Azo dyes:	
	Tartrazine	0.1, 1, 10
	New coccine	0.1, 1, 10
	Sunset yellow	0.1, 1, 10
3	Control (lactose)	100, 100
4	Benzoates:	
	Sodium benzoate	50, 500
	4-Hydroxybenzoic acid	50, 200
5	Carotene	50, 100, 100
	Canthazanthine	10, 200, 200
6	Annatto	5, 10
7	BHT-BHA	1, 10, 50, 50
8	Yeast extract	600
9	Control (lactose)	100, 100
10	Aspirin	0.1, 1, 10, 100, 250, 500
11	Sorbic acid	50, 200, 200
12	Control	
13	Sodium nitrite	100
	Sodium nitrate	100
14	Sodium glutamate	100, 200
15	Quinoline yellow	1, 5, 10
16	Potassium metabisulfate	1, 5, 10, 50

Data from references 43 and 117.

Food Flavorings

Salicylates. A broad range of salicylic acid esters are used to flavor foods such as cake mixes, puddings, ice cream, chewing gum, and soft drinks. The mechanism of action of these agents is thought to be similar to that of aspirin.[17]

Salicylates are also found naturally in many foodstuffs. It is estimated that daily salicylate intake from foods is in the range of 10 to 200 mg/day.[82] Because this is very close to the level of salicylates used in clinical testing (usually 300 mg), dietary salicylate may be a significant factor in aspirin-sensitive individuals.

Most fruits, especially berries and dried fruits, contain salicylates. Raisins and prunes have the highest amounts. Salicylates are also found in appreciable amounts in candies made of licorice and peppermint. Moderate levels of salicylate are found in nuts and seeds. Vegetables, legumes, grains, meat, poultry, fish, eggs, and dairy products typically contain insignificant levels of salicylates. Salicylate levels are especially high in some herbs and condiments, including curry powder (turmeric), paprika, thyme, dill, and oregano. Although the intake of these herbs and spices is relatively small, they can make a contribution to total dietary salicylate.[82]

Other Flavoring Agents. Other flavoring agents, such as cinnamon, vanilla, menthol, and other volatile compounds, may produce urticaria in some individuals.[17] For example, the artificial sweetener aspartame has been shown to induce urticaria.[87]

Food Preservatives

Benzoates. Benzoic acid and benzoates are the most commonly used food preservatives. Although the incidence of adverse reactions to these compounds is thought to be less than 1% for the general population, the frequency of positive challenges in patients with chronic urticaria varies from 4% to 44%, as illustrated in Table 211-2.

Fish and shrimp frequently contain extremely high quantities of benzoates. This may be one reason why adverse reactions to these foods are so common in patients with urticaria.

Butylated Hydroxytoluene and Butylated Hydroxyanisole. Butylated hydroxytoluene (BHT) and butylated hydroxyanisole are the primary antioxidants used in prepared and packaged foods. Typically, 15% of patients with chronic urticaria test positive to oral challenge with BHT.[30,43,52,56] The use of chewing gum containing BHT was enough to induce urticaria in one patient.[84]

Sulfites. Sulfites, like tartrazine, have been shown to induce asthma, urticaria, and angioedema in sensitive individuals.[85,86] The source may be varied, because these compounds are ubiquitous in foods and drugs. They are typically added to processed foods to prevent microbial spoilage and keep them from browning or changing color. The earliest known use of sulfites was in the treatment of wines with sulfur dioxide by the Romans. Sulfites are sprayed on fresh foods such as shrimp, fruits, and vegetables. They are also used as antioxidants and preservatives in many pharmaceuticals. Sulfites have caused such a wide range of health problems, such as asthma and urticaria, that their use on fresh fruits and vegetables (except potatoes) was banned in the United States in 1986.[78]

The average person consumes an average of 2 to 3 mg/day of sulfites. Wine and beer drinkers typically consume up to 10 mg/day, and individuals who frequent restaurants for meals may ingest up to 150 mg/day.[85]

Normally, the enzyme sulfite oxidase metabolizes sulfites to safer sulfates, which are excreted in the urine. People with a poorly functioning sulfoxidation system, however, have an increased ratio of sulfite to sulfate in their urine. Sulfite oxidase depends on the trace mineral molybdenum. Although most nutrition textbooks list molybdenum deficiency as uncommon, an Austrian study of 1750 patients found that 41.5% were molybdenum deficient.[87]

Food Emulsifiers and Stabilizers

A variety of compounds is used to emulsify and stabilize many commercial foods to ensure that the solids, oils, and liquids do not separate out. Most of the foods containing these compounds are heterogeneous, because they usually contain antioxidants, preservatives, and dyes. Polysorbate in ice cream has been reported to induce urticaria, and vegetable gums such as acacia, gum arabic, tragacanth, quince, and carrageenan may also induce urticaria in susceptible individuals.[17]

Infections

Infections are a major cause of urticaria in children.[2] Apparently, in adults, immunologic tolerance occurs to many microorganisms owing to repeated massive antigen exposure. The role of bacteria, viruses, and yeast *(C. albicans)* in urticaria is briefly reviewed here. Chronic *Trichomonas* infections have also been found to cause urticaria.

Bacteria

As noted previously, *H. pylori* has been implicated in chronic urticaria. Bacterial infections contribute to urticaria in two other major settings—acute streptococcal tonsillitis in children and chronic dental infections in adults. In the first setting, acute urticaria predominates, whereas in the second, chronic urticaria predominates.[2]

Viruses

Hepatitis B is the most common cause of virally induced urticaria. One study found that 15.3% of patients with chronic urticaria had anti–hepatitis B surface antibodies.[88] Urticaria has also been strongly linked to infectious mononucleosis and may develop several weeks before clinical manifestations. The incidence of urticaria during infectious mononucleosis is 5%.[2]

Candida albicans

The association between *C. albicans* and chronic urticaria has been suggested in several clinical studies. The number of patients with chronic urticaria who react positively to an immediate skin test with *Candida* antigens is 19% to 81%, compared with 10% to 15% of normal subjects.[32,89-95] It appears that sensitivity to *C. albicans* is an important factor in at least 25% of patients with chronic urticaria.[92] Approximately 70% of patients with a positive skin reaction also react to oral provocation tests using foods prepared with yeasts.

Treatment with nystatin has demonstrated that elimination of the organism can achieve a cure in a number of individuals with positive skin test results, although a placebo response cannot be ruled out. However, more patients have responded to a "yeast-free" diet than to simple elimination of the organism in clinical trials. The yeast-free diet employed excluded breads, buns, sausage, wine, beer, cider, grapes, sultanas, marmite, Bovril, vinegar, tomato, ketchup, pickles, and prepared foods containing food yeasts. For example, in a study of 49 patients with proved sensitivity to *Candida,* 9 showed responses to a 3-week course of nystatin, whereas 18 became symptom free only after adopting the yeast-free diet.[92] This finding would seem to support the importance of diet along with elimination of the yeast.

Further support for the importance of diet can be found in a study of 36 patients with a positive skin-prick test response to *Candida*. Only 3 patients became asymptomatic with nystatin alone, compared with 23 with diet therapy after the nystatin therapy.[93]

Desensitizing patients to *C. albicans* with the use of a *Candida* cell wall extract has also demonstrated encouraging results in some patients, although the treatment of these individuals also included increasing gastrointestinal fermentation and acidity as well as elimination of yeast.[94,95]

THERAPEUTIC CONSIDERATIONS

Psychological Aspects

In one retrospective study involving 236 cases of chronic urticaria, psychological factors, such as stress, were reported to be the most common primary cause.[96] Stress appears to play an important role through a reduction of intestinal secretory IgA levels.

In one study of 15 patients with chronic urticaria, relaxation therapy and hypnosis were shown to provide significant benefit.[97] Patients were given an audiotape and asked to use the relaxation techniques described on the tape at home. At a follow-up examination 5 to 14 months after the initial session, 6 patients were free of hives and 7 others reported improvement.

Ultraviolet Light Therapy

Ultraviolet light has been shown to be of some benefit to patients with chronic urticaria.[98,99] Both ultraviolet A and ultraviolet B light therapies have been used. Patients with cold, cholinergic, and dermographic urticarias display the greatest therapeutic response.

Thyroid

The association of thyroid disease and autoimmunity with urticaria has been established for decades.[100-105] The prevalence of antithyroid antibodies in the normal population has been estimated at 3% to 6%, and they are commonly found in association with other autoimmune conditions, such as pernicious anemia and vitiligo.[103] A subset of patients with chronic urticaria may be best helped by suppressing thyroiditis, by thyroid hormone therapy (as described in the following studies), by surgery, or by antithyroid medication.

One study evaluated a group of 624 patients with presumed idiopathic chronic urticaria and angioedema. From these, 90 patients were found to have thyroid autoimmunity.[104] Forty-six of these patients were treated with L-thyroxine therapy, 8 of whom had remission within 4 weeks of therapy. Four patients with high thyroid antibody titers had repeated exacerbations when therapy was discontinued and had repeated remissions when therapy with L-thyroxine was resumed. Although in most cases treatment with L-thyroxine did not improve the patient's urticaria or angioedema, a few did demonstrate a dramatic response.

Another study reported that thyroid hormone replacement therapy dramatically improved chronic urticaria in patients who had normal thyroid function but had evidence of thyroid autoimmunity. Of 7 patients with chronic urticaria, 5 were started on thyroid hormone; doses were increased in 2. Their urticaria resolved within 2 to 4 weeks, at which time the thyroid therapy was discontinued. In 5 patients, the symptoms returned within 4 weeks, then resolved within 4 weeks of restarting the hormone therapy. Antithyroid antibodies did not correlate with clinical response.[104]

There have been cases in which resolution of chronic urticaria associated with thyrotoxicosis has also been seen in patients treated with antithyroid medication and in those treated with radioactive iodine.[103] Subclinical hypothyroidism is an increasingly recognized entity and may underlie the thyroid-urticaria association in some cases.

Although the usefulness of thyroid hormone therapy in patients who are euthyroid and have chronic urticaria has not been demonstrated in a controlled trial, looking for thyroid autoimmunity is certainly warranted in cases refractory to other forms of therapy.

Traditional Chinese Medicine/Acupuncture Therapy

Acupuncture has long been used in traditional Chinese medicine (TCM) to effectively treat urticaria[106,107] and type I allergic conditions.[108] Known as "wind wheal," urticaria is also referred to by Chinese practitioners as the "hidden rash," owing to its ephemeral nature.

Three standard TCM etiologies are considered for urticaria. Urticarial disease due to wind heat typically manifests as red rashes with pruritus. Wind damp etiology correlates with lighter-colored rashes and a heavy sensation in the body. Alternatively, red rashes that appear with concomitant epigastric or abdominal pain and diarrhea or constipation are considered a derivation of stomach and small intestinal heat. Acute urticaria can be easily and effectively treated with acupuncture, in which LI11 (Quchi), Sp10 (Xuehai), Sp6 (Sanyinjiao), and S36 (Zusanli) are the acupuncture points most commonly prescribed.[108] Auricular acupuncture may also accompany body acupuncture points for enhanced effect. External herbal washes with *Fructus arctii* (burdock) are also used in TCM.

Controlled studies are needed to fully elucidate the benefits of TCM for allergic disease and urticaria, but given its safety and history of effective use, it is certainly worth a try.

Supplements

Vitamin B_{12}

Vitamin B_{12} has been anecdotally reported to be of value in the treatment of acute and chronic urticaria.[109,110] Although serum vitamin B_{12} levels are normal in most patients, additional vitamin B_{12} appears to be of value. However, because injectable vitamin B_{12} was used, the placebo effect (see Chapter 7) cannot be ruled out.

Quercetin

Considering the importance of mast cell degranulation in the pathogenesis of urticaria, quercetin's significant in vitro activity as a mast cell stabilizer (and inhibitor of many of the pathways of inflammation; see Chapter 95) suggests that it may be very useful in treating urticaria. This possibility is strengthened by the observation that sodium cromoglycate (at 200 to 400 mg four times daily), a compound similar to quercetin, confers excellent protection against the development of urticaria and angioedema in response to ingested food allergens.[111]

Fish Oil

Three patients with salicylate-induced urticaria experienced alleviation of symptoms following dietary supplementation with omega-3 fatty acids. All three patients experienced severe urticaria, asthma requiring systemic steroid therapy, and anaphylactic reactions. After dietary supplementation with 10 g daily of fish oil providing 3000 mg EPA+DHA for 6 to 8 weeks, all three experienced

complete or virtually complete resolution of symptoms, allowing discontinuation of systemic corticosteroid therapy. Symptoms relapsed after dose reduction.[112]

DIAGNOSIS

Physical Evaluation and History

A thorough history and physical evaluation are imperative for the proper diagnosis of urticaria and should include a careful history listing all medications, supplements, and botanicals. Evaluation should also detail travel, recent infection, occupational exposure, timing and onset of lesions, morphology, associated symptoms, family medical history, and pre-existing allergies. Contact sensitivities such as latex allergy[113] and exposure to physical stimuli should be documented. History of tattoos should be explored for possible correlations. A diet and lifestyle diary that chronicles date and time, foods eaten, major activities, bowel and urine habits, and stress should be gathered in order to fully to characterize the potential temporal relationships of urticaria with specific ingested foods and activities. A comprehensive physical examination can also uncover important diagnostic clues that may help to diagnose comorbidities.

Laboratory Testing

The appropriate role of laboratory testing and studies in chronic urticaria remains controversial.[10] One review of 29 large studies of laboratory testing in chronic urticaria, involving 6462 patients, demonstrated no relationship between numbers of identified diagnoses and numbers of performed tests.[114] This review noted that systemic diseases (which excluded physical urticarias, allergens, infections, and psychological causes) were identified and believed to be related causally to the urticaria only in 1.6% of patients; these diseases included vasculitis, thyroid disease, systemic lupus erythematosus, other rheumatic disease, hereditary angioedema, and hematologic or oncologic conditions.

The use of screening skin testing for food allergies is also controversial.[10,59] It is known that many patients with food-induced urticaria have diagnosed themselves without the help of a specialist. Skin testing for foods in the patient with chronic urticaria is fraught with false-positive and false-negative results. In the absence of a specific history suggestive of a particular food allergy (history of exposure and time course of subsequent symptoms consistent with typical food allergy), such skin testing can be counterproductive, particularly in patients with dermatographism and "twitchy" mast cells.[10]

If symptoms do not remit after proper history and physical examination have been performed and the therapies listed here have been tried, it may be useful to perform a complete blood count with differential, urinalysis, erythrocyte sedimentation rate measurement, liver function tests, antinuclear antibody titer measurements, and thyroid panel with antithyroid autoantibody measurements. These tests may help ferret out most of the uncommon cases with a detectable but unsuspected underlying cause (such as infectious, parasitic, rheumatic, thyroid, and hematologic conditions).

Although not recommended for most cases of chronic urticaria, some medical literature suggests that a skin biopsy specimen can provide useful information to rule out urticarial vasculitis when this condition is suspected clinically.[10] Research laboratories can also focus on autoimmune urticaria and detect the presence of anti-FcεRIα autoantibodies, but these tests are neither standardized nor routinely or widely available. Some urticaria specialists assess for such autoantibodies clinically and indirectly through autologous serum skin testing, whereby the patient's serum is centrifuged and used for skin-prick testing in this form of a semiquantitative functional assay for autoimmunity to IgE or IgE receptors bound to cutaneous mast cells. This test is about 75% sensitive and 74% specific for the presence of the autoantibodies.[10]

THERAPEUTIC APPROACH

Regarding conventional management of chronic urticaria, patients often show incomplete responses to antihistamines and are often uncomfortable and frustrated by chronic pruritus. Some cases do respond to systemic corticosteroids, but the potentially serious side effects associated with these medications preclude their safe chronic use.[10] The wide variety of drugs used singly or in combination for this condition is a testament to conventional medicine's inability to fully address and treat the symptoms as well as the underlying causes of urticaria; see Box 211-3 for a complete list of conventional drugs used to treat urticaria.

The basic natural therapeutic approach involves the identification and control of all factors that promote the patient's urticarial response. Obtaining a careful and thorough history is paramount to this process. Acute urticaria is usually a self-limited disease, especially once the eliciting agent has been removed or reduced. Chronic urticaria also responds to the removal of the eliciting agent or agents if they can be identified. In severe anaphylaxis, appropriate emergency care procedures should be followed.

Diet

Although rarely used in conventional medical therapy, even the standard medical literature is beginning to recognize the wisdom of the elimination diet.[10] An elimination or oligoantigenic diet is of utmost importance in the treatment of chronic urticaria (see Chapters 19 and 54). The diet should eliminate not only suspected allergens but also all food additives.

The strictest elimination diets allow only water, lamb, rice, pears, and vegetables. Those foods most commonly associated with inducing urticaria (i.e., milk, eggs, chicken, fruits, nuts, and additives) should definitely be avoided.[66] Foods containing vasoactive amines should be eliminated even if no direct allergy to them is noted. The primary foods to eliminate are cured meat, alcoholic beverages, cheese, chocolate, citrus fruits, and shellfish.

The importance of eliminating food additives cannot be overstated. If food additives do in fact increase the number of perivascular mast cells in the skin, they may also do the same in the small intestine, thereby greatly raising the risk of developing a "leaky gut."

Also of value is control of arachidonic acid–dependent prostaglandins through the use of a diet low in animal fat.

Supplements

- Vitamin C: 1 g three times/day
- Vitamin B_{12}: 1000 mcg intramuscularly per week
- Quercetin: 200 to 400 mg 20 minutes before meals
- Fish oil: 3000 mg EPA+DHA a day

Psychological

The patient should perform relaxation techniques daily. Listening to audio relaxation programs may be an appropriate way to induce the desired state. Appropriate "mind-body" management programs

BOX 211-3 **Drugs Used to Treat Urticaria**

Second-generation histamine$_1$ (H_1) receptor antagonists:
- Cetirizine (Zyrtec)
- Fexofenadine (Allegra D)
- Desloratadine (Clarinex)
- Loratadine (Claritin)

First-generation H_1 receptor antagonists:
- Hydroxyzine (Atarax)
- Diphenhydramine (Benadryl)
- Ranitidine (Zantac)

H_1 and histamine$_2$ (H_2) receptor antagonists:
- Doxepin (Sinequan)—sedation, increased appetite, resultant weight gain
- Cyproheptadine (Periactin)
- Cimetidine (Tagamet)—interference with hepatic microsomal enzymes and androgen receptors

Leukotriene modifiers:
- Montelukast (Singulair)
- Zafirlukast (Accolate)
- 5-Lipoxygenase inhibitors (e.g. Zileuton (Zyflo))
- Nonsteroidal antiinflammatory drugs

Corticosteroid:
- Prednisone

Immunosuppressive treatments:
- Cyclosporin A
- Tacrolimus
- Azathioprine
- Cyclophosphamide
- Mycophenolate mofetil
- Plasmapheresis
- Intravenous immunoglobulin

Others:
- Calcium channel blocker antihypertensives
- Hydroxychloroquine
- Dapsone
- Colchicine
- Methotrexate
- Sulfasalazine
- Intramuscular gold
- Capsaicin
- Impeded androgens
- Warfarin

Data from references 1 and 8.

leading to good clinical outcomes for chronic urticaria is dependent on the clinician's ability to discern unique patient "stories."

Physical Medicine

Daily sunbathing for 15 to 20 minutes or the use of an ultraviolet solarium, especially in chronic physical urticaria, is recommended. Tepid oatmeal baths may also help calm urticarial symptoms, but caution should be exercised with physical modalities when physical triggers such as heat, cold, and water are salient for a particular patient.

Traditional Chinese Medicine/Acupuncture

Acupuncture can work quite well together with naturopathic therapies to treat the causes and symptoms of urticaria.

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CHAPTER 212

Uterine Fibroids

Tori Hudson, ND

CHAPTER CONTENTS

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DIAGNOSTIC SUMMARY

- Most are asymptomatic.
- Symptoms include vague feeling of discomfort, pressure, congestion, bloating, heaviness; can include pain with vaginal sexual activity, urinary frequency, backache, abdominal enlargement, and abnormal bleeding.
- Abnormal bleeding occurs in 30% of women with fibroids.
- Fibroids can undergo degenerative changes with necrosis, resulting in cystic degeneration.
- Calcification can occur.
- Examination by pelvic palpation and/or pelvic ultrasonography.
- The main diagnostic consideration is differentiating a possible fibroid from ovarian malignant tumor, abscess in the fallopian tube/ovarian region, diverticulum from the colon, pelvic kidney, endometriosis, adenomyosis, congenital anomalies, and uterine sarcoma.

GENERAL CONSIDERATIONS

Uterine fibroids are not actually fibrous but consist of muscle, probably both smooth muscle cells and connective tissue. The growth of fibroids is thought to be stimulated by estrogen. The tendency of fibroids to arise during the reproductive years, grow during pregnancy, and regress postmenopausally implicates estrogen as one factor in their cause and growth. Fibroids often demonstrate a growth spurt in the perimenopausal years, likely because of anovulatory cycles with a relative estrogen excess that commonly occurs irregularly during this time.

Uterine fibroids occur in 20% to 25% of women by age 40 and in more than 50% of women overall, with African American women experiencing a higher incidence. Fibroids are the most common indication for major surgery in women and the most common solid tumor in women.

The cause of uterine fibroids remains poorly understood. Increases in local estradiol concentration within the fibroid itself may play a role in its cause and growth. Concentrations of estrogen receptors in fibroid tissue are higher than in the surrounding myometrium but lower than in the endometrium.

Fifty percent to 80% of fibroids do not cause symptoms. Abnormal bleeding, including menorrhagia and metrorrhagia, occurs in 30% of women with fibroids. Other symptoms are pelvic pressure, bloating, congestion, urinary frequency, backache, and pain with vaginal sexual activity. Sometimes the urinary complications may be a cause for concern because they may be due to compression of the ureter, which can then cause hydronephrosis. Fibroids are thought to be the cause of 2% to 10% of cases of infertility. Large fibroids can also interfere with a normal pregnancy by interfering with fetal growth or causing premature rupture of membranes, retained placenta, postpartum hemorrhage, abnormal labor, or an abnormal fetal lie. The incidence of miscarriage due to fibroids is estimated to be two to three times greater than that in women without fibroids.

Fibroids can undergo degenerative changes. One type of degenerative change occurs when the continued growth of the fibroid outpaces the blood supply. A more common type of degenerative change involves a loss of cellular detail as a result of a decrease in the tumor's vascularity. Necrosis leads to cystic degeneration. Calcification can occur over time and is usually seen in postmenopausal women.

DIAGNOSIS

On the basis of mitotic count, nuclear atypia, and other morphologic features, uterine smooth muscle tumors can be classified as leiomyomas, smooth muscle tumors of uncertain malignant potential, and leiomyosarcomas.

A presumptive diagnosis of fibroids can often be made simply with a thorough history and adequate pelvic examination. An enlarged firm uterus or a uterus with irregular edges is the main palpation finding. The diagnostician must distinguish a possible fibroid from an ovarian malignant tumor, fallopian tube or ovarian region abscess, diverticulum, pelvic kidney, endometriosis, congenital anomalies, pelvic adhesions, and a retroperitoneal tumor (rare). Not all of these distinctions can be made with a medical history, physical examination, and pelvic ultrasonography. Submucosal pedunculated fibroids can be visualized with laparoscopy, as can intramural and subserous fibroids.

Uterine fibroids are classified according to their location, as follows:

- Submucosal (just under the endometrium)
- Intramural (within the uterine muscle wall)
- Subserosal (from the outer wall of the uterus)
- Interligamentous (in the cervix between the two layers of the broad ligament)
- Pedunculated (on a stalk, either submucosal or subserous)

THERAPEUTIC CONSIDERATIONS

Natural therapies for uterine fibroids largely involve managing any troublesome symptoms. Women who are seeking an alternative to surgical intervention for uterine fibroids will not find a reliable alternative to shrink their tumors. The following therapies may be able to help to keep a fibroid from growing larger and are usually able to successfully resolve or improve most symptoms related to the tumor. Expectations to reduce the size of fibroids must be low, although there are individual case reports of such results. Reduction in fibroid size due to treatment is difficult to assess, especially in perimenopausal women in their 40s, who at some point will have lower endogenous estrogen production with resultant diminution of the fibroid.

Diet

No dietary approach is known to prevent or shrink uterine fibroids. However, there are very strong rationales for several dietary interventions. For example, a diet high in saturated fats is associated with higher blood levels of estrogen and therefore could have the potential to exacerbate fibroids. Also, low-fiber diets are associated with elevated estrogen levels and poor excretion of estrogen. Dietary change by itself is unlikely to reduce the size of fibroids, but good dietary habits are still important for general health; moreover, they may reduce some of the gastrointestinal symptoms that can be associated with large fibroids or pedunculated fibroids and an enlarged uterus. Clinical observation has demonstrated that natural therapies work best in the context of a healthy lifestyle, including dietary changes. Improving one's diet can help to decrease heavy bleeding or the pain and discomfort caused by the fibroids. In addition to these potential benefits, dietary improvements enhance general well-being.

The tradition of naturopathic medicine holds firmly to the influence of the health of the liver on the health and vitality of an individual. The liver metabolizes estrogen, which can be eliminated from the body by converting it to estrone and finally to estriol, a weaker form of estrogen that has very little ability to stimulate the uterus. Failure of the liver to effectively metabolize estradiol may be one mechanism by which the uterus becomes overestrogenized and responds with fibroid growths.

Saturated fats, sugar, caffeine, alcohol, and "junk foods" are presumably problematic in two main ways. First, they interfere with the body's ability to metabolize estradiol to estrone to estriol. Second, some of them are deficient in B vitamins or interfere with B-vitamin metabolism. If B vitamins are lacking in the diet, the liver will lack some of the raw materials it needs to carry out its metabolic processes and regulate estrogen levels.

Whole grains—such as brown rice, oats, buckwheat, millet, and rye—are excellent sources of B vitamins. Whole grains also help the body excrete estrogens through the bowel. The role of whole-grain fiber in lowering estrogen levels was first reported in 1982.[1] This study found that vegetarian women who eat a high-fiber, low-fat diet have lower blood estrogen levels than omnivorous women with low-fiber diets. Once again, the logic of a high-fiber diet would have implications in preventing and perhaps reducing uterine fibroids because of the stimulating effect of estrogen on fibroid growth.

A high-fiber diet may also help to relieve some of the bloating and congestion sometimes associated with fibroids. Fiber, by bulking up the stool and regulating bowel movements, may relieve some of these symptoms. Some women have a hard time tolerating increased fiber in their diets because their digestive function is otherwise compromised.

Because there is an association between having uterine fibroids and a fourfold increase in the risk of endometrial cancer,[1] three dietary considerations stand out above the others: to increase dietary fiber, lower dietary fat, and increase the intake of soy products and other legumes. A case-control study in a multiethnic population (Japanese, white, Native Hawaiian, Filipino, and Chinese) examined the roles of dietary soy, fiber, and related foods and nutrients as related to the risk of endometrial cancer.[2] A total of 332 women with endometrial cancer were compared with women in the general multiethnic population, and all were interviewed by means of a dietary questionnaire. The researchers found positive associations between a higher level of fat intake and endometrial cancer, between a higher level of fiber intake and a reduction in risk for endometrial cancer, and between a high consumption of soy products and other legumes and a decreased risk of endometrial cancer. Similar reductions in risk were found for a greater consumption of other sources of phytoestrogens, such as whole grains, vegetables, fruits, and seaweeds. The researchers concluded that plant-based diets low in calories from fat, high in fiber, and rich in legumes (especially soybeans), whole-grain foods, vegetables, and fruits reduce the risk of endometrial cancer. These dietary associations may explain at least in part the lower rates of uterine cancer in Asian countries as compared with the United States.

Some have suggested that because soy foods are high in phytoestrogens (specifically isoflavones), which have a weak estrogenic effect, women with uterine fibroids or endometrial cancer should avoid phytoestrogens. This issue deserves some clarification. Soy phytoestrogens do not appear to have an estrogenic effect on the human uterus except in doses higher than 150 mg isoflavones daily in postmenopausal women. They appear to be selective in terms of the tissues on which they have an estrogenic effect and the tissues or organs on which they have an antiestrogenic effect. Soy foods may be analogous to a newer class of drugs called selective estrogen receptor modulators: they act one way in one part of the body and another way in a different part of the body. It seems that in the uterus, soy isoflavones have an antiestrogenic effect.

Nutritional Supplements

Many of the symptoms related to uterine fibroids can be effectively treated with natural therapies. This section presents nutritional supplements that may control or diminish the growth of fibroids. Unfortunately, these recommendations are based more on tradition, theory, logic, and clinical experiences than on scientific evidence.

Lipotropic Factors

Supplements such as inositol and choline exert a lipotropic effect—that is, they promote the removal of fat from the liver. Lipotropic supplements usually are a combination vitamin-and-herbal formulation and sometimes an animal liver extract designed to support the liver's function in removing fat, detoxifying the body's wastes, detoxifying external harmful substances (pesticides, fossil fuels, etc.), and metabolizing and excreting estrogens. These lipotropic products vary in their formulations, depending on the manufacturer, but they are all similar and are intended for the same uses. Many now contain anticancer phytonutrients found in cabbage-family vegetables such indole-3-carbinol (I3C), diindoylmethane (DIM), and sulforaphane. Research has shown that these compounds help to breakdown cancer-causing forms of estrogens to non-toxic forms making them especially important in women with uterine fibroids.[2a,2b]

Pancreatic Enzymes

Supplementation with pancreatic enzymes is usually done to treat pancreatic insufficiency with symptoms of abdominal bloating, gas, indigestion, undigested food in the stool, and malabsorption. The logic for their use in the treatment of uterine fibroids is that the pancreatic enzymes help digest the fibrous/smooth muscle tissue and thus dissolve the fibroids. When used for this purpose, the pancreatic enzyme supplement must be taken between rather than with meals.

Botanical Medicines

Traditional Herbs

Many plants have been used in traditional herbal medicines in an attempt to treat women with uterine fibroids. The plants and herbal formulations described here are used in attempting to reduce uterine fibroids or slow their growth. They have been anecdotally reported to achieve modest success in reducing the size and number of uterine fibroids. There is no scientific research to document the outcomes, but the protocol is presented here as an option.

Scudder's Alterative. Scudder's alterative should be used at 30 to 40 drops in a small amount of warm water three times daily. Its components are as follows:

- Corydalis tubers *(Dicentra canadensis)*
- Black alder bark *(Alnus serrulata)*
- Mayapple root *(Podophyllum peltatum)*
- Figwort flowering herb *(Scrophularia nodosa)*
- Yellow dock root *(Rumex crispus)*

Compounded Echinacea/Red Root.

- Echinacea (*Echinacea* spp.)
- Red root *(Ceanothus americanus)*
- Baptisia root *(Baptisia tinctoria)*
- Thuja leaf *(Thuja occidentalis)*
- Stillingia root *(Stillingia sylvatica)*
- Blue flag root *(Iris versicolor)*
- Prickly ash bark *(Xanthoxylum clava-herculus)*

Compounded Fraxinus/Ceonothus. The constituents of compounded *Fraxinus/Ceonothus* are as follows:

- Mountain ash bark *(Fraxinus americanus)*
- Red root *(Ceanothus americanus)*
- Life root *(Senecio aureus)*
- Mayapple root *(Podophyllum peltatum)*
- Helonias root *(Chamaelirium luteum)*
- Goldenseal root *(Hydrastis canadensis)*
- Lobelia *(Lobelia inflata)*
- Ginger root *(Zingiber officinalis)*

Compounded Gelsemium/Phytolacca. Compounded *Gelsemium/Phytolacca* is also known as the Turska formula. It has the following constituents:

- Gelsemium root *(Gelsemium sempervirens)*
- Poke root *(Phytolacca americana)*
- Aconite *(Aconitum napellus)*
- Bryonia root *(Bryonia dioica)*

Other Herbal Extracts to Consider.

- Chaste tree *(Vitex agnus castus)*
- Nettles *(Urtica dioica)*
- Burdock root *(Arctium lappa)*
- Dandelion root *(Taraxacum officinalis)*
- Oregon grape *(Berberis aquifolium)*
- Crila *(Crinum latifolium)*

Crila has been a part of Vietnamese history and folkore for generations. Numerous benefits of *Crinum* have been reported over the years but none had been clinically studied until recently. Of the 12 varieties of Crila, one specific variety in particular, the *C. latifolium* "Tram," named after the leading researcher, has been studied in women with uterine fibroids. A 3-month study of 195 women with uterine fibroid tumors was conducted in three hospitals in Vietnam in 2007. Crila decreased the size or stopped the growth of the fibroid tumors in 79.5% of the women. In 20.5%, tumor growth continued at a very slow rate. Whereas a heavy menstrual flow was reported by 36% of the women before taking Crila, this had decreased to only 1% after treatment. Side effects reported were slight, including nausea, headache, vaginal dryness, and hot flashes, but these decreased over time.[3]

Topical Applications.

- Poke root oil: Rub onto the belly over the uterus nightly before bed for 1 month then two to three times weekly.
- Castor oil packs: Apply over pelvis three to five times weekly.

Herbal Phytoestrogens

Three types of phytoestrogens are found in medicinal plants: resorcylic acid lactones, steroids and sterols, and phenolics. Phytoestrogens are present in virtually every plant in at least modest levels, with some plants having particularly high levels. Resorcylic acid lactones are not true phytoestrogens because they come from plant mold contamination rather than being synthesized by the plant.

Steroids are the classic steroidal estrogens, estradiol and estrone, which are found in very minute amounts in a few plants such as apple seeds, date palms, and pomegranate seeds in the range of 1 to 10 parts per billion.[4-6] Diosgenin is a steroid derivative found in at least 20 plants, including wild yam species.

Beta-sitosterol is the most common phytosterol and hence is distributed widely throughout the plant kingdom. It is found in plants oils such as wheat germ oil, cottonseed oil, and soybean oil and is the dominant phytosterol found in garlic and onions. Herbal sources include licorice root, saw palmetto, and red clover. Stigmasterol is closely related to beta-sitosterol. Soybean oil is an important source of stigmasterol; it is a better source for laboratory

synthesis of progesterone than beta-sitosterol. Some herbal sources are burdock, fennel, licorice, alfalfa, anise, and sage. The phenolic phytoestrogens are members of the largest single family of plant substances, the flavonoids, which has over 4000 individual members. The term *flavonoid* derives from the Latin *flavus,* meaning "yellow," because the flavonoids are responsible for the yellow, red, white, and blue pigments in plants.

Phenolics include the following substances:

- Isoflavones, which are present in higher concentrations in legumes, especially soybeans, than in any other plants.
- Coumestans, of which coumestrol is the one known estrogenic member. Coumestrol is approximately six times more estrogenic than the isoflavones.[7] Red clover is a medicinal plant with considerable coumestans.
- Lignans, found in high concentrations in grains and cereals and highest in flaxseeds.

There has been some concern and controversy about how phytoestrogens affect the uterus as well as whether, because they have an estrogenic effect, they should be avoided in women with uterine fibroids or endometrial cancer. Research has shown that phytoestrogens actually reduce the incidence of uterine cancer.

Most of the research on the effects of phytoestrogens on the uterus is found in relation to the agriculture industry and the health of grazing animals. In the 1940s, it was reported that the grazing of sheep on red clover in Australia was responsible for their infertility.[8] A Finnish study of pasture legumes identified red clover as containing the highest concentrations of phytoestrogens[9] and showed that abundant intake of red clover resulted in fertility problems in cattle.[10]

In one study on the effects of phytoestrogens in sheep, it was noted that both coumestans and isoflavones produce changes similar to stimulation with steroidal hormones such as estradiol in all of the target organs.[11] Among these changes was an increase in uterine weight. Other investigators have examined the binding of phytoestrogens to the uterus and vagina. Coumestrol has temporarily enhanced the uptake of estradiol by the uterus and vagina only 1 hour after injection into mice.[12] The researchers of this study also noted that coumestrol actually inhibited the uptake of estradiol by the uterus in a prolonged manner; they postulated that there was actually an inhibitory effect at the estradiol receptor sites. Other researchers have observed that coumestans and isoflavones compete with estradiol for uterine receptor sites but have less affinity for them than estradiol does.[13]

Coumestrol has been found to increase uterine weight at a 100-mcg dose when given to rats at a certain time in the development of glands.[14] The estrogenic effect of phytoestrogens appears to be dose-dependent. When given in high enough doses, phytoestrogens have estrogenic effects on all the tissues that are targets of estradiol. Two questions must be answered: What is an excessively high dose and are the observations in animals translatable to humans? One way of answering the first question is to note that countries with a high intake of phytoestrogens (Japan, Thailand, China) do not have increased rates of uterine fibroids.

As in the case of breast cancer, data on women of different cultures support the conclusion that soy phytoestrogens are not an estrogen stimulus for the endometrium. Soy is probably an estrogen antagonist in the uterus, at least at doses of less than 150 mg/day, and it is associated with low rates of endometrial cancer in countries where the intake of soy phytoestrogens is high.[15]

One recent study did raise some concern about high doses of soy phytoestrogens and endometrial effects.[16] A total of 298 women completed a 5-year study of either 150 mg/day of soy isoflavones or placebo tablet. Of the women using 150 mg of soy isoflavones, 70% had an endometrium classified as atrophic, versus 81% of those receiving the placebo. The occurrence of endometrial hyperplasia was higher in the soy group versus the placebo group as well (3.37% vs 0%). There were no endometrial cancers in either group. The estrogenic effect was not detectable at 30 months but only at the end of the 5-year study.

Tripterygium wilfordii Hook F

An uncontrolled but well-designed study looked at the efficacy of a traditional Chinese herbal therapy, *T. wilfordii* Hook F, on uterine fibroids.[17] The researchers used several objective measures for clinical response, including ultrasonographic measurement of fibroid size and determination of blood estradiol, progesterone, testosterone, follicle-stimulating hormone, luteinizing hormone, and prolactin levels by radioimmunoassay. Measurements were taken at baseline and 3 and 6 months. Treatment was effective and time dependent; 28% of fibroids responded in 3 to 4 months and 52% in 5 to 6 months. A total of 25 of the 65 patients were amenorrheic during the course of treatment. Compared with pretreatment values, treatment with *T. wilfordii* induced a rise in mean LH and FSH levels and a decrease in mean estradiol and progesterone levels. The researchers speculated that this result was likely due to a reversible inhibitory effect on the ovaries.

Bioidentical Progesterone

Several older studies have suggested that progesterone may inhibit growth of uterine fibroids. Lipschutz[18] demonstrated that progesterone administered to guinea pigs prevented the formation of tumors that would otherwise be induced by estrogen. In 1946, Goodman[19] reported six cases of clinically diagnosed uterine fibroids that regressed after the use of progesterone therapy. In relation to uterine fibroids, the expression and responsiveness of estrogen and progesterone receptor sites to these hormones is a complex issue.[20]

Lee[21] posited that because uterine fibroids are a result of estrogen stimulation and what he calls "estrogen dominance," the problem is a relative progesterone deficiency and the corrective is to use natural progesterone. He asserted that estrogen dominance is a much greater problem than is recognized by conventional medicine:

Because many women in their mid-thirties begin to have nonovulating cycles, they are producing much less progesterone than expected but still producing normal (or more) estrogen. They retain water and salt, their breasts swell and become fibrocystic, gain weight (especially around the hips and torso), become depressed and lose sex drive; in addition, their bones suffer mineral loss and they develop fibroids. All are signs of estrogen dominance relative to a progesterone deficiency. When sufficient natural progesterone is replaced, fibroid tumors no longer grow in size (they generally decrease in size) and can be kept from growing until menopause, after which they will atrophy. This is the effect of reversing estrogen dominance.

The preferred form of natural progesterone for treating fibroids (unless the patient has heavy bleeding) is a topical cream with about 400 mg of progesterone per one ounce of cream. The cream is to be applied one quarter teaspoon, one to two times daily for 1 week after the menses, and then one quarter to one half teaspoon twice daily for the next 2 weeks (the second half of the menstrual cycle). The progesterone cream is not used for 1 week during the menstrual flow. The cream is applied to the inner arms, chest, inner thighs, and/or palms.

Another theory and counteropinion about the relationship of progesterone to uterine fibroids raises some questions about the use of the hormone in women with fibroids. Rein et al[22] at Brigham and Women's Hospital published a report in 1995 stating not only

that is there no evidence of estrogen directly stimulating myoma growth but also that progesterone and progestins promote the growth of fibroids.[22] The report cites the biochemical, histologic, and clinical evidence supporting an important role for progesterone and progestins in the growth of uterine myomas. This comprehensive hypothesis is based on the analysis of many different technical studies, which according to the reviewers suggests that the development and growth of myomas involve a multistep chain of events.

THERAPEUTIC APPROACH

Diet

The patient should consume a diet low in fat and high in fiber, whole grains, flaxseeds, and soy foods while avoiding saturated fats, sugar, caffeine, and alcohol.

Nutritional Supplements

- Lipotropic factors: 1000 mg of choline and 1000 mg of methionine and/or cysteine a day. Alternatively, S-adenosylmethionine (SAMe) can be used at a dosage of 200 to 400 mg a day.
- Choose one or a combination of the following:
 - Indole-3-carbinol: 300 to 600 mg a day
 - Diindoylmethane (DIM): 100 to 200 mg a day taken with food
- Proteolytic enzymes such as mixed enzyme preparations or pancreatin (8-10× USP): 350 to 750 mg between meals three times/day; or Bromelain: 250 to 750 mg (1800 to 2000 MCU) between meals three times/day

Herbal Medicines

- Echinacea/red root compound: 30 drops in a small amount of warm water three times a day
- *Fraxinus*/*Ceonothus* compound: 30 drops in a small amount of warm water three times a day
- Scudder's alternative: 30 to 40 drops in a small amount of warm water three times a day
- Turska formula: 5 drops in a small amount of warm water three times a day

Topical Treatment

- Bioidentical progesterone cream: one quarter tsp twice a day from day 15 to day 26
- Topical poke root oil over uterus every night for 1 month, then once to three times a week

Conventional Medicine Therapies

Where fibroids cause heavy bleeding, medical management with progestogens or oral contraceptives may be used to manage the bleeding. Some fibroids and uteri are large enough that presurgical treatment with leuprolide acetate (Lupron) may facilitate a less radical surgical option. High-intensity focused ultrasound is a new monmedial technique being used to treat fibroids. In addition, selective progesterone receptor modulators are being investigated as a treatment for fibroid pain and bleeding and for reducing the size of fibroids.

Surgery

Some women will have to consider their surgical options, which are based on the size, number, and location of fibroids, as follows:
- Myomectomy
- Laparoscopic surgery for subserous and pedunculated fibroids
- Uterine embolization
- Hysteroscopic resection of submucous fibroids
- Supracervical hysterectomy (some fibroids may lend themselves to a supracervical laparoscopic hysterectomy)
- Laparoscopy-assisted vaginal hysterectomy

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CHAPTER 213

Vaginitis

Tori Hudson, ND

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DIAGNOSTIC SUMMARY

- Increased volume of vaginal secretions.
- Abnormal color, consistency, or odor of vaginal secretions.
- Vulvovaginal itching, burning, or irritation.
- Introitus may show patchy erythema, and vaginal mucosa may exhibit congestion, or petechiae.
- Dysuria or dyspareunia may be present.

GENERAL CONSIDERATIONS

Vaginitis, one of the most common reasons for women to seek medical attention, is the most common gynecologic problem encountered by physicians providing primary care to women. It affects all age groups and has a variety of etiologies. An initial vaginitis may be easily diagnosed if the practitioner uses objective tools and easily treated, but recurrent vaginitis can be among the most troublesome and challenging conditions for both practitioners and patients. Early misdiagnosis leads to repeat office visits as well as inappropriate or delayed treatment. Undetected coinfections or an incorrect diagnosis can also have consequences, sometimes serious, especially in pregnant women.

In addition to causing physical discomfort and embarrassment, vaginitis is medically important for several reasons. It may coexist with cervicitis and may be related to a sexually transmitted infection; some of these organisms may be able to ascend and cause pelvic inflammatory disease (PID). PID may in turn lead to tubal scarring, infertility, or ectopic pregnancy. Chronic asymptomatic vaginal infections have been implicated in recurrent urinary tract infections through their action as reservoirs of the infectious agent.[1,2] Some types of vaginal infections, such as bacterial vaginitis (BV) during pregnancy, are associated with preterm delivery, premature rupture of membranes, amnionitis, chorioamnionitis, and postpartum endometritis; if present at delivery, they may be associated with an increased incidence of neonatal infection, with potentially serious or fatal consequences.

The vaginal ecosystem is an environment consisting of an important relationship between normal endogenous microflora, metabolic products of the microflora and the host, estrogen, and the pH level. The normal microflora of a healthy vagina is made up of numerous microorganisms, including *Candida, Lactobacillus* species, gram-negative aerobic bacteria, and facultative organisms *(Mycoplasma* species and *Gardnerella vaginalis)* as well as obligate anaerobic bacteria (primarily *Prevotella, Peptostreptococcus* species, *Eubacterium* species, and *Mobiluncus*). *Lactobacillus* species dominate the healthy vagina of a reproductive-age woman, and although it is difficult to say with certainty which species are most common, molecular biology methods and at least one study have found that *Lactobacillus plantarum, Lactobacillus rheuteri,* and *Lactobacillus acidophilus* are the most often present.[3] Yet another study has found that the most frequent *Lactobacillius* species were *L. crispatus, L. gasseri, L. jensenii,* and *L. rhamnosus*.[4]

The normal microflora of the vagina, dominated by lactobacilli, is capable of inhibiting the adhesion and growth of pathogens; it depletes nutrients available to pathogens and modulates the host immune response and vaginal environment.[5,6] Lactobacilli act via at least three mechanisms: (1) they help to produce lactic acid and other acids as a by-product of glycogen metabolism in the vaginal vault cells and provide a normal vaginal acidic environment of 3.5 to 4.5. Many pathologic microbes

cannot survive or flourish in this pH. (2) Many species of lactobacilli produce hydrogen peroxide, which also inhibits microbial growth. (3) The lactobacilli are competitive with the pathogenic microorganisms for adherence to the vaginal epithelial cells.

TYPES OF VAGINITIS

Vaginitis is commonly classified as being caused by yeast, bacterial vaginosis (BV), *Trichomonas vaginalis,* or atrophic vaginitis. However, these traditional classifications have left gaps in the proper diagnosis and treatment of several atypical scenarios of vaginitis. Experts in this field have proposed three additional categories, which include desquamative vaginitis (DIV), *Mobiluncus* vaginitis and lactobacillosis. Even with the addition of these three categories, there still appear to be two patterns of altered flora in symptomatic women that do not fall into any of the other designated categories. Stuart Fowler of the Mayo Clinic in Scottsdale, Arizona, had proposed two additional categories of altered flora: the first he describes as noninflammatory vaginitis (NV) and the second as inflammatory vaginitis (IV). With the recognition of these two patterns of altered flora, clinical presentations that do not fit the usual criteria for the diagnosis of BV, *Trichomonas, Candida,* atrophic vaginitis, DIV or lactobacillosis can now be recognized and treated. Details regarding these additional types of vaginitis can be found in Fowler's published paper.[7]

Atrophic Vaginitis

Atrophic vaginitis is primarily a problem of perimenopausal and postmenopausal women, although it can also occur in prepubertal girls owing to poorly estrogenized vaginal and vulvar tissue and in postpartum women because of sudden declines in their hormone levels. The vagina undergoes several changes with declining estrogenic stimulation, including a decrease in *Lactobacillus* species in the vagina, a shift to a more alkaline pH, thinning of the vaginal wall, less lubrication, more easily irritated and inflamed tissue, and greater susceptibility to infection. The most commonly reported symptoms are itching or burning and a thin watery discharge, which may occasionally be tinged with blood. (Note that any vaginal bleeding in a postmenopausal woman requires a complete evaluation to rule out endometrial hyperplasia and endometrial carcinoma.) The pH is typically equal to or greater than 5.5, but there is no infection. Other common complaints include dyspareunia and/or vaginal dryness with vaginal sexual activity.

Infectious Vaginitis

More than 90% of vaginitis in reproductive-aged women is caused by BV, candidiasis, or trichomoniasis. BV is the most common of the three. Less common causes of infectious vaginitis include herpes simplex virus, gonorrhea, and *Chlamydia*. Infections of the vulva—including folliculitis, hydradenitis, scabies, condyloma, herpes, syphilis, human papillomavirus and *Candida*—can cause local itching and/or discharge. Rare conditions of the vulva causing itching and/or discharge include chancroid, lymphogranuloma venereum inguinale, and molluscum contagiosum.

Infectious vaginitis (e.g., trichomoniasis) may be sexually transmitted or may arise from a disturbance to the delicate ecology of the healthy vagina (e.g., *Candida* and BV). Vaginal "infections" frequently involve common organisms found in the cervix and vagina of many healthy asymptomatic women.[8]

The unifying factor in the pathogenesis of vaginal infections is not so much a matter of the organisms present in the patient's genital tract but rather of what happens to the patient to make her susceptible to infection.

Factors influencing the vaginal environment are the pH, glycogen content, glucose level, presence of other organisms (particularly lactobacilli), estrogen, semen exposure, nanoxynol-9 spermicide exposure, douching, menstrual blood, and presence of antibodies and other compounds in the vaginal secretions. Many of these factors are, in turn, affected by the woman's internal milieu and general health.

Immune dysfunction may predispose a woman to increased infections, including vaginal infections. Depressed immunity may occur as a result of nutritional deficiencies, medications (e.g., steroids), pregnancy, or serious illness such as HIV. Other medical conditions may predispose a woman to infectious agents, such as diabetes mellitus, hypothyroidism, leukemia, Addison's disease, Cushing's syndrome, and pregnancy.

Predisposing factors for sexually transmitted infections include a higher number of sex partners, unsafe sex, birth control pills, steroids, antibiotics, tight-fitting garments, occlusive materials, douches, chlorinated pools, perfumed toilet paper, and decreased levels of lactobacilli in the vagina. Table 213-1 summarizes the diagnostic differentiation of the most common causes of infectious vaginitis.

Trichomonas vaginalis

Trichomonas vaginalis is a flagellated protozoan slightly larger than a leukocyte. It may be found in the lower urogenital tract of both men and women. Humans appear to be its only host, and sexual transmission appears to be its primary mode of dissemination. *Trichomonas* does not invade tissues and rarely causes serious complications. The most common symptom is leukorrhea associated with itching and burning. The discharge is frequently malodorous, greenish yellow, and frothy. The "strawberry cervix" with punctate hemorrhages is found in only a small percentage of patients with *Trichomonas* infection. Trichomonads grow optimally at a pH of 5.5 to 5.8.[9] Thus, conditions that elevate the pH, such as increased progesterone, will favor overgrowth of *Trichomonas*. Conversely, a vaginal pH of 4.5 in a woman with vaginitis is suggestive of an agent other than *Trichomonas*. A saline wet mount of fresh vaginal fluid demonstrates the presence of small motile organisms to confirm the diagnosis in 80% to 90% of symptomatic carriers.[10,11]

Candida albicans

Both the relative frequency and the total incidence of candidal vaginitis have risen dramatically, 2.5-fold, in the past 20 years. This increase parallels a declining incidence of gonorrhea and trichomoniasis.[12] Several factors have contributed to this increased incidence, chief among them being the greater use of antibiotics. The alterations that antibiotics make in both intestinal and vaginal ecology favor the growth of *Candida*. In the 1970s, Miles et al[11] found a 100% correlation between genital and gastrointestinal *Candida* cultures, leading to the suggestion that significant intestinal colonization with *Candida* may be the single most significant predisposing factor in vulvovaginal candidiasis. However, this suggestion has not been confirmed by adequate research.

Steroids, oral contraceptives, and the continuing rise in incidence of diabetes mellitus all contribute to the problem. *Candida* is 10 to 20 times more common during pregnancy owing to the elevated vaginal pH, increased vaginal epithelial glycogen, elevated blood glucose, and intermittent glycosuria. Yeast infections are three times more prevalent in women wearing pantyhose than those wearing cotton underwear because the pantyhose prevent drying of the area.[13]

TABLE 213-1 **Diagnostic Differentiation of the Common Causes of Infectious Vaginitis**

	CANDIDA	NON-SPECIFIC VAGINITIS	TRICHOMONAS	TRICHOMONAS	HERPES	CHLAMYDIA
Keynote symptoms	Itching	Odor	Odor and itching	Asymptomatic or cervicitis	Vesicles or ulcers	Asymptomatic
Discharge						
pH	<4.5	>4.5	>5.0	<4.5	<4.5	<4.5
Odor	None	Fishy/amines	May be fishy	None	None	None
Appearance	Curdy, adherent, scant to thick	Gray, homogeneous	Greenish, yellow, frothy	Mucopurulent cervicitis	None	None
Pelvic examination	Adherent white patches with an erythematous border	Unremarkable	May show petechial lesions on cervix or vagina mucosa; a "strawberry cervix"	Cervical discharge; may have adenexal tenderness	Small multiple vesicles or ulcers on cervix or vulva	Unremarkable or may show signs of pelvic inflammatory disease
Microscopic examination	Mycelia (10% KOH)	"Clue cells"; few white blood cells (WBCs)	Motile flagellated organisms; few WBCs	Many WBCs with gram-negative intracellular diplococci	Unremarkable	Unremarkable
Culture media	Sauerbaud	Blood culture media	Diamond	Thayer-Martin	Live cell	Live cell or antibody test

A woman who has four or more episodes of vulvovaginal candidiasis within 1 year is classified as having recurrent disease. Many cases of recurrent yeast infections may be caused by non-*albicans* strains of *Candida*. These resistant strains have become more problematic in recent years as women have been using more and more antifungal agents (see Box 213-1). There are three main theories to explain why women have recurring yeast vaginitis: (1) the intestinal reservoir theory, which hypothesizes that a patient's reinoculation is due to *Candida* populating in the gastrointestinal tract and migrating into the vagina; (2) the sexual transmission theory, which points to the possibility that the sex partner is the source of the recurrence; and (3) the vaginal relapse theory, which maintains that some women retain small numbers of yeasts, even after treatment, that later cause a resurgence of symptoms. A considerable body of research supports this last theory.[14,15] These studies include immunologic research suggesting that women with recurrent infections have an abnormal immune response to infection, which leaves them susceptible to further episodes.[16]

The primary symptom of candidal vaginitis is vulvar itching, which can be severe. Burning of the vulva may also be experienced and can be exacerbated by urination or vaginal sexual activity. It is also common to have an increase or change in the consistency of the vaginal discharge. In a classic case, this is associated with the presence of a thick, curdy, or "cottage cheese" discharge that adheres to the vaginal walls. The presence of such a discharge is strong evidence of a yeast infection, but its absence does not rule out *Candida*. Fewer than 20% of symptomatic patients with candidal infection actually display classic thrush patches. Other clues to a candidal etiology are the presence of erythema of the vulva and excoriations due to scratching. The vaginal pH is not usually altered. Neither the character of the discharge nor the symptomatology is sufficient alone to make a diagnosis of *Candida*. A wet mount in saline or 10% KOH should always be performed and the presence of mycelia confirmed. Budding forms of yeast may be found in both normal and symptomatic vaginas, but the mycelial stage is found only in symptomatic women.

BOX 213-1 **Factors Predisposing to Candidal Vaginitis**

- Allergies
- Antibiotics
- Diabetes mellitus
- Elevated vaginal pH
- Gastrointestinal candidiasis
- Oral contraceptives
- Pantyhose
- Pregnancy
- Steroids

Bacterial Vaginosis

The term *bacterial vaginosis* has now been used most often to describe a shift in flora from a predominance of lactobacilli to a predominance of anaerobes and facultative bacteria, which results in a degradation of the mucins that form a natural gel barrier on the vaginal epithelium. This destruction of the mucin layer causes a vaginal discharge characteristic of BV. In addition, destruction of these mucins exposes the cervical epithelium and allows other organisms to affect the cervix, resulting in the appearance of clue cells. The changes on the epithelial surface also cause immunologic shifts. Women with BV have an upregulation of interleukin-1-beta and a decrease in protectant molecules such as secretory leukocyte protease inhibitor.

Three main factors have been identified to explain how the shift from a lactobacilli-dominant environment to one in which the anaerobes and facultative bacteria dominate and therefore why some women experience BV—sexual activity, douching, and the absence of peroxide-producing lactobacilli in the vagina. A new sex partner and frequent sexual activity are associated with an increased incidence of BV. Overall, sexual transmission of BV is not well understood. It may not be truly sexually transmitted but rather may occur by various mechanisms other than the sexual transmission of pathogens. Routine douching is associated with a loss of vaginal

lactobacilli and the occurrence of BV. Women who douche regularly have BV twice as often as women who do not.[17] It is possible that women with an absence of peroxide-producing lactobacilli in the vagina did not have the normal inhabitation of lactobacilli at menarche, or perhaps the lactobacilli were present but were eliminated through the use of broad-spectrum antibiotics.

Other factors have been associated with the development of BV. Cigarette smoking is associated with BV but may be related to the downregulation of the immune response. Racial background has also been associated with BV. Hispanic women are 50% more likely to have BV, and African American women are twice as likely.[18] Although the reasons for these differences are not clear, we do know that African American women practice douching twice as often as white women and that African American women are less likely to have lactobacilli in the vagina.

Examination for BV involves a medical history, observation of the discharge, and determination of vaginal pH. In the woman with symptomatic BV, the vagina has a fishy odor. The characteristic discharge is thin, dark, or dull gray. Itching is not common with BV but may be present if there is a profuse discharge. A whiff test should be performed, and a wet mount test to detect clue cells and observe the vaginal flora. An abundance of various bacteria and the absence or decrease in lactobacilli is consistent with a diagnosis of BV. The numbers of bacteria rise from 100-fold to 1000-fold. For a diagnosis of BV to be made, three of the following four criteria must be met:

- Thin, dark or dull gray, homogeneous, malodorous discharge that adheres to the vaginal walls
- Vaginal pH greater than 4.5
- Positive KOH (whiff/amine) test result
- Presence of clue cells on wet mount microscopic examination

The pH is elevated to 5 to 5.5 in most cases, and there appears to be a correlation between elevated pH and the presence of odor.[19]

When a patient has four or more BV episodes in a year, her underlying problem is most likely an inability to re-establish a normal vaginal ecosystem with the dominant lactobacilli. There is no definition of recurrent BV, but most clinicians would probably agree that more than four episodes in a year would define the disorder. About 30% of women experience a recurrence of symptomatic BV within 1 to 3 months, and about 70% have a recurrence within 9 months.[20] It is not always clear whether the recurrence represents a relapse or a reinfection. Another possibility is that a woman may be asymptomatic at times but, because of the abnormal vaginal ecosystem, she has a chronic underlying condition, so that she is sometimes symptomatic and at other times is not. Women who are asymptomatic yet have no lactobacilli are four times more likely to experience BV. Unfortunately we do not have a proved treatment for asymptomatic women.

There are potential significant consequences of altered vaginal flora in addition to susceptibility to BV. Women with BV and without sufficient lactobacilli are more susceptible to human immunodeficiency virus (HIV) and gonorrhea.[21,22] PID is also associated with BV. There is also now good evidence that the organisms in pregnant women with BV can ascend the genital tract and cause preterm delivery, and such women are more likely to have postpartum endometritis. Women with BV are also at increased risk for infection after gynecologic surgery.

THERAPEUTIC CONSIDERATIONS

Dietary Considerations

The internal milieu of the vagina is a reflection of the condition of the entire body. Vaginal secretions are continuously released that affect and are affected by the microbial flora. These secretions contain water, nutrients, electrolytes, and proteins, such as secretory immunoglobulin (Ig) A. The quantity and character of these components are altered by hormonal and dietary factors. A general healthful diet is recommended in all cases to ensure the availability of all nutrients in sufficient quantity to optimize the body's ability to respond to changing conditions. A well-balanced diet low in fats, sugars, and refined foods is particularly important in vaginitis due to infectious organisms, particularly *Candida.* Patients with depressed immunity are susceptible to higher rates of infection, particularly those due to *Candida, Trichomonas,* and herpes (see Chapter 56 for further discussion of the effects of diet on immune function).

Nutrients particularly important for proper immune function are zinc; vitamins A, C, and E; manganese; and vitamin B complex.

A diet high in lysine-containing foods and low in arginine-containing foods reduces the number and severity of herpetic outbreaks. However, many of the foods that are high in lysine are animal products, which are also high in fats. A low-arginine diet combined with lysine supplements ensures adequate levels of lysine without an excessive intake of fats.

No other food can be considered as specifically medicinal as *Lactobacillus* yogurt. A 1992 study investigated the effects of the daily ingestion of yogurt containing *L. acidophilus* on 33 women with five or more episodes per year of candidal vaginitis. Thirteen women completed the study. The women were randomized into two groups, with the first group receiving 8 oz of *L. acidophilus* yogurt daily for 6 months and then no yogurt for 6 months. The other group consumed the yogurt-free diet for the first 6 months and then the diet including yogurt for the second 6 months. There was a threefold reduction in infections and in candidal colonization during the yogurt diet compared with the non-yogurt diet.[23]

There are also studies that do not support a role for yogurt in the prevention of recurrent candidal vaginitis.[24]

Nutritional Supplements

For general maintenance of health and immune competence, a high-quality multivitamin/multimineral supplement provides low-cost compensation for most dietary inadequacies. In addition, the nutrients discussed here may be useful in one or more types of vaginitis.

Vitamin A and Beta-Carotene

Both vitamin and beta-carotene are necessary for the normal growth and integrity of epithelial tissues, such as the vaginal mucosa. Vitamin A is essential for adequate immune response and resistance to infection. Secretory IgA, a major factor in resistance to infection, is lower in vitamin A–deficient subjects.[25] Beta-carotene is a source of nontoxic vitamin A precursors. In addition, it has been shown to enhance T-cell numbers and to favorably alter their ratios.[26] Excessive vitamin A can be toxic and teratogenic. This is of particular concern in women of reproductive age. Total vitamin A intake should be limited to 5000 IU/day. If larger doses of vitamin A are used, patients should be cautioned to be particularly careful about contraception. Mixed carotenoids rather than synthetic beta-carotene should be used.

B Vitamins

The body requires one or more of the B vitamins for virtually every metabolic activity. B vitamins are needed for carbohydrate metabolism, protein catabolism and synthesis, cell replication,

and immune function. Vitamins B_2 and B_6 have been shown to have estrogen-like effects and to act synergistically with estradiol. Vitamin B_1 and pantothenic acid enhance the action of estradiol, although they have no estrogenic activity themselves.[27] This finding suggests that B vitamins may be of use in estrogen deficiency conditions such as atrophic vaginitis, especially if combined with phytoestrogens.

Vitamin C and Bioflavonoids

Vitamin C and bioflavonoids are essential in any process related to immune function. Deficiency of vitamin C reduces the phagocytic activity of leukocytes. Both vitamin C and bioflavonoids improve connective tissue integrity, thus reducing the spread of infection. Both nutrients are also useful in diminishing the frequency and severity of herpetic outbreaks.[27-32]

Vaginal vitamin C has been used to treat BV. A randomized double-blind placebo-controlled study used a 250-mg tablet of vitamin C inserted vaginally once a day for 6 days.[33] Of the 100 participants, 50 were given the active treatment and 50 placebo. At the end of the study, significantly more patients still had BV in the placebo group (35.7%) compared with the vitamin C tablet group (14%). There were no clue cells in 79% of patients receiving the vitamin C, versus 53% in the placebo group. Bacteria disappeared in 77% of the vitamin C group versus 54% in the placebo group, and lactobacilli reappeared in 79.1% of the vitamin C group versus 53.3% in the placebo group.

Vitamin E

Lack of vitamin E depresses immune response and host resistance. This situation may be corrected by high doses of supplemental vitamin E. Several experiments have shown increased resistance to chlamydial infection when subjects were supplemented with vitamin E. Vitamin E also regulates retinol in humans, and an inadequacy of vitamin E hinders the utilization of vitamin A despite adequate retinol intake.[34] The use of vitamin E for the treatment of atrophic vaginitis has been reported since the 1930s.

Excessive vitamin E intake (>1200 IU/day), however, may be immunosuppressive and may transiently elevate blood pressure. This vitamin is reported to improve glycogen storage and the tone of heart muscle. Thus, extra caution should be exercised in patients with diabetes, hypoglycemia, hypertension, or heart disease. For such high-risk patients, supplementation should begin with a daily dose of 100 IU; with monitoring of blood glucose or blood pressure values, the dose should be increased slowly over time (e.g., by 50 IU/day).

Zinc

All DNA and RNA polymerases and repair and replication enzymes require zinc. Zinc enhances prostaglandin (PG) E_1 synthesis, normalizes lymphocyte activity, and enhances epithelial growth. Low levels of zinc are associated with depressed immunity and thymic atrophy, both of which are correctable when zinc is replenished. Zinc is also essential for the proper utilization of vitamin A. Many otherwise well-nourished adults receive less than 50% of the recommended dietary allowance of zinc from their diets and have one or more measurable signs of zinc deficiency.[35-37]

Treatment with topical and oral zinc has been shown to reduce the duration and severity of herpes outbreaks. This may be due either to the effect of zinc on production of prostaglandins or to the direct antiviral activity of the zinc ion. High levels of zinc are also toxic to *Chlamydia* and *Trichomonas* and have been used successfully in vaginitis that did not respond to antibiotic therapy.[38-42]

Botanical Medicines

Glycyrrhiza glabra

Licorice *(G. glabra)* has antiviral activity against RNA and DNA viruses and has been used successfully in the treatment of herpes. The number and severity of recurrences may be reduced by the repeated application of licorice gel to active lesions.[43] 18-beta glycyrrhetinic acid has been shown in vitro to be effective against *Candida*.[44] (For further discussion, see Chapter 96.)

Chlorophyll

Chlorophyll has bacteriostatic action and soothing actions. Water-soluble chlorophyll may be added to douching solutions for symptomatic relief of vaginitis.[45-47]

Allium sativum

Garlic *(A. sativum)*—which is antibacterial, antiviral, and antifungal—has been shown to be effective even against some antibiotic-resistant organisms.[48-52] The major growth-inhibitory component in garlic extract is allicin; therefore, garlic products with the highest amount of allicin are preferable. Garlic cloves may be carefully peeled so as not to nick them and then pierced with thread and used as tampons. A garlic capsule may also be inserted into the vagina.

Hydrastis canadensis and Berberis vulgaris

Goldenseal *(H. canadensis)* and Oregon grape *(B. vulgaris)* contain berberine, which has a significant effect against many bacteria. Berberine enhances immune function when taken internally as a tea and offers symptomatic local relief when used in douching solutions because it is soothing to inflamed mucous membranes.[53-56] (For further discussion, see Chapter 97).

Melaleuca alternifolia

An alcoholic extract of the oil of the tea tree *(M. alternifolia),* diluted to 1% in water, exerts a strong antibacterial and antifungal action. It was shown in one study to be effective in treating trichomoniasis, candidiasis, and cervicitis. Treatment consists of daily douching combined with saturated tampons used weekly. No adverse reactions were reported, and patients commented favorably on its soothing effect[57] (for further discussion, see Chapter 102). Various tea tree oil preparations have demonstrated antimicrobial activity against *Staphylococcus aureus* and *C. albicans*.[58]

Botanical Mixture

Women with abnormal vaginal discharge who presented to a gynecologic clinic in India were randomly assigned to receive either a cream containing *Azadirachta indica* (neem) seed oil, *Sapindus mukerossi* (reetha) saponin extract, and quinine or placebo. They applied the cream intravaginally at bedtime for 14 days. The results were quite impressive. Symptomatic and microbial assessment showed that 10 of 12 women with *C. trachomatis* vaginitis recovered within 1 week, and 10 of 17 with BV recovered within 2 weeks. No benefit was found in women with candidal or trichomonal infections, and none of the women using the placebo recovered from any of the infections.[59]

Other Agents

Lactobacillus Species

Lactobacilli are the dominant organisms in the vagina of a healthy reproductive-aged premenopausal woman. Properties of these strains—including their adhesiveness, ability to produce acids and hydrogen peroxide, and production of bacteriocidins and

biosurfactants—confer protection on the host. Selection of *Lactobacillus* species and strains for therapeutic purposes with these properties should be a guiding principle for their use in treatment. Substantial data have been published on a number of strains, their properties, and their ability to fight pathogens. Many species and specific strains have demonstrated antipathogenic activity; these include *L. rhamnosus* GG, *L. acidophilus* NCFM, *L. casei Shirota, L. reuteri* MM-53*, L. casei* CRL-431, *L. rhamnosus* GR-1, *L. fermentum* RC-14 (now called *L. rheuteri*), *L. plantarum* 299V, and *L. salivarius.*[60] Other *Lactobacillus* strains, such as *L. johnsonii* LC1, *L. plantarum* 299V, and *L. crispatus* CTV05 also have excellent potential owing to their ability to colonize the vagina and produce hydrogen peroxide, although more data are needed.

Several studies have supported the use of Lactobacillus in the prevention and treatment of vaginitis. One study on treating BV found that both vaginal administration and oral-plus-vaginal administration of lactobacilli were effective at reducing the vaginal pH, treating the current infection, and preventing recurrence over the subsequent 3 months.[61] Another study examined the effectiveness of weekly intravaginal *L. acidophilus* versus clotrimazole (antifungal) tablets in HIV-positive women, a group highly susceptible to recurrent yeast vaginitis, and found the two treatments to be similarly effective at preventing candidiasis.[62] After any conventional treatment with antibiotics, vaginal lactobacilli can be restored by the coadministration of *Lactobacillus* and low-dose vaginal estriol.[63] Another randomized double-blind placebo controlled trial of BV was conducted with 100 women who were given a 2% vaginal clindamycin cream for 7 days and then randomized to receive vaginal capsules for 10 days containing either a placebo or a combination of *L. gasseri* and *L. rhamnosus* (10 billion colony forming units/capsule); this was then repeated for 3 cycles. The probiotics did not improve efficacy of BV treatment during the first month of treatment. However, women initially "cured" were followed for 6 menstrual cycles or until relapse within that time. At the end of 6 months, 64.9% of the probiotic-treated group were still BV-free compared with 46.2% in the placebo group.[85]

Another study enrolled 125 premenopausal women diagnosed with BV by presence of vaginal irritation, discharge and 'fishy' odor, and Nugent criteria and detection of sialidase enzyme. The subjects were treated with oral metronidazole (500 mg) twice daily from days 1 to 7, and randomized to receive oral Lactobacillus rhamnosus GR-1 (1 × 10[9]) and Lactobacillus reuteri RC-14 (1 ×10[9]) or placebo twice daily from days 1 to 30. Primary outcome was cure of BV as determined by normal Nugent score, negative sialidase test, and no symptoms or signs of BV at day 30. A total of 106 subjects returned for 30-day follow-up, of which 88% were cured in the antibiotic/probiotic group compared with 40% in the antibiotic/placebo group (P <0.001). Of the remaining subjects, 30% subjects in the placebo group and none in the probiotic group had BV, while 30% in the placebo and 12% in the probiotic group fell into the intermediate category based upon Nugent score, sialidase result and clinical findings. High counts of *Lactobacillus sp.* (>10[5] CFU/mL) were recovered from the vagina of 96% probiotic-treated subjects compared with 53% controls at day 30. In summary, this study showed efficacious use of lactobacilli and antibiotic in the eradication of BV in black African women.[86]

There are more studies showing these specific species in the treatment of BV. In another clinical trial, 64 premenopausal women with diagnosed BV received a single dose of tinidazole (2 g) and either one capsule of *L. rhamnosus* GR-1 (1 × 10[9]) and *L. reuteri* RC-14 (1 × 10[9]) or placebo orally, twice a day, from days 1 to 28. At day 28, the probiotic group had a higher cure rate (Nugent score and Amsel test) of BV compared with placebo (87.5% vs 50%; P = 0.001). According to the Gram-stain Nugent score, more women in the probiotic group were assessed with "normal" vaginal microbiota compared with placebo (75% vs 34.4%; p = 0.011).[87]

Another way to use these probiotic species is after conventional treatment. In one clinical trial, 95 women (39 with BV, 45 with VVC and 11 had both infections) were randomized to receive a vaginal capsule containing *L. gasseri* LN40, *L. fermentum* LN99, *L. casei rhamnosus* LN113, *P. acidilactici* LN23 (10[8]-10[10] cfu) or placebo for 5 days following conventional treatment. Probiotic strains were present in vaginal cultures 2 to 3 days after administration (53% colonized after one menstruation). Ninety-three percent of women in the probiotic group were cured after 2 to 3 days compared with 83% in the placebo group (78% vs 71% after first menstruation). The probiotic group also had significantly less malodorous discharge.[88]

A clinical trial for vulvovaginal candidiasis employed *Lactobacillus* GG suppositories which were given twice a day for 7 days to women with more than 5 infections per year.[64] Four of the five women with positive yeast cultures had negative cultures after receiving this treatment. All the women reported improvement of their vaginal symptoms of erythema and discharge.

Another study examined the ability of intravaginal *Lactobacillus* to reduce the risk of VVC in 164 HIV-positive women.[65] These women were randomized into three groups with one group receiving *L. acidophilus* intravaginally once a week. The second group received vaginal clotrimazole weekly, and the third group received a placebo. During the 21-month study, the relative risk of developing VVC was 0.5 for the lactobacilli group and 0.4 for the prescription antifungal group compared with placebo. In addition, women who used the lactobacilli went for a longer period of time until they became infected compared with the women who received a placebo.

Other studies have demonstrated that when lactobacilli are given orally, they do colonize the vagina and/or reduce vaginal candidal infections. Three studies, all using *L. rhamnosus* GR-1 and *L. fermentum* RC-14, have been positive and showed a significant reduction in yeast[66] or reduction in the recurrences of yeast vaginitis[67] or restoration of normal vaginal flora in women with a history of VVC.[68]

A review of *Lactobacillus* treatments for VVC in 2003[69] found that vaginally administered or orally ingested *Lactobacillus* is able to colonize the vaginal ecosystem and that supplementation generally had to continue 2 to 6 months in order to sustain continued colonization. The author also concluded that controlled trials are encouraging but few, and that these trials had small numbers of participants, inadequate controls or lack of blinding, high attrition rates, and were not consistent in the form of *Lactobacillus* used. In addition, they produced conflicting results.

There are a few studies that do not support a role for probiotics in the prevention of recurrent VVC or BV.[24,70]

Alone or in combination with other vaginal or oral therapies, selected combination species and strains of *Lactobacillus* can provide the key to establishing normal vaginal microflora, preventing recurring infections, and treating acute candidal and bacterial infections of the vagina.

Iodine

Iodine used topically is effective against a wide range of organisms, including *Trichomonas, Candida, Chlamydia,* and nonspecific vaginitis. Povidone-iodine (Betadine) has all the advantages of iodine without the disadvantages of stinging and staining. A study published in 1969 found povidone-iodine to be effective in treating 100% of cases of candidal vaginitis, 80% of cases due to

Trichomonas, and 93% of combination infections. Although douching has not been as strongly recommended, this study found a douching solution diluted to 1 part iodine in 100 parts water (e.g., 1.5 to 3 teaspoons povidone-iodine to 1 quart of water) used twice daily for 14 days to be effective against most organisms.[69,71-78]

Boric Acid

Boric acid suppositories have been around for a very long time and are both antibacterial and antifungal although its exact mechanism of action is not clear. One hypothesis is the vaginal acidification of boric acid, which then leads to fungal cell wall penetration and disruption of the fungal cell membrane. However, because boric acid's minimum inhibitory concentration works best at a pH similar to a normal uninfected vagina, the hypothesis of increased acidity may not explain its therapeutic effects.

Vaginal capsules of boric acid have been shown to treat candidiasis with success rates equal to or better than those for nystatin. In the most impressive study, 100 women with chronic resistant yeast vaginitis for whom extensive and prolonged conventional therapy had failed were treated with vaginal suppositories containing 600 mg of boric acid twice a day for 2 or 4 weeks. This regimen was effective in curing 98% of the women with failure of response to the most commonly used antifungal agents,[78] thus offering an inexpensive, easily accessible therapy for vaginal yeast infections.[79,80]

A recent review of boric acid for recurrent candida vaginitis sheds some light on its effectiveness.[89] Fourteen studies, including two randomized clinical trials, nine case series, and four case reports were included in this review of the clinical evidence utilizing intravaginal boric acid for vulvovaginal candidiasis. Boric acid was compared with nystatin, gterconazole, flucytosine, itraconazole, clotrimazole, ketoconazole, fluconazole, buconazole, and miconazole. The mycologic and clinical cure rates were as follows:

- Boric acid: varied from 40% to 100%
- Nystatin: 50%
- Terconazole: 70%
- Flucytosine: 90%
- Itraconazole: 90.9%
- Clotrimazole: 36%
- Ketoconazole: 50%
- Fluconazole: 28.6% to 92.3%
- Buconazole: 100%
- Miconazole: 100%

The recurrence rates ranged from 0% to 45.5% in those using boric acid. None of the studies found statistically significant recurrence rates. Vaginal burning sensation was reported in less than 10% of the cases, and watery discharge during treatment and vaginal erythema were reported in seven studies.

Kudzu (Pueraria mirifica)

P. mirifica was examined for its effect on vaginal symptoms, vaginal health index, vaginal pH, and vaginal cytology in postmenopausal women.[81] In this randomized double-blind placebo-controlled study, the participants were given either 20, 30, or 50 mg of *P. mirifica* in capsule or placebo daily for 24 weeks. The average vaginal dryness symptoms in the treatment group decreased after 12 weeks and the maturation index increased after 24 weeks. This effect is evidence of an estrogenic effect on vaginal tissue due to this plant and points to its clinical use for vaginal dryness and dyspareunia due to vaginal atrophy.

Hops

A study was conducted using a combination gel containing phytoestrogens from hops extract, hyaluronic acid, liposomes, and vitamin E.[82] This open noncontrolled trial was performed on 150 postemenopausal women presenting with vaginal dryness and related symptoms. One vaginal suppository per day was inserted for the first 14 days and then one suppository every other day for 14 days. The primary endpoint was the evaluation of vaginal dryness by both the patient and the investigator. The secondary endpoints were the evaluation of other symptoms, including vaginal itching, burning, dyspareunia, inflammation, swelling or irritation, or vulvovaginal abrasions. Among the 130 women who completed the study, the average vaginal dryness scale decreased from 7.92 to 0 by the end of the treatment. Itching disappeared progressively throughout the treatment period and only 4 women still had itching at the end of the treatment. Burning was severe in 92 women at baseline, moderate in 26 and mild in 11. By the end of the treatment, only 4 women complained of mild burning. Dyspareunia also improved progressively; by the end, only 5 women of the 130 who reported mild to moderate or severe dyspareunia had mild dyspareunia. Inflammation and irritation of vulvar and vaginal mucosa also improved significantly from the beginning to the end of the treatment period.

Estrogens

Estrogen therapy is the most effective treatment for moderate to severe atrophic vulvovaginitis. Systemic estrogen therapies and estrogen-progestogen therapies are effective for treating these symptoms. However, when urogenital atrophy is the main or only indication for estrogen, local vaginal estrogen therapy is recommended and not systemic hormone therapy.

Vaginal DHEA

A prospective, randomized, double-blind, placebo-controlled trial evaluated the effect of daily local intravaginal DHEA ovules for 12 weeks in postmenopausal women. The main assessment criteria were sexual dysfunction parameters of libido, arousal, orgasm, and dyspareunia in postmenopausal women with vaginal atrophy.[83] A total of 218 postmenopausal women were randomized to receive a daily ovule of either no DHEA, 3.25 mg DHEA, 6.5 mg DHEA, or 13 mg DHEA. The ovules contained Prasterone, in a lipophilic agent manufactured by Recipharm of Sweden. At 12 weeks, compared with placebo, the 13-mg ovule improved symptoms by 68% in the abbreviated sex function/arousal/sensation domain, in the arousal/lubrication domain by 39%, orgasm by 75%, and dryness during intercourse by 57%. DHEA also fared better than placebo in the desire domain of menopause-specific quality of life inventory by 49% to 23%.

In a related study by the same authors, serum levels of vaginal DHEA showed no or minimal changes during the study period, which lasted up to 12 weeks. All values remained within the normal range of postmenopausal women.[84] This bodes well for safety issues.

DIAGNOSTIC APPROACH

Some women are hesitant to mention symptoms of vaginitis to their doctors out of embarrassment, associating them with poor personal hygiene or promiscuity. Because of the relative frequency of occurrence of vaginitis and the potential for serious consequences if it is untreated, all female patients should be questioned directly regarding the presence of pruritus, vaginal discharge, dysuria, or other symptoms of vaginitis. The following protocol outlines the basic approach to diagnosis:

1. Obtain a complete gynecologic and sexual history, including details of the sexual activity and practices of the patient and her partner or partners. Determine method of contraception, personal hygiene habits, and any self-medications. Rule out the presence of associated symptoms suggestive of PID or systemic infection. Inquire about previous occurrences and their diagnosis, treatment, and resolution.
2. Identification of the causative agent is essential for successful treatment and evaluation. To facilitate diagnosis, the patient should be instructed to avoid douching, intercourse, and vaginal medications for 1 to 2 days prior to the office visit.
3. Determine by speculum examination whether the discharge emanates from the vagina or the cervix. Note the condition of the vaginal mucosa and the character of any discharge. Specimens should be collected and then placed on slides for saline and KOH examination. Use pH paper, amines testing strips, and microscopy of wet mounts.
4. Assess pH.
5. Use microscopy when needed for diagnosis (e.g., KOH wet prep).
6. Appropriate culture specimens should be taken if the diagnosis remains in question or if screening for gonococcus or *Chlamydia* is desired (highly recommended). An abdominal/bimanual examination should be done. A genital culture can be used to diagnose beta strep, yeast, BV (not well), *Staphylococcus aureus*, and *Escherichia coli*. A yeast culture can be ordered and a request to identify different strains of *Candida* can be made. A Group B strep DNA probe or group B strep culture should be ordered for pregnant patients.
7. The Affirm VP III test is used to diagnose *Candida* species, BV, and trichomoniasis.
8. The Thin prep can actually test for many different pathogens including the detection and identification of human papillomavirus and its genotype, HPV 16/18, *Chlamydia*, gonococcus, *Trichomonas*, yeast, *Actinomyces*, herpesviruses I and II, Group B strep, BV, syphilis, *Ureaplasma*, and *Mycoplasma*.

THERAPEUTIC APPROACH

Because approximately 90% of all cases of vaginitis are due to *Candida, Trichomonas,* or *Gardnerella* infections, the following recommendations are primarily directed to treatment of these organisms. Owing to the infectious nature of these organisms, immune support (through proper diet, nutritional supplementation, and botanical medicines) is an important aspect of the therapy. For further recommendations on treating atrophic vaginitis, see Chapter 188; for herpes simplex, see Chapter 172.

Diet

For all causes of vaginitis, a nutrient-dense diet is recommended. All refined foods and simple carbohydrates should be eliminated, and trans fats and saturated fats kept to a minimum. If food allergies are suspected, they should be determined and eliminated.

Supplements

- Vitamin A: 5000 IU/day or beta-carotene 50,000 IU/day
- Vitamin C: 500 to 1000 mg every 4 hours
- B complex: a good balanced B complex averaging 20 to 50 mg of each of the major components
- Zinc: 10 to 15 mg/day
- Vitamin E: 200 IU/day
- *Lactobacillus* species orally and vaginally; dose depends on duration and kind of infection

Botanical Medicines

Hydrastis canadensis (goldenseal)

Dosages three times a day are as follows:
- Dried root or infusion (tea): 2 to 4 g
- Tincture (1:5): 6 to 12 mL (1.5 to 3 tsp)
- Fluid extract (1:1): 2 to 4 mL (0.5 to 1 tsp)
- Solid (powdered dry) extract (4:1 or 8% to 12% alkaloid content): 250 to 500 mg

Allium sativum (garlic): dose equivalent to 4000 mcg allicin.

General Recommendations

1. In treating infectious vaginitis, the following natural medicine concepts should be kept in mind:
 - Remove/limit obstacles to cure
 - Improve vaginal immunity
 - Support systemic immunity
 - Restore vaginal pH
 - Restore vaginal microenvironment
 - Restore gut ecology
 - Decrease inflammation/irritation
 - Provide symptom relief
 - Correct coexisting medical conditions
2. In all cases of chronic vaginitis, *Lactobacillus* capsules or *Lactobacillus* yogurt should be used daily, at least orally if not vaginally, to reinoculate the vagina with these desirable organisms. Oral use should continue for 2 to 6 months to assure colonization.
3. Treatment failures may be due to incorrect diagnosis, reinfection, failure to treat predisposing factors, or patient resistance to the treatment used.
4. *Trichomonas* infections in women require concurrent treatment of the male partner.
5. In cases of recurrent or chronic BV or yeast vaginitis, the clinician should consider treating both male and female partners, infection in whom is a possible explanation for recurrent disease.

Specific Recommendations/Sample Treatments

Acute candidal vaginitis

- 8 oz of *Acidophilus* yogurt every day
- *Lactobacillus* sp. 2 to 10 billion colony-forming units twice a day for 14 days
- Boric acid: 600 mg placed in capsules twice a day for 3 to 7 days

Chronic candida vaginitis

- 8 oz of *Acidophilus* yogurt every day
- *L. species* (e.g., *rhamnosus, rheuteri*) 1-5 billion; twice daily for 1 to 6 months
- Boric acid: 600 mg vaginal suppositories twice a day for 2 weeks (4 weeks if patient is not free of symptoms and wet mount examination still shows organisms at 2 weeks)
- To prevent vulvar irritation from the boric acid dispensed from the dissolved capsule, vitamin E oil or petroleum jelly can be applied to the external genitalia.

Bacterial vaginosis

- Vitamin C vaginal tablet for 6 days and then boric acid suppositories once a day for 1 week

- Multiple *Lactobacillus* species/strains 2 billion or more a day for 2 weeks
- Systemic immune support

Trichomonas

- Povidone-iodine: applied twice a day
- Zinc sulfate: applied a day
- *M. alternifolia* oil: applied a day

Atrophic Vaginitis

- Intravaginal Estriol cream, 1 mg/g. Insert 1 g a day for 2 weeks, then 1 g twice a week as maintenance. Other vaginal estrogen options: vaginal estradiol 0.1% cream, Premarin cream, Estring, Vagifem.
- Consider vaginal DHEA ovules 13 mg/day for 12 weeks, then twice a week.

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CHAPTER 214

Varicose Veins

Michael T. Murray, ND

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Diet, *1834*
Botanical Medicines, *1834*

DIAGNOSTIC SUMMARY

- Dilated, tortuous superficial veins in the lower extremities.
- May be asymptomatic or associated with fatigue, aching discomfort, feeling of heaviness, or pain.
- Edema, pigmentation, and ulceration of the skin of the distal leg may develop.
- Women are affected four times as frequently as men.

GENERAL DISCUSSION

Veins are fairly frail structures. Defects in the wall of a vein lead to dilation of the vein and damage to the valves. When the valves become damaged, the higher static pressure results in the bulging veins known as *varicose veins*.

Varicose veins affect nearly 50% of middle-aged adults. The subcutaneous veins of the legs are the veins most commonly affected, owing to the gravitational pressure that standing exerts on them. When an individual stands for long periods, the pressure buildup in the vein can increase up to 10 times. Hence, individuals with occupations that require long periods of standing are at greatest risk for the development of varicose veins.

Women are affected about four times as frequently as men; obese individuals have a much greater risk; and the risk rises with age owing to loss of tissue tone, loss of muscle mass, and weakening of the walls of the veins. Pregnancy, which increases venous pressure in the legs, may also lead to the development of varicose veins.

In general, varicose veins pose little risk if the involved vein is near the surface. These types of varicose veins are, however, cosmetically unappealing. Although significant symptoms are not common, the legs may feel heavy, tight, and tired. If the varicose veins are associated with significant chronic venous insufficiency, leg ulcers may form that are often difficult to resolve.

A more serious form of varicose vein involves obstruction and valve defects of the deeper veins of the leg. This type of varicose vein can lead to problems such as thrombophlebitis, pulmonary embolism, myocardial infarction, and stroke. Phlebography and Doppler ultrasonography are the most accurate methods of diagnosing deep venous involvement.

ETIOLOGY

The following theories have been advanced to explain the cause of varicose veins:

- Genetic or functional weakness of the veins or venous valves.
- Excessive venous pressure due to increased straining during defecation, often caused by a low-fiber diet.
- Long periods of standing and/or heavy lifting.
- Damage to the veins or venous valves secondary to thrombophlebitis.

The major cause of varicose veins is weakness of the vascular walls due to either abnormalities in the proteoglycans of the interendothelial cement substance or excessive expression/activity/release of matrix metalloproteinases (MMPs) such as β-*N*-acetylglucosaminidase, β-glucuronidase, and arylsulfatase, which degrade extracellular matrix proteins and affect the structural integrity of the vein wall, leading to increased capillary permeability and loss of venous structural integrity. The MMPs also affect the endothelium and smooth muscle components of the vein wall, thereby causing changes in the properties of venous constriction/relaxation.

Endothelial cell injury also triggers leukocyte infiltration, activation, and inflammation, which leads to further damage to the vein wall and thus chronic and progressive venous insufficiency and varicose vein formation.[1,2]

THERAPEUTIC CONSIDERATIONS

The treatment of varicose veins ranges from conservative measures to surgical interventions. Conservative therapy involves the following:

- Elevating the legs periodically.
- Wearing graduated compression stockings with variable pressure gradients, especially if standing for long periods of time is unavoidable.
- Exercise, especially walking, riding a bike, or jogging, is thought to be helpful, because contraction of the leg muscles pushes pooled blood back into circulation.
- Achieving or maintaining one's ideal body weight.
- Maintaining adequate intake of dietary fiber to avoid increasing venous pressure consequent to straining during defecation.
- Using nutritional and botanical agents to assist in improving the structural integrity of the veins.

For severely affected veins, more aggressive treatment may be necessary. The traditional surgical treatment has been vein stripping to remove the affected veins. Newer, less invasive treatments that seal the main leaking vein at the highest point of valvular dysfunction on the thigh include ultrasound-guided foam sclerotherapy, radiofrequency ablation, and endovenous laser treatment. Because most of the blood in the legs is returned by the deep veins, the superficial veins, which return only about 10% of the total blood of the legs, can usually be removed or ablated without serious harm. Sclerotherapy with segmental phlebectomy (stripping of the vein) is also popular. In sclerotherapy with segmental phlebectomy, a sclerosing agent is injected at the highest portion of the affected vein. Only the most badly diseased segments of vein are stripped away with segmental phlebectomy.

Dietary Factors

Fiber

A low-fiber diet that is high in refined foods contributes to the development of varicose veins.[3,4] Individuals consuming a low-fiber diet tend to strain more during bowel movements because their smaller and harder stools are more difficult to pass. This straining raises the pressure in the abdomen, obstructing the flow of blood up the legs. Over time, this increased pressure may significantly weaken the vein walls, leading to the formation of varicose veins or hemorrhoids, or it may weaken the wall of the large intestine and produce diverticuli.[5]

A diet rich in vegetables, fruits, legumes, and grains promotes peristalsis, and many fiber components attract water and form a gelatinous mass, which keeps the feces soft, bulky, and easy to pass. The net effect of a high-fiber diet is significantly less straining during defecation.

Natural bulking compounds can also be used. These substances, particularly psyllium seed, pectin, and guar gum, possess a mild laxative action owing to their ability to attract water and form a gelatinous mass. This process, as previously mentioned, keeps the feces soft and promotes peristalsis, significantly reducing straining during defecation. These types of fibers are generally less irritating than wheat bran and other cellulose fiber products.

Flavonoid-Rich Berries

Berries, such as hawthorn berries, cherries, blueberries, and blackberries appear to be beneficial in the prevention and treatment of varicose veins. These berries are very rich sources of proanthocyanidins and anthocyanidins,[6-8] flavonoids are noted for their ability to improve the integrity of ground substance and the vascular system. Extracts of several of these berries are used widely in Europe for various circulatory conditions.[6-8]

Another rich source of flavonoids is buckwheat, which is high in rutin. In one double-blind placebo-controlled study, 77 patients with chronic venous insufficiency were given placebo tea or *Fagopyrum esculentum* (buckwheat) tea for 12 weeks. The tea was standardized to contain 5% total flavonoids, yielding a daily dosage of 270 mg of rutin. A statistically significant reduction in total leg volume was seen in the treated group, along with statistically insignificant improvements in capillary permeability and symptoms. No adverse effects were noted.[9]

The efficacy of these extracts is related to their ability to accomplish the following[6-8]:

- Reduce capillary fragility
- Increase the integrity of the venous wall
- Inhibit the breakdown of the compounds composing the ground substance
- Improve the muscular tone of the vein

Consumption of these berries or of their extracts or other flavonoid-rich extract like grape seed or pine bark (see Chapter 117) is indicated for individuals with varicose veins as well as those who wish to prevent them.

Botanical Medicines

Horse chestnut *(Aesculus hippocastanum)* was once native to western Asia but has been widely distributed all over the world because of its beauty. In addition to enhancing the appearance of city streets and parks, this hearty tree possesses significant medicinal effects. In particular, the seeds of the horse chestnut tree have been valued for centuries for their ability to improve hemorrhoids and varicose veins.[10] This historical use, seemingly successful, ultimately has led to the development of topical and oral preparations with confirmed clinical benefits for these same conditions.[11,12]

The chief component of horse chestnut seed extract (HCSE) is escin, a triterpenic saponin, although other molecules such as proanthocyanidin A_2 and esculin also exert significant effects.[11] These horse chestnut compounds have shown a number of pharmacologic effects beneficial in the treatment of chronic venous insufficiency. First, all three active components have been shown to exert significant vasoprotective and venotonic effects, such as antioxidant effects, combined with an ability to inhibit enzymes that destroy venous structures, such as collagenase, hyaluronidase, β-glucuronidase, and elastase, thus shifting the equilibrium between degradation and synthesis of proteoglycans and other critical venous structures toward a net synthesis. In addition, HCSE prevents the accumulation of leukocytes in varicose vein–affected limbs and their subsequent activation, an important pathophysiologic mechanism in varicose veins. It appears that the ultimate effect of HCSE treatment is the prevention of vascular leakage along with an increase in the tone of the vein itself.[13]

The therapeutic benefits of HCSE has been confirmed in more than 16 double-blind clinical trials demonstrating a positive effect in the treatment of varicose veins and thrombophlebitis.[11] In fact, extracts of HCSE standardized for escin appear to be as effective as compression stockings, but without the nuisance. For example, in a well-designed study, the effectiveness of HCSE versus compression stockings was examined in 240 patients with varicose veins.[14] Patients received either HCSE (50 mg/day of escin), compression stockings, or a placebo for 12 weeks. Effectiveness was evaluated

by a phlethysmograph—a machine that measures the volume of fluid in the leg. After the 12-week trial, lower-leg volume of the more severely affected leg decreased an average of 56.5 mL with compression therapy and 53.6 mL with HCSE, whereas it rose by 9.8 mL with the placebo.

In the treatment of varicose veins, escin can be given orally as well as topically. The topical formula is also of benefit in the treatment of bruises, owing to escin's ability to reduce capillary fragility and swelling.

Centella asiatica

When given orally, an extract of *C. asiatica* containing 70% triterpenic acids (asiatic acid, madecassic acid, and asiatoside) has demonstrated impressive clinical results in the treatment of cellulite, venous insufficiency of the lower limbs, and varicose veins (see Chapter 75 for more information).[15-19]

Several experimental studies have discovered that *Centella* exerts a normalizing effect on the metabolism of connective tissue. Specifically, it possesses an ability to enhance connective tissue integrity by stimulating glycosaminoglycan synthesis without promoting excessive collagen synthesis or cell growth.[16] Glycosaminoglycans are the major components of the amorphous intercellular matrix (ground substance), in which collagen fibers are embedded. The net outcome of *Centella*'s effect on connective tissue is the development of normal tissue.

The effect of *Centella* in venous insufficiency and varicose veins appears to be related to its ability to enhance connective tissue structure, reduce sclerosis, and improve blood flow through the affected limbs.[15-19] (For further information, see Chapter 75.)

Ruscus aculeatus (Butcher's Broom)

The shrub butcher's broom (*Ruscus aculeatus*) is a member of the lily family that grows in the Mediterranean region. The rhizome from butcher's broom has a long history of use in treating venous disorders such as hemorrhoids and varicose veins. This historical effect has been confirmed in experimental and double-blind studies in patients with varicose veins.[20-22] The active ingredients in butcher's broom are ruscogenins. These compounds have demonstrated a wide range of pharmacologic actions, including anti-inflammatory and vasoconstrictor effects. In Europe, butcher's broom extracts are used extensively, both internally and externally, in the treatment of varicose veins and hemorrhoids. Double-blind clinical studies have shown that these preparations offer benefits in terms of both symptomatic relief and improved venous blood flow.[20-22]

Flavonoids and Flavonoid-Rich Extracts

As mentioned above, flavonoids and flavonoid-rich extracts are useful in the prevention and treatment of varicose veins. The most useful single flavonoid for varicose veins may be micronized diosmin. Micronization involves a high-technology grinding process with a jet of air at supersonic velocities, reducing the size of standard particles from more than 20 to less than 2 micrometers. As a result, there is better and faster absorption and thus an increased bioavailability, which lends greater clinical efficacy. In addition to showing considerable improvements in signs and symptoms, purified micronized diosmin decreases the levels of some plasma markers of endothelial activation, including soluble endothelial adhesion molecules.[23] Micronized diosmin has also shown considerable benefits in promoting the healing of venous ulcers and hemorrhoids.[24] For more information, see Chapter 92.

Bromelain and Other Fibrinolytic Compounds

Individuals with varicose veins have a decreased ability to break down fibrin.[25] This fact is extremely important because fibrin is deposited in the tissue near the varicose veins. The skin then becomes hard and "lumpy" owing to the presence of the fibrin and fat (lipodermatosclerosis). In addition, decreased fibrinolytic activity raises the risk of thrombus formation, which may result in thrombophlebitis, myocardial infarction, pulmonary embolism, or stroke.

Herbs that increase the fibrinolytic activity of the blood are therefore indicated. Capsicum (cayenne),[26] garlic,[27] onion,[28] and ginger[29] all promote fibrin breakdown. Liberal consumption of these spices in foods is recommended for individuals with varicose veins and other disorders of the cardiovascular system.

The proteolytic enzyme from pineapple, bromelain, also appears to be indicated in the treatment of varicose veins. Vein walls are an important source of plasminogen activator, which promotes the breakdown of fibrin. Veins that have become varicosed have decreased levels of plasminogen activator. Bromelain acts in a similar manner to plasminogen activator to cause fibrin breakdown.[30] Bromelain may help prevent the development of the hard and lumpy skin found around varicosed veins.

THERAPEUTIC APPROACH

Conservative therapy as described above should be employed as early as possible in patients with varicose veins. It may halt the progression and prevent further need for more aggressive therapy.

Diet

A diet rich in dietary fiber is indicated. The diet should contain liberal amounts of proanthocyanidin- and anthocyanidin-rich foods, such as blackberries, cherries, and blueberries. Garlic, onions, ginger, and cayenne should also be consumed liberally.

Botanical Medicines

Choose one or more of the following:

- *A. hippocastanum*: bark of root, 500 mg three times a day
- Escin: 50 mg two or three times a day; alternatively, escin preparations may be applied topically in a 1% concentration
- *C. asiatica* extract (70% triterpenic acid content): 30 mg three times a day
- *R. aculeatus* extract (9% to 11% ruscogenin content): 100 mg three times a day
- Grape seed (*Vitis vinifera*) extract (95% procyanidolic oligomers): 150 to 300 mg/day
- Pine bark extract (*Pinus pinaster*): 150 to 300 mg/day
- Micronized diosmin: 500 to 1000 mg/day
- Hydroxyethyrutosides: 1000 to 3000 mg/day

The following may be useful as an adjunct:

- Bromelain (minimum 1500 MCU): 500 to 750 mg three times a day between meals

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APPENDIX 1 | Candida Questionnaire*

PURPOSE

The purpose of this questionnaire is to estimate the likelihood of having an overgrowth of intestinal yeast.

QUESTIONNAIRE

History

	Point score
1. Have you taken antibiotics for acne for 1 month or longer?	25
2. Have you, at any time in your life, taken other "broad-spectrum" antibiotics for respiratory, urinary, or other infections for 2 months or longer, or in short courses four or more times in a 1-year period?	20
3. Have you ever taken a broad-spectrum antibiotic (even a single course)?	6
4. Have you, at any time in your life, been bothered by persistent prostatitis, vaginitis, or other problems affecting your reproductive organs?	25
5. Have you been pregnant?	
One time	3
Two or more times	5
6. Have you taken birth control pills?	
For 6 months to 2 years	8
For more than 2 years	15
7. Have you taken prednisone or other cortisone-type drugs?	
For 2 weeks or less	6
For more than 2 weeks	15
8. Does exposure to perfumes, insecticides, fabric shop odors, and other chemicals provoke:	
Mild symptoms	5
Moderate to severe symptoms	20
9. Are your symptoms worse on damp, muggy days or in moldy places?	20
10. Have you had athlete's foot, ringworm, "jock itch," or other chronic infections of the skin or nails?	
Mild to moderate	10
Severe or persistent	20
11. Do you crave sugar?	10
12. Do you crave breads?	10
13. Do you crave alcoholic beverages?	10
14. Does tobacco smoke really bother you?	10
Total score for this section	___

Major Symptoms

For each of your symptoms, enter the appropriate number in the "point score" column:

- If a symptom is occasional or mild, score 3 points.
- If a symptom is frequent or moderately severe, or both, score 6 points.
- If a symptom is severe or disabling, or both, score 9 points.

	Point score
1. Fatigue or lethargy	___
2. Feeling of being "drained"	___
3. Poor memory	___
4. Feeling "spacey" or "unreal"	___
5. Depression	___
6. Numbness, burning, or tingling	___
7. Muscle aches	___
8. Muscle weakness or paralysis	___
9. Pain and/or swelling in joints	___
10. Abdominal pain	___
11. Constipation	___
12. Diarrhea	___
13. Bloating	___
14. Persistent vaginal itch	___
15. Persistent vaginal burning	___
16. Prostatitis	___
17. Impotence	___
18. Loss of sexual desire	___
19. Endometriosis	___
20. Cramps or other menstrual irregularities, or both	___
21. Premenstrual tension	___
22. Spots in front of eyes	___
23. Erratic vision	___
Total score for this section	___

Other Symptoms

For each of your symptoms, enter the appropriate figure in the "point score" column:

- If a symptom is occasional or mild, score 1 point.
- If a symptom is frequent or moderately severe, or both, score 2 points.
- If a symptom is severe or disabling, or both, score 3 points.

*Modified from Crook WG. The yeast connection, ed 2. Jackson, TN: Professional Books, 1984.

	Point score
1. Drowsiness	___
2. Irritability	___
3. Incoordination	___
4. Inability to concentrate	___
5. Frequent mood swings	___
6. Headache	___
7. Dizziness/loss of balance	___
8. Pressure above ears, feeling of head swelling and tingling	___
9. Itching	___
10. Other rashes	___
11. Heartburn	___
12. Indigestion	___
13. Belching and intestinal gas	___
14. Mucus in stools	___
15. Hemorrhoids	___
16. Dry mouth	___
17. Rash or blisters in mouth	___
18. Bad breath	___
19. Joint swelling or arthritis	___
20. Nasal congestion or discharge	___
21. Postnasal drip	___
22. Nasal itching	___
23. Sore or dry throat	___
24. Cough	___
25. Pain or tightness in chest	___
26. Wheezing or shortness of breath	___
27. Urinary urgency or frequency	___
28. Burning on urination	___
29. Failing vision	___
30. Burning or tearing of eyes	___
31. Recurrent infections or fluid in ears	___
32. Ear pain or deafness	___
Total score for this section	___
TOTAL SCORE FOR ALL THREE SECTIONS	___

TABLE A1-1 **Interpretation**

YEAST-CONNECTED HEALTH PROBLEMS	WOMEN	MEN
Almost certainly present	>180	>140
Probably present	120-180	90-140
Possibly present	60-119	40-89
Less likely present	<60	<40

APPENDIX 2

Cervical Escharotic Treatment Instructions: For the Practitioner

Tori Hudson, ND

1. Before beginning the treatment, prepare the following items:
 a. Zinc/chloride ($ZnCl_2$)/Sanguinaria solution (90 g $ZnCl_2$/60 mL sterilized water; made at a compounding pharmacy). Take ¼ tsp $ZnCl_2$ solution and place in empty cup. Add ¾ tsp Sanguinaria tincture to this same cup. This will now be the mixture used for one treatment.
 b. One cup distilled water.
 c. ⅓ cup calendula succus.
 d. A cup containing two powdered bromelain capsules or tablets
2. Insert speculum and visualize the cervix.
3. Blot the cervix dry with large cotton swab or cotton ball on the end of a ring forceps.
4. Dip a large cotton swab into the distilled water and then squeeze out the water with your fingers. Place the damp swab into the bromelain and attempt to thickly cover the face of the cervix with the powder. This will have to be repeated two to four times to cover properly. The same step must be done in the endocervical canal with a small cotton tip applicator; i.e., dampen it, place in the bromelain, and apply to endocervix one to three times. Use a new cotton tip applicator each time.
5. Leave the bromelain on the cervix and in the endocervical canal for 15 minutes. A gynecologic lamp should be placed facing the vagina so that gentle heat is provided during this portion of the treatment.
6. Now remove the bromelain by placing a large cotton swab in the calendula succus and then applying it to the cervix, thus washing off the bromelain. This must also be done with a small cotton tip applicator to the endocervical canal. Be liberal; repeat two to four times. Take a dry large swab and absorb the washings that have pooled in the vagina.
7. Now soak a large swab in the $ZnCl_2$/Sanguinaria mixture prepared earlier. Apply this to the cervix once. Repeat this procedure with a small cotton tip applicator and insert in the endocervical canal. Leave on for one minute. If this causes pain, wash the cervix with a small amount of distilled water. Avoid contact of the $ZnCl_2$/Sanguinaria mixture with the vaginal wall.
8. Wash off the $ZnCl_2$/Sanguinaria mixture with swabs of calendula succus. Wash the endocervical canal as well with a cotton tip applicator. Absorb the liquid that has pooled in the vagina with a dry cotton swab.
9. Insert two "Vag Pack" suppositories (See Appendix 12, "Vaginal Depletion Pack"). Using forceps or other appropriate instruments, attempt to have the suppositories lie lengthwise across the cervix. Instruct the patient to leave the suppositories in place for 24 hours (using a small sanitary napkin due to leakage).
10. After the last escharotic treatment:
 Week 1: Vitamin A suppository every night for 6 nights
 Week 2: Herbal vaginal suppository every night (herbal suppository: myrrh, echinacea, slippery elm, golden seal root, marshmallow root, geranium, and yarrow) for 6 nights or alternate suppository (vitamin A, thuja, lomatium isolate, green tea)
 Week 3: Vitamin A suppository every night for 6 nights
 Week 4: Herbal vaginal or alternate suppository every night for 6 nights

Note: The Escharotic Treatment is best done twice a week with two full days between treatments.

APPENDIX 3 | Crohn's Disease Activity Index

Patient name: _____ Chart #: _____

Date: _____

		Day 1 2 3 4 5 6 7	Sum	×	Factor	=	Subtotal
X_1	Number of liquid or very soft stools	\| \| \| \| \| \| \|	___	×	2	=	_____
X_2	Abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe)	\| \| \| \| \| \| \|	___	×	5	=	_____
X_3	General well-being (0 = well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible)	\| \| \| \| \| \| \|	___	×	7	=	_____
X_4	Number of six listed categories the patient now has: 1. Arthritis/arthralgia 2. Iritis/uveitis 3. Erythema nodosum/pyoderma gangrenosum/ aphthous stomatitis 4. Anal fissure, fistula, or abscess 5. Other fistula 6. Fever higher than 100° F during past week		___	×	20	=	_____
X_5	Taking Lomotil/opiates for diarrhea (0 = no, 1 = yes)		___	×	30	=	_____
X_6	Abdominal mass (0 = none, 2 = questionable, 5 = definite)		___	×	10	=	_____
X_7	Hematocrit (HCT):___ (standard: males = 47, females = 42)	Standard – HCT (add or subtract according to sign)		×	6	=	_____
X_8	Body weight (BW): ___ Standard weight (SW): ___	(SW – BW)/SW (add or subtract according to sign)		×	100	=	_____
Crohn's disease activity index (sum of X_1 through X_8)					CDAI	=	___

APPENDIX 4

Fasting—Patient Guidelines

Alan Goldhamer, DC, Stephen Helms, NMD, and Trevor K. Salloum, BA, ND

WHY FAST?

Fasting is one of the quickest ways to increase elimination of wastes and to enhance the reparative processes of the body. Fasting has been practiced throughout history and is universally employed in the animal kingdom.

Scientific inquiry into fasting began in the early 1900s. Research found it to be useful in the treatment of the following:

- Diabetes
- Epilepsy
- Obesity
- Psychological illnesses
- Arthritis
- Heart disease
- Skin disease
- Toxic poisoning

Loss of minerals or vitamins is usually not a concern during a short fast; humans have effective biochemical mechanisms for adapting to long periods without food.

The short fast (3 to 5 days) is a good chance for the body to acquire optimal rest, both mental and physical. This is an opportunity to build health, break old habits, and increase awareness of oneself. Although longer fasts are required in chronic disease, the short fast can be conducted at home, rather than in an inpatient facility.

The ideal time to begin a fast is when hunger disappears or at the first sign of an illness. Although a short fast can be implemented at any time, it is better to begin on a weekend or during a time when you can be inactive. The more rest, the better the results: energy can be directed toward healing instead of other body functions.

Before embarking on a fast, check with your physician. If you are on any medications (including herbs and nutritional supplements) or have any chronic disease, slight alterations may be necessary. A physical examination is important before a fast to ensure there are no contraindications and to allow your physician to monitor your progress more effectively.

A positive mental outlook is important. The benefits of fasting include:

- Decreased weight
- Clearer skin
- Increased elimination of toxins
- Tissue repair
- Decreased pain and inflammation
- Increased concentration
- Relaxation and spare time
- Savings in food costs

Perhaps the greatest benefit is the satisfaction that you are taking a major role in improving your health.

FASTING DIRECTIONS

Starting Your Fast

Prepare for your fast on the day before you stop eating by making your last meal one of only fresh fruits and vegetables (some authorities recommend a full day of raw food to start a fast). In addition, finish all last-minute errands so that you can establish an environment as free of stress and responsibility as possible.

During the Fast

Only water—distilled or spring water is best—should be taken by mouth while fasting. (Some authorities recommend fruit or vegetable juice, but this is actually an elimination diet rather than a fast.) The quantity of water should be dictated by thirst, but drink at least a few glasses every day.

Take no coffee, tea, juice, soft drinks, cigarettes, or anything else by mouth except water. If possible, avoid the smell and sight of food. If you have to prepare food for other family members, satisfy your senses with the aroma—no sampling!

Try to keep your mind away from food by reading a book (especially a book on fasting), listening to music, writing a letter, watching a movie, taking a leisurely walk in a park, driving to a pleasant destination, etc.

Exercise is not usually encouraged while fasting. You want to conserve fuel and allow maximal healing. Short walks and light stretching are useful, but heavy workouts tax the system and inhibit repair and elimination.

Cleansing the skin with lukewarm water is encouraged, but extremes of temperature can be tiring. Try to avoid deodorants, soaps, sprays, detergents, synthetic shampoos, and exposure to other chemicals. These only hinder elimination and add to the body's detoxification and elimination burden.

Sunlight is essential for healthy cells, but excessive exposure will strain the body's protective systems. Try to obtain at least 10 to 20 minutes of direct sun exposure per day. Many fasting institutions have solariums in which guests sunbathe.

Rest is one of the most important aspects of the fast. Try to take a nap or two during the day. You will probably require less sleep at night because your daily activity has decreased.

Enemas are not usually necessary, but this will depend on your individual health. If you are worried about constipation, a longer pre-fast period of fresh fruits and vegetables will assist elimination.

Body temperature usually drops during a fast, as do blood pressure and pulse and respiratory rates—all measures of the slowing metabolic rate of the body. Therefore, it is important to stay warm. If needed, you may use a hot water bottle at night.

Breaking Your Fast

Breaking your fast is a good time for you to consider carefully what you are eating and why. While breaking your fast, as outlined in Table A4-1, and in the days that follow, it can be helpful to you and your physician to carefully record what you eat and how you feel after eating. Many of today's health problems are due to food allergies and overeating. Take this time to choose which eating habits you truly want to establish. As you break your fast, eat slowly, chew thoroughly, limit quantities, eat foods at room temperature, and enjoy!

TABLE A4-1 **Breaking Your Fast**

BREAKFAST	LUNCH	DINNER
Day 1: One of the following: ½ melon ½ nectarine ½ pineapple	A different fruit from the breakfast list	8 oz of any fruit
Day 2: 12 oz of one type of fresh fruit	14 oz of whole pears, papaya, or citrus fruit	Raw vegetable salad with leafy greens, tomato, celery, and cucumber or 2 pears, 2 apples, and an avocado
Day 3: Resume healthy diet—raw fresh fruits, raw/steamed vegetables, whole grains, nuts, seeds, and legumes		

If You Have Problems

Most discomfort during fasting is usually brief as the body works quickly to restore homeostasis. You may experience headaches, dizziness, nausea, coated tongue, bad odor, mild palpitations, and mucous discharge. If your symptoms are intolerable and persist, notify your physician or break your fast with an orange and resume fasting when symptoms disappear.



SUMMARY

Importantly, although fasting is an effective way to improve your health, it is only one part of a total health-building program, not a panacea. Fresh air, rest, exercise, sunshine, pure food and water, emotional health, and wholesome foods eaten in appropriate quantities are equally important in building and maintaining health.

APPENDIX 5 | Gluten and Gliadin Content of Select Foods

FOOD	TOTAL PROTEIN	PROLAMINES* (% OF TOTAL PROTEIN)	GLIADIN (MG/100 G)	GLUTELINS† (% OF TOTAL PROTEIN)	CROSS-REACTIVITY WITH GLIADIN
Wheat	10-15	40-50	6900	30-40	++++
Rye	9-14	30-50	580	30-50	+++
Oats	8-14	10-15	100	≈5	++
Corn (maize)	7-13	50-55	0	30-45	+
Rice	8-10	1-5	0	85-90	—
Sorghum	9-13	>60	NA	NA	NA
Millet	7-16	57	0	30	NA
Buckwheat	13-15	NA	4	High	—

Data from Baker PG. Facts about gluten. Lancet 1975;ii:1307; Friis SU. Enzyme-linked immunosorbent assay for quantitation of cereal proteins toxic in coeliac disease. Clin Chim Acta 1988;178:261-270; and Chartrand LJ, Russo PA, Duhaime AG, et al. Wheat starch intolerance in patients with celiac disease. J Am Diet Assoc 1997;97:612-618.

NA, no data available; +, degree of reactivity; —, no reactivity.

*Primarily gliadin.

†Primarily gluten.

APPENDIX 6

Glycemic Index, Carbohydrate Content, and Glycemic Load of Select Foods

A complete list of the glycemic index (GI) and glycemic load (GL) of all tested foods is beyond the scope of this book—it would be a book in itself. Therefore, we have selected the most common foods. This listing provides a general sense of what are high and low GL foods. We have listed the items by food groups, from low to high GLs. Some food groups are not listed. For example, nuts, seeds, fish, poultry, and meats are not listed—they have little impact on blood sugar levels because they are low in carbohydrates.

For a more complete listing, visit www.mendosa.com, a free website operated by medical writer Rick Mendosa.

TABLE A6-1 **Low- to High-Glycemic Foods by Food Groups**

FOOD	GLYCEMIC INDEX	CARBOHYDRATES (g)	FIBER (g)	GLYCEMIC LOAD
Beans (legumes)				
Soybeans, cooked, 1/2 cup, 100 g	14	12	7	1.6
Peas, green, fresh, frozen, boiled, 1/2 cup, 80 g	48	5	2	2
White navy beans, boiled, 1/2 cup, 90 g	38	11	6	4.2
Kidney beans, boiled, 1/2 cup, 90 g	27	18	7.3	4.8
Peas, split, yellow, boiled, 1/2 cup, 90 g	32	16	4.7	5.1
Lentils, 1/2 cup, 100 g	28	19	3.7	5.3
Lima beans, baby, 1/2 cup cooked, 85 g	32	17	4.5	5.4
Black beans, canned, 1/2 cup, 95 g	45	15	7	5.7
Pinto beans, canned, 1/2 cup, 95 g	45	13	6.7	5.8
Chickpeas, canned, drained, 1/2 cup, 95 g	42	15	5	63
Kidney beans, canned and drained, 1/2 cup, 95 g	52	13	7.3	6.7
Broad beans, frozen, boiled, 1/2 cup, 80 g	79	9	6	7.1
Peas, dried, boiled, 1/2 cup, 70 g	22	4	4.7	8
Baked beans, canned in tomato sauce, 1/2 cup, 120 g	48	21	8.8	10
Black-eyed peas, soaked, boiled, 1/2 cup, 120 g	42	24	5	10
Bread				
Multigrain, unsweetened, 1 slice, 30 g	43	9	1.4	4
Oat bran and honey loaf, 1 slice, 40 g	31	14	1.5	4.5
Sourdough, rye, 1 slice, 30 g	48	12	0.4	6
Stoneground whole wheat, 1 slice, 30 g	53	11	1.4	6
Wonder, enriched white bread, 1 slice, 20 g	73	10	0.4	7
Sourdough, wheat, 1 slice, 30 g	54	14	0.4	7.5
Pumpernickel, 1 slice, 60 g	41	21	0.5	8.6
Whole wheat, 1 slice, 35 g	69	14	1.4	9.6
Healthy Choice, hearty 7-grain, 1 slice, 38 g	56	18	1.4	10
White (wheat flour), 1 slice, 30 g	70	15	0.4	10.5
Healthy Choice, 100% whole grain, 1 slice, 38 g	62	18	1.4	11
Gluten-free multigrain, 1 slice, 35 g	79	15	1.8	12
French baguette, 30 g	95	15	0.4	14
Hamburger bun, 1 prepacked bun, 50 g	61	24	0.5	15
Rye, 1 slice, 50 g	65	23	0.4	15
Light rye, 1 slice, 50 g	68	23	0.4	16
Dark rye, black, 1 slice, 50 g	76	21	0.4	16
Croissant, 1, 50 g	67	27	0.2	18
Kaiser roll, 1 roll, 50 g	73	25	0.4	18
Pita, 1 piece, 65 g	57	38	0.4	22
Bagel, 1, 70 g	72	35	0.4	25

Continued

TABLE A6-1 **Low- to High-Glycemic Foods by Food Groups—cont'd**

FOOD	GLYCEMIC INDEX	CARBOHYDRATES (g)	FIBER (g)	GLYCEMIC LOAD
Breakfast Cereals				
Oat bran, raw, 1 tbsp, 10 g	55	7	1	4
Bran with psyllium, 1/3 cup, 30 g	47	12	12.5	5.6
Bran, 1/3 cup, 30 g	58	14	14	8
All-Bran Soy 'n Fiber, 1/2 cup, 45 g	33	26	7	8.5
All-Bran, 1/2 cup, 40 g	42	22	6.5	9.2
Oatmeal (cooked with water), 1 cup, 245 g	42	24	1.6	10
Shredded wheat, 1/3 cup, 25 g	67	18	1.2	12
Mini Wheats (whole wheat), 1 cup, 30 g	58	21	4.4	12
All-Bran Fruit 'n Oats, 1/2 cup, 45 g	39	33	6	13
Weet-Bix, 2 biscuits, 30 g	69	19	2	13
Cheerios, 1/2 cup, 30 g	74	20	2	15
Frosties, 1/2 cup, 30 g	55	27	1	15
Corn Bran, 1/2 cup, 30 g	75	20	1	15
Honey Smacks, 3/4 cup, 30 g	56	27	1	15
Wheatbites, 30 g	72	22	2	16
Total, 30 g	76	22	2	16.7
Healthwise for Heart Health, 45 g	48	35	2	16.8
Mini Wheats (blackcurrant), 1 cup, 30 g	71	24	2	17
Puffed wheat, 1 cup, 30 g	80	22	2	17.6
Bran Flakes, 3/4 cup, 30 g	74	24	2	18
Crunchy Nut Cornflakes (Kellogg's), 30 g	72	25	2	18
Froot Loops, 1 cup, 30 g	69	27	1	18
Cocoa Puffs, 3/4 cup, 30 g	77	26	1	20
Team, 30 g	82	25	1	20.5
Corn Chex, 30 g	83	25	1	20.75
Just Right, 3/4 cup, 30 g	60	36	2	21.6
Corn Flakes, 1 cup, 30 g	84	26	0.3	21.8
Rice Krispies, 1 cup, 30 g	82	27	0.3	22
Rice Chex, 1 cup, 30 g	89	25	1	22
Crispix, 30 g	87	26	1	22.6
Just Right Just Grains, 1 cup, 45 g	62	38	2	23.5
Oat 'n Honey Bake, 45 g	77	31	2	24
Raisin Bran, 1 cup, 45 g	73	35	4	25.5
Grape Nuts, 1/2 cup, 58 g	71	47	2	33.3
Cake				
Angel food, 1 slice, 30 g	67	17	<1	11.5
Sponge cake, 1 slice, 60 g	46	32	<1	14.7
Cup cake, with icing and cream filling, 1 cake, 38 g	73	26	<1	19
Chocolate fudge, mix (Betty Crocker), 73 g cake + 33 g frosting	38	54	<1	20.5
Banana cake, 1 slice, 80 g	47	46	<1	21.6
Pound cake, 1 slice, 80 g	54	42	<1	22.6
French vanilla (Betty Crocker), 73 g cake + 33 g frosting	42	58	<1	24.4
Lamingtons, 1, 50 g	87	29	<1	25
Flan, 1 slice, 80 g	65	55	<1	35.75
Scones, made from packet mix, 1 scone, 40 g	92	90	<1	83
Crackers				
Corn Thins, puffed corn cake, 2, 12 g	87	9	<1	7.8
Kavli, 4, 20 g	71	13	3	9.2
Breton wheat crackers, 6, 25 g	67	14	2	9.4

TABLE A6-1 **Low- to High-Glycemic Foods by Food Groups—cont'd**

FOOD	GLYCEMIC INDEX	CARBOHYDRATES (g)	FIBER (g)	GLYCEMIC LOAD
Ryvita or Wasa, 2, 20 g	69	16	3	11
Stoned Wheat Thins, 5, 25 g	67	17	1	11.4
Premium soda crackers, 3, 25 g	74	17	0	12.5
Water cracker, 5, 25 g	78	18	0	14
Graham, 1, 30 g	74	22	1.4	16
Rice Cake, 2, 25 g	82	21	0.4	17
Milk, Soy Milk, and Juices				
Milk, full fat, 1 cup, 250 mL	27	12	0	3
Soy, 1 cup, 250 mL	31	12	0	3.7
Milk, skim, 1 cup, 250 mL	32	13	0	4
Grapefruit juice, unsweetened, 1 cup, 250 mL	48	16	1	7.7
Nesquik chocolate powder, 3 tsp in 250 mL milk	55	14	0	7.7
Milk, chocolate flavored, low fat, 1 cup, 250 mL	34	23	0	7.8
Orange juice, 1 cup, 250 mL	46	21	1	9.7
Gatorade, 1 cup, 250 mL	78	15	0	11.7
Pineapple juice, unsweetened, canned, 250 mL	46	27	1	12.4
Apple juice, unsweetened, 1 cup, 250 mL	40	33	1	13.2
Cranberry juice cocktail (Ocean Spray USA), 240 mL	68	34	0	23
Coca-Cola, 375 mL	63	40	0	25.2
Other soft drinks, 375 mL	68	51	0	34.7
Milk, sweetened condensed, 1/2 cup, 160 g	61	90	0	55
Fruit				
Cherries, 20 cherries, 80 g	22	10	2.4	2.2
Plums, 3-4 small, 100 g	39	7	2.2	2.7
Peach, fresh, 1 large, 110 g	42	7	1.9	3
Apricots, fresh, 3 medium, 100 g	57	7	1.9	4
Apricots, dried, 5-6 pieces, 30 g	31	13	2.2	4
Kiwi, 1, raw, peeled, 80 g	52	8	2.4	4
Orange, 1 medium, 130 g	44	10	2.6	4.4
Peaches, canned, natural juice, 1/2 cup, 125 g	38	12	1.5	4.5
Pears, canned in pear juice, 1/2 cup, 125 g	43	13	1.5	5.5
Watermelon, 1 cup, 150 g	72	8	1	5.7
Pineapple, fresh, 2 slices, 125 g	66	10	2.8	6.6
Apple, 1 medium, 150 g	38	18	3.5	6.8
Grapes, green, 1 cup, 100 g	46	15	2.4	6.9
Apple, dried, 30 g	29	24	3.0	6.9
Prunes, pitted (Sunsweet), 6 prunes, 40 g	29	25	3.0	7.25
Pear, fresh, 1 medium, 150 g	38	21	3.1	8
Fruit cocktail, canned in natural juice, 1/2 cup, 125 g	55	15	1.5	8.25
Apricots, canned, light syrup, 1/2 cup, 125 g	64	13	1.5	8.3
Peaches, canned, light syrup, 1/2 cup, 125 g	52	18	1.5	9.4
Mango, 1 small, 150 g	55	19	2.0	10.4
Figs, dried, tenderized (water added), 50 g	61	22	3.0	13.4
Sultanas, 1/4 cup, 40 g	56	30	3.1	16.8
Banana, raw, 1 medium, 150 g	55	32	2.4	17.6
Raisins, 1/4 cup, 40 g	64	28	3.1	18
Dates, dried, 5, 40 g	103	27	3.0	27.8
Grains				
Rice bran, extruded, 1 tbsp, 10 g	19	3	1	0.57
Barley, pearled, boiled, 1/2 cup, 80 g	25	17	6	4.25

Continued

TABLE A6-1 **Low- to High-Glycemic Foods by Food Groups—cont'd**

FOOD	GLYCEMIC INDEX	CARBOHYDRATES (g)	FIBER (g)	GLYCEMIC LOAD
Millet, cooked, 1/2 cup, 120 g	71	12	1	8.52
Bulgur, cooked, 2/3 cup, 120 g	48	22	3.5	10.6
Brown rice, steamed, 1 cup, 150 g	50	32	1	16
Couscous, cooked, 2/3 cup, 120 g	65	28	1	18
White rice, boiled, 1 cup, 150 g	72	36	0.2	26
Arborio risotto rice, white, boiled, 100 g	69	35	0.2	29
Basmati rice, white, boiled, 1 cup, 180 g	58	50	0.2	29
Buckwheat, cooked, 1/2 cup, 80 g	54	57	3.5	30
Instant rice, cooked, 1 cup, 180 g	87	38	0.2	33
Tapioca (steamed 1 h), 100 g	70	54	<1	38
Tapioca (boiled with milk), 1 cup, 265 g	81	51	<1	41
Jasmine rice, white, long grain, steamed, 1 cup, 180 g	109	39	0.2	42.5
Ice Cream				
Low-fat French vanilla, 100 mL	38	15	0	5.7
Full fat, 2 scoops, 50 g	61	10	0	6.1
Jam				
No sugar, 1 tbsp, 25 g	55	11	<1	6
Sweetened, 1 tbsp	48	17	<1	8
Muffins and Pancakes				
Chocolate butterscotch muffins, from mix, 50 g	53	28	1	15
Apple muffins, oat and sultana, from mix, 50 g	54	28	1	15
Apricot muffins, coconut and honey, from mix, 50 g	60	27	1.5	16
Banana muffins, oat and honey, from mix, 50 g	65	28	1.5	18
Apple muffins, 1 muffin, 80 g	44	44	1.5	19
Bran muffins, 1 muffin, 80 g	60	34	2.5	20
Blueberry muffins, 1 muffin, 80 g	59	41	1.5	24
Buckwheat pancakes, from dry mix, 40 g	102	30	2	30
Pancake, from dry mix, 1 large, 80 g	67	58	1	39
Pasta				
Tortellini, cheese, cooked, 180 g	50	21	2	10.5
Ravioli, meat-filled, cooked, 1 cup, 220 g	39	30	2	11.7
Vermicelli, cooked, 1 cup, 180 g	35	45	2	15.7
Rice noodles, fresh, boiled, 1 cup, 176 g	40	44	0.4	17.6
Spaghetti, whole meal, cooked, 1 cup, 180 g	37	48	3.5	17.75
Fettucini, cooked, 1 cup, 180 g	32	57	2	18.2
Spaghetti, gluten free in tomato sauce, 1 small tin, 220 g	68	27	2	18.5
Macaroni and cheese, packaged, cooked, 220 g	64	30	2	19.2
Star pastina, cooked, 1 cup, 180 g	38	56	2	21
Spaghetti, white, cooked, 1 cup, 180 g	41	56	2	23
Rice pasta, brown, cooked, 1 cup, 180 g	92	57	2	52
Sugars				
Fructose, 10 g	23	10	0	2.3
Honey, 1/2 tbsp, 10 g	58	16	0	4.6
Lactose, 10 g	46	10	0	4.6
Sucrose, 10 g	65	10	0	6.5
Glucose, 10 g	102	10	0	10.2
Maltose, 10 g	105	10	0	10.5
Snacks				
Corn chips, Doritos original, 50 g	42	33	<1	13.9
Snickers, 59 g	41	35	0	14.3

TABLE A6-1 **Low- to High-Glycemic Foods by Food Groups—cont'd**

FOOD	GLYCEMIC INDEX	CARBOHYDRATES (g)	FIBER (g)	GLYCEMIC LOAD
Tofu frozen dessert (nondairy), 100 g	115	13	<1	15
Real fruit bars, strawberry, 20 g	90	17	<1	15.3
Twix cookie bar (caramel), 59 g	44	37	<1	16.2
Pretzels, 50 g	83	22	<1	18.3
Mars candy bar, 60 g	65	41	0	26.6
Skittles, 62 g	70	55	0	38.5
Soups				
Tomato, canned, 220 mL	38	15	1.5	6
Black bean, 220 mL	64	9	3.4	6
Lentil, canned, 220 mL	44	14	3	6
Split pea, canned, 220 mL	60	13	3	8
Vegetables				
Carrots, raw, 1/2 cup, 80 g	16	6	1.5	1
Low-glycemic vegetables:	≈20	≈7	≈1.5	≈1.4
Asparagus, 1 cup cooked or raw				
Broccoli, 1 cup cooked or raw				
Brussels sprouts, 1 cup cooked or raw				
Cabbage, 1 cup cooked or raw				
Cauliflower, 1 cup cooked or raw				
Cucumber, 1 cup				
Celery, 1 cup cooked or raw				
Eggplant, 1 cup				
Green beans, 1 cup cooked or raw				
Kale, 1 cup cooked, 2 cups raw				
Lettuce, 2 cups raw				
Mushrooms, 1 cup				
Spinach, 1 cup cooked, 2 cups raw				
Tomatoes, 1 cup				
Zucchini, 1 cup cooked or raw				
Carrots, peeled, boiled, 1/2 cup, 70 g	49	3	1.5	1.5
Beets, canned, drained, 2-3 slices, 60 g	64	5	1	3
Pumpkin, peeled, boiled, 1/2 cup, 85 g	75	6	3.4	4.5
Parsnips, boiled, 1/2 cup, 75 g	97	8	3	8
Sweet corn on the cob, boiled 20 min, 80 g	48	14	2.9	8
Corn, canned and drained, 1/2 cup, 80 g	55	15	3	8.5
Sweet potato, peeled, boiled, 80 g	54	16	3.4	8.6
Sweet corn, 1/2 cup boiled, 80 g	55	18	3	10
Potatoes, peeled, boiled, 1 medium, 120 g	87	13	1.4	10
Potatoes, with skin, boiled, 1 medium, 120 g	79	15	2.4	11
Yam, boiled, 80 g	51	26	3.4	13
Potatoes, baked in oven (no fat), 1 medium, 120 g	93	15	2.4	14
Potatoes, mashed, 1/2 cup, 120 g	91	16	1	14
Potatoes, instant, prepared, 1/2 cup	83	18	1	15
Potatoes, new, unpeeled, boiled, 5 small (cocktail), 175 g	78	25	2	20
Cornmeal (polenta), 1/3 cup, 40 g	68	30	2	20
French fries, fine cut, small serve, 120 g	75	49	1	36
Gnocchi, cooked, 1 cup, 145 g	68	71	1	48
Yogurt				
Yogurt, low fat, artificial sweetener, 200 g	14	12	0	2
Yogurt, with fruit, 200 g	26	30	0	8
Yogurt, low fat, 200 g	33	26	0	8.5

APPENDIX 7

Hydrochloric Acid Supplementation: Patient Instructions

PURPOSE

The purpose of this self-test is to estimate the amount of supplemental hydrochloric acid (HCl) you need to reestablish adequate stomach acid. Adequate stomach acid is critical for initiating digestion and protecting the intestinal tract from microbial pathogens.

DIRECTIONS

1. Begin by taking one HCl capsule (500 to 600 mg) at your next large meal. At every meal after that of the same size, take one more capsule (one capsule at the next meal, two at the meal after that, then three at the next meal, and so on).
2. Continue to increase the dose until you reach seven capsules or you feel a warmth in your stomach, whichever occurs first. A feeling of warmth in the stomach means that you have taken too many capsules for a meal of that size. Take one fewer capsule the next time. However, it is a good idea to try the larger dose again at another meal to make sure that it was the HCl that caused the warmth and not something else.
3. After you have determined the largest dose that you can take at your large meals without feeling any warmth, maintain that dose at all meals of similar size. Take fewer capsules with smaller meals.
4. When taking several capsules, it is best to take them throughout the meal rather than all at once.
5. As your stomach begins to regain the ability to produce the amount of HCl needed to properly digest your food, you will notice the warm feeling again. This is the time to start decreasing the dose level.
6. Every 3 days, decrease the dose by one capsule per meal. If the warmth continues, decrease more rapidly. If maldigestion symptoms return, add capsules back until digestion improves again.

APPENDIX 8 | The Optimal Health Food Pyramid

The Optimal Health Food Pyramid, shown in Figure A8-1, incorporates the best from two of the most healthful diets ever studied—the traditional Mediterranean diet and the traditional Asian diet. In addition, the Optimal Health Food Pyramid more clearly defines what the healthy components within the categories are and stresses the importance of vegetable oils and regular fish consumption as part of a healthful diet (Table A8-1).

FOODS TO AVOID ENTIRELY

- Refined white flour products: pastas, cakes, muffins, pretzels, etc.
- Refined sugar–loaded cereals, candies, baked goods, etc.
- Processed foods packed full of empty calories (sugar and fat) or salt (e.g., soups, theater-style popcorn, chips, etc.)
- Margarine, butter, and shortening
- Smoked or cured meats: bacon, hot dogs, smoked luncheon meats, sausages, ham, spam, etc.
- Meats cooked at extremely high temperatures or cooked to well done
- Heavily sweetened or artificially sweetened soft drinks, Kool-Aid, juice-flavored drinks, etc.
- Fried foods, including French fries, potato chips, corn chips, and doughnuts

VEGETABLES: FIVE TO SEVEN SERVINGS DAILY

In Latin, the word vegetable means "to enliven or animate." Vegetables give us life and should be the main focus of any health-promoting diet. Vegetables provide the broadest range of nutrients of any food class. They are rich sources of vitamins, minerals, carbohydrates, and protein. Vegetables also provide high quantities of anticancer phytochemicals.

It is very important not to overcook vegetables. Overcooking not only results in loss of important nutrients, but it also alters the flavor of the vegetable. Light steaming, baking, and quick stir frying are the best ways to cook vegetables. Do not boil vegetables unless you are making soup, because much of the nutrients will leach into the water. If fresh vegetables are not available, frozen vegetables are preferred over their canned counterparts. The only exception is tomato products (e.g., soup, paste, sauce, etc.), especially when they also contain oil; canned tomato products actually provide more absorbable lycopene than raw tomatoes.

We have divided vegetable intake into three categories: green leafy and cruciferous vegetables, low-glycemic vegetables, and starchy vegetables. This approach encourages eating a variety of these life-giving foods, helps achieve a "rainbow assortment" in the diet, and enables a focus on low-glycemic choices.

One serving of vegetables equals any of the following:

- 1 cup raw leafy vegetables (such as lettuce or spinach)
- 1/2 cup raw nonleafy vegetables
- 1/2 cup cooked vegetables or fresh vegetable juice

Box A8-1 offers easy tips to increase the daily intake of fruits and vegetables.

Green Leafy and Cruciferous Vegetables: Two to Four Servings Daily

- Alfalfa sprouts
- Beet greens
- Bok choy
- Broccoli
- Brussels sprouts
- Cabbage
- Cauliflower
- Chard
- Chinese cabbage
- Collard greens
- Dandelion
- Endive
- Escarole
- Kale
- Lettuce (the darker, the better)
- Mustard greens
- Parsley
- Spinach
- Turnip greens
- Watercress

Low-Glycemic Vegetables: Two to Three Servings Daily

- Artichoke (one medium)
- Asparagus
- Bean sprouts
- Bell peppers

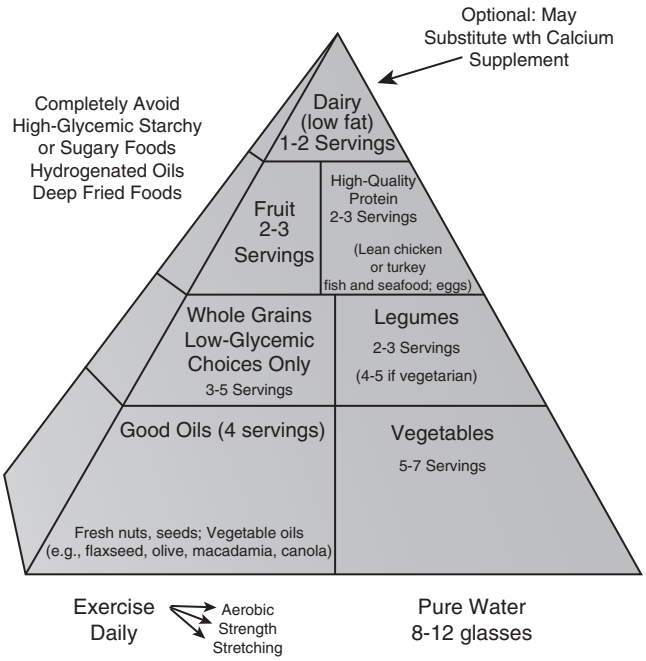


FIGURE A8-1 The Optimal Health Food Pyramid.

TABLE A8-1 **Daily Food Group Recommendations for a 2000-calorie Diet**

FOOD	NUMBER OF SERVINGS
Vegetables:	
Total servings	5-7
Green leafy and cruciferous vegetables	2-4
Low-glycemic vegetables	2-3
Other vegetables	1-2
Good Oils:	
Total servings	4
Nuts and seeds	1
Olive, macadamia, flaxseed, or canola oil	2-3
Whole grains	3-5
Legumes	2-3 (4-5 if vegetarian)
High-quality protein	2-3
Fruit	2-3
Dairy	1-2 (optional)

- Carrots
- Celery
- Cucumber
- Fennel
- Mushrooms
- Okra
- Onions
- Peas (fresh or frozen)
- Radishes
- Rhubarb
- String beans, green or yellow
- Summer squash
- Tomatoes, tomato paste, tomato sauce, tomato juice, vegetable juice cocktail
- Zucchini

Starchy Vegetables: One to Two Servings Daily

- Beets
- Parsnip
- Potato
- Pumpkin
- Rhubarb
- Rutabaga
- Winter, acorn, or butternut squash
- Yam or sweet potato

NUTS, SEEDS, AND GOOD OILS: FOUR SERVINGS DAILY

Nuts and seeds provide the beneficial oils, especially the monounsaturated and medium-chain fatty acids. Regular consumption of nuts has been shown to improve blood sugar regulation and lower the risk for diabetes, heart disease, obesity, and cancer. Focus on raw nuts and seeds. Definitely avoid nuts and seeds roasted in oils or coated with sugar. Nuts and seeds make excellent additions to salads and sautéed greens. Try to eat a variety of nuts and seeds, such as almonds, Brazil nuts, walnuts, pecans, flaxseeds, sunflower seeds, and pumpkin seeds.

Use olive, macadamia, flaxseed, or canola oil both in salad dressings and to replace butter, margarine, and the shortening used for cooking. Never cook with flaxseed oil; it is too rich in polyunsaturated fats, which are easily damaged by heat. Coconut and macadamia nut oils are the best cooking oils because of their ability to remain stable during high temperatures, but olive oil is a good choice for sautéed vegetables, and canola oil is usually best for baked goods because it has the mildest flavor. Coconut oil is also very stable in cooking and is fine to use in small quantities; it contains saturated fat but is metabolized differently from animal-derived saturated fats and can be used safely in moderation. Avoid using safflower, sunflower, soy, and corn oils because they contain too much omega-6 fatty acid (as discussed in Chapter 44).

We recommend at least one serving of nuts or seeds (one serving equals 1/4 cup) and 3 tbsp of the healthy oils daily. In addition, we recommend taking a high-quality fish oil supplement.

BOX A8-1 **Easy Tips to Increase the Daily Intake of Fruits and Vegetables**

- Buy many kinds of fruits and vegetables when grocery shopping, so plenty of choices are available.
- Stock up on frozen vegetables for easy cooking so that a vegetable dish can easily be served with every dinner.
- Use the fruits and vegetables that go bad quickly (peaches, asparagus) first. Save hardier varieties (apples, acorn squash) or frozen goods for later in the week.
- Keep fruits and vegetables where they are easily and frequently seen. The more often they are seen, the more likely they are to be eaten.
- Keep a bowl of cut-up vegetables on the top shelf of the refrigerator.
- Make a big tossed salad with several kinds of greens, cherry tomatoes, cut-up carrots, red pepper, broccoli, scallions, and sprouts. Refrigerate in a large glass bowl with an air-tight lid, so a delicious mixed salad will be ready to enjoy for several days.
- Keep a fruit bowl on your kitchen counter, table, or desk at work.
- Treat yourself to a fruit sundae: top a bowl full of your favorite cut-up fruits with vanilla yogurt, shredded coconut, and a handful of nuts.
- Pack a piece of fruit or some cut-up vegetables in your briefcase or backpack; carry moist towelettes for easy clean up.
- Add fruits and vegetables to lunch by having them in soup or salad or cutting them up to eat raw.
- Use thinly sliced pears or apples in omelets.
- At dinner, serve steamed or microwaved vegetables.
- Increase portions when serving vegetables. One easy way of doing so is by adding fresh greens such as Swiss chard, collards, or beet greens to stir-fry dishes.
- Serve fresh fruit for dessert. Add visual and taste appeal by serving with nuts, cheese, or yogurt. For example, serve grapes or sliced apple with cheese, or a fruit parfait made with low-fat yogurt or topped with berries.
- Add extra varieties of vegetables to soups, sauces, and casseroles (for example, add grated carrots and zucchinis to spaghetti sauce).
- Take advantage of salad bars, which offer ready-to-eat raw vegetables and fruits and prepared salads made with fruits and vegetables.
- Use vegetable-based sauces, such as marinara sauce, and juices, such as low-sodium vegetable juice (V-8) or tomato juice.
- Freeze lots of blueberries and grapes, to use as summer replacements for ice cream, popsicles, and other sugary foods.

WHOLE GRAINS: THREE TO FIVE SERVINGS DAILY

It is very important to choose whole-grain products (e.g., whole-grain breads, whole-grain flour products, brown rice) over their

TABLE A8-2 **Single Servings of Whole Grains**

Bread: whole wheat, rye, or other whole grain	1 slice
Cereals: whole grain	1/2 cup
Corn:	
Cooked whole kernel corn	1/2 cup
Corn on the cob	1 small
Flour and flour products:	
Whole-wheat flour (uncooked)	2-1/2 tbsp
Whole-grain pasta (cooked)	1/2 cup
Whole grains (cooked): rice, oats, wheat, barley, quinoa, spelt, etc.	1/2 cup

processed counterparts (white bread, white flour products, white rice, etc.). Whole grains provide substantially more nutrients and health-promoting properties. Whole grains are a major source of complex carbohydrates, dietary fiber, magnesium and other minerals, and B vitamins. The content and quality of the protein in whole grains are also greater than in refined grains. Diets rich in whole grains have been shown to be helpful in both the prevention and treatment of diabetes, heart disease, and cancer.

Table A8-2 defines servings of various whole grains.

BEANS (LEGUMES): TWO TO THREE SERVINGS DAILY

Beans are a mainstay in most diets of the world and are second only to grains in supplying calories and protein to the world's population. Compared with grains, they supply about the same number of total calories, but usually provide two to four times as much protein, and are a richer source of the soluble fiber that lowers cholesterol and stabilizes blood glucose levels. Although we do not recommend using canned vegetables or fruit, canned beans retain their fiber content and anticancer flavonoids. Plus, given the long preparation time for cooking beans, canned beans are extremely quick and convenient.

A serving size for beans is 1/2 cup.

FRUITS: THREE TO FOUR SERVINGS DAILY

Fruits are a rich source of many beneficial nutrients, and regular fruit consumption has been shown to offer significant protection against chronic degenerative diseases, including cancer, heart disease, cataracts, diabetes, and strokes. Fruits make nutrient-dense, easy between meal snacks and desserts (e.g., nothing could be simpler than phytonutrient-rich fresh berries alone). It is easy to get into the habit of eating only a few varieties of fruit. We encourage eating a "rainbow assortment" of fruits over the course of a week.

A general rule of thumb is that one serving of fruit equals one of the following:

- One medium fruit
- 1/2 cup of small or cut-up fruit
- 4 oz of 100% juice
- 1/4 cup dried fruit

See Box A8-1 for easy tips to increase the daily intake of fruits and vegetables.

HIGH-QUALITY PROTEIN: TWO TO THREE SERVINGS DAILY

The detriment of diets high in saturated fat and cholesterol has been stressed for decades. Likewise, the importance of the omega-3 fatty acids in the battle against development of chronic disease is now also well known. Fish consumption, in particular, has shown tremendous protection against heart disease and cancer. Choose smaller species of fatty fish, such as wild salmon, mackerel, herring, and sardines. Their smaller size and shorter lifespan translate into a lower accumulation of mercury (Box A8-2).

BOX A8-2 **Fish Consumption Caution**

Fish consumption offers significant protection against heart disease and many forms of cancer, especially the major cancers, like those of the lung, colon, breast, and prostate. Although we encourage the eating of more fish, some guidelines are necessary. Nearly all fish contain trace amounts of methyl mercury. In most cases this is of little concern, because the level is so low. The fish most likely to have the lowest level of methyl mercury are salmon (usually nondetectable levels), cod, mackerel, cold water tuna, farm-raised catfish, and herring. However, certain seafood, particularly swordfish, shark, and some other large predatory fish, may contain high levels of methyl mercury. Fish absorb methyl mercury from water and aquatic plants. Larger predatory fish also absorb mercury from their prey. Methyl mercury binds tightly to the proteins in fish tissue, including muscle; cooking does not reduce the mercury content significantly.

We suggest limiting intake to no more than about 2 lb (1 kg) per week. That translates to six 7-oz servings per week maximum. Limit intake of swordfish, shark, and warm water tuna to no more than once a week (or once a month for women of childbearing age who might get pregnant).

We therefore recommend eating fish at least three, but no more than six, times per week. Keep intake of red meat (beef, veal, or lamb) to no more than two servings per month, and choose the leanest cuts possible; keep the portion size limited to about the size of a deck of cards, and do not charbroil or cook the meat until well done, because this practice increases the formation of cancer-causing compounds. Also, consider some of the alternatives to beef, such as venison, buffalo, elk, rabbit, and ostrich; these emerging beef alternatives are lower in saturated fat and provide higher levels of omega-3 fatty acids.

Chicken and turkey can also provide excellent protein with very little fat, especially if only the white meat (breast) without the skin is eaten. Eggs are also a very good source of high-quality protein, and if produced by free-range hens fed flaxseed meal, they will be rich in beneficial omega-3 fatty acids.

One serving equals about the size of a deck of cards; that translates to roughly 4 oz.

DAIRY: ONE OR TWO SERVINGS DAILY (OPTIONAL)

We have found that many people are allergic to milk or lack the enzymes necessary to digest dairy products. Even for people who do tolerate dairy foods, milk consumption should be limited to no more than one or two servings per day. Use nonfat or reduced fat dairy products rather than whole milk varieties. Also, fermented dairy products like yogurt, kefir, and acidophilus-fortified milk are preferred over milk. Some of the soy milk alternatives to cow's milk are delicious, especially when flavored with vanilla or chocolate. If dairy products are not consumed, we recommend a calcium supplement.

One serving of dairy products equals 1 cup of milk, yogurt, or cottage cheese or 1 oz of cheese.

APPENDIX 9

Patient Instructions for Measuring Basal Body Temperature

PURPOSE

Your body temperature reflects your metabolic rate, which is largely determined by hormones secreted by the thyroid gland and by the ability of your cells to convert these hormones to their more active form. Your level of thyroid activity can be determined simply by measuring your basal body temperature. All you need is a high-quality thermometer.

PROCEDURE

1. Place the thermometer by your bed before going to sleep at night. If using a mercury thermometer, shake it down to below 95°F.
2. On waking, place the thermometer in your armpit for a full 10 minutes. It is important to make as little movement as possible. Lying and resting with your eyes closed is best. Do not get up until the 10-minute measurement is completed.
3. After 10 minutes, read and record the temperature and date (a convenient form is printed as Table A9-1).
4. Record the temperature for at least three mornings (preferably at the same time of day) and give the information to your physician. Menstruating women must perform the test on the second, third, and fourth days of menstruation. Men and postmenopausal women can perform the test at any time.

INTERPRETATION

Your basal body temperature should be between 97.6°F and 98.2°F. Low basal body temperatures are quite common and may reflect hypothyroidism. Common signs and symptoms of hypothyroidism are as follows:

- Depression
- Difficulty in losing weight
- Dry skin
- Headaches
- Lethargy or fatigue
- Menstrual problems
- Recurrent infections
- Sensitivity to cold

High basal body temperatures (higher than 98.6°F) are less common but may be evidence of hyperthyroidism. Common signs and symptoms of hyperthyroidism are as follows:

- Bulging eyeballs
- Fast pulse
- Hyperactivity
- Inability to gain weight
- Insomnia
- Irritability
- Menstrual problems
- Nervousness

TABLE A9-1 **Form for Recording Temperature and Date When Measuring Basal Body Temperature**

NAME_____

MONTH	DAY	TEMP.	MONTH	DAY	TEMP.	MONTH	DAY	TEMP.
———	1	———	———	1	———	———	1	———
	2	———		2	———		2	———
	3	———		3	———		3	———
	4	———		4	———		4	———
	5	———		5	———		5	———
	6	———		6	———		6	———
	7	———		7	———		7	———
	8	———		8	———		8	———
	9	———		9	———		9	———
	10	———		10	———		10	———
	11	———		11	———		11	———
	12	———		12	———		12	———
	13	———		13	———		13	———
	14	———		14	———		14	———
	15	———		15	———		15	———
	16	———		16	———		16	———
	17	———		17	———		17	———
	18	———		18	———		18	———
	19	———		19	———		19	———
	20	———		20	———		20	———
	21	———		21	———		21	———
	22	———		22	———		22	———
	23	———		23	———		23	———
	24	———		24	———		24	———
	25	———		25	———		25	———
	26	———		26	———		26	———
	27	———		27	———		27	———
	28	———		28	———		28	———
	29	———		29	———		29	———
	30	———		30	———		30	———
	31	———		31	———		31	———

APPENDIX 10

Rotation Diet Master Chart and Plan

Sally J. Rockwell, PhD, CCN

TABLE A10-1 **Rotation Diet Master Chart and Plan**

FOOD FAMILY	DAY 1 (GREEN)	DAY 2 (YELLOW)	DAY 3 (BLUE)	DAY 4 (RED)
Proteins				
Fin fish	Fish may be eaten daily as long as a different fish is selected each day			
Shellfish	Mussel, escargot, clam	Shrimp	Oysters, scallops, abalone	Crab, squid, octopus
Fowl flesh and eggs	Chicken, goose	Turkey ↔	Cornish game hen, quail, pheasant	Duck
Red meat	Beef (veal, liver, etc.)		Pork (ham, bacon, etc.), lamb	Rabbit
Dairy	Cow (milk, yogurt, cheeses)		Goat (milk, yogurt, cheeses)	
Legumes	Kidney, soy, and lima beans		Pinto, garbanzo, and black beans; black-eyed and split peas	
Sprouts	Nuts, seeds, and legumes	Nuts and seeds	Nuts, seeds, and legumes	Nuts and seeds
Nuts, seeds, and oils	Soy, walnuts	Almonds	Peanuts, pecans, pumpkin seeds	Cashews, pistachios
	Filberts ↔	Pine nuts ↔	Chestnuts ↔	Safflower, corn
	Sesame ↔	Brazil nuts ↔	Macadamias ↔	Avocado ↔
		Sunflower, apricots		Olive ↔
Grains and flours	Buckwheat, soy, quinoa, tofu, arrowroot, guar gum	Rice, millet, rye, potato, flaxseed, xanthan gum	Amaranth, garbanzo, kudzu root, chestnut	Barley oats, wheat, corn, tapioca, agar ↔
Sweeteners	Honey, raisins	Dates, molasses, rice syrup	Figs, currants	Coconut, malt, sago palm, maple syrup
Vegetables				
Beet	Beets, Swiss chard	Carrots, parsley	Spinach	Avocado
Mustard	Cabbage, broccoli, white radish, kale, nappa		Bok choy, red radish, Brussels sprouts, cauliflower	Parsnip, celery
Composite		Leaf and bib lettuce, common artichoke		Iceberg lettuce, romaine
Gourd	Cucumber, winter squash		Summer squash, pumpkin, zucchini	
Lily	Onion, garlic		Chives, leeks, shallots, asparagus	
Nightshade		White potato, peppers	Chestnuts	Tomato, eggplant, peppers
Miscellaneous	String beans	Yams ↔	Peas	Bamboo shoots
		Jicama ↔	Okra ↔	Jerusalem artichoke ↔
		Mushrooms ↔	Olives ↔	Sweet potato ↔
Fruits				
Plum		Plum, prune, apricot		Peach, cherry, nectarine
Apple	Apple		Pear, quince	
Citrus		Lemon, orange, kumquat		Lime, grapefruit, tangerine
Berries	Boysenberry, blackberry, strawberry	Huckleberry, cranberry	Logan berry, raspberry, gooseberry	Blueberry
Gourd	Melons		Cantaloupe, melons	Pomegranate ↔
Miscellaneous	Rhubarb, grapes	Kiwi ↔	Pineapple ↔	Mango, banana ↔
	Papaya ↔	Guava ↔		
	Persimmon ↔			
Bulk	Pectin	Flaxseed ↔	Chia seed ↔	Psyllium seed

All information from The Rotation Game, Copyright 2003. All rights reserved, SJ Rockwell, PhD.

↔, A food that is essentially the only food of a family and that will not cross-react with other foods.

APPENDIX 11 | Supplier Certification Questionnaire Guidance

SUPPLIER CERTIFICATION: COMPLIANCE GUIDE AND QUESTIONNAIRE

This guidance was prepared to assist practitioners in their review of suppliers. To effectively use the supplier certification and quality assurance questionnaires, some background information is needed. The questionnaire asks a series of questions regarding the quality practices and Good Manufacturing Practice (GMP) compliance of the supplier. These questions should be reviewed using a graded approach to determine the level of quality practices the supplier has in place.

In this version of the questionnaire (total of 22 questions), the following questions and their related answers are considered critical, major, or minor points to an appropriate quality system.

Critical Questions: 8, 12, 14A, 15, 18, 19, 20, and 22

Missing answers to the critical questions show potential adulteration and/or contamination problems with materials and/or products supplied. These questions deal with information about the supplier's quality control personnel, specifications, and related testing of raw materials and/or finished products, possible contamination of materials and/or products due to inadequate sanitation practices, inability to substantiate label information, and noncompliance with current food labeling regulations for potential allergens. If the supplier's answers indicate possible contamination and/or adulteration issues with materials and/or products, the use of the supplier should be rejected.

Major Questions: 6, 7, 11, 14B, 16, 17, and 21

Missing answers to the major questions show serious gaps in the supplier's quality program. These gaps include lack of the following: designated quality control personnel, necessary quality procedures, suitable employee training program, adequate internal GMP audit program, suitable review of raw material suppliers, appropriate monitoring of contract laboratories, required testing of raw materials, adequate re-testing of released raw materials, suitable use of expiration dates, appropriate retained samples, and appropriate monitoring and/or verification of subcontracted production. If the supplier's answers indicate possible gaps in the quality program, the number of gaps must be reviewed to determine how much of the quality system is missing or compromised. If the majority of these questions are not answered appropriately, it is recommended these be treated in the same manner as critical issues.

Minor Questions: 1, 2, 3, 4, 5, 9, 10, and 13

Information required by the minor questions should be readily available because it deals with the supplier's name and address, manufacturer's name and address, and contact personnel. The remaining minor questions deal with items that are not mandatory for food producers, such as: GMP audit of the supplier by a third party, written employee training program, frequency of internal GMP audits and how reports are handled, auditing of raw material suppliers, and basis for re-testing of released raw materials.

Any issues surrounding testing of raw materials and/or finished products should be carefully scrutinized. If it appears the supplier is not performing adequate testing and/or examination to provide proof of a material's identity, purity, strength, or composition, the material should be considered suspect and not eligible for use. If they are relying on outside sources for analytic data, it is necessary to ask how they validate the source of that information.

Typically, it only takes one critical issue question to derail use of a supplier, because the questions concern material and/or product contamination and/or adulteration issues. In each situation, after the initial review is completed, the supplier should be notified of the results of the review. Suppliers should be given the opportunity to correct deficiencies and provide proof of the corrections.

Practice Name _____

Address _____

FOREWORD

Our suppliers are the essence of our success. We cannot succeed without quality materials and services. We have therefore embarked on a program designed to develop working partnerships with our valued suppliers. We feel that development of an open, trusting, cooperative relationship with our suppliers is a prerequisite to a meaningful certification process.

Vendor certification is an important component of a total quality management system that assures that a supplier's product is produced, packaged, and shipped under a controlled process that results in consistent conformance to our requirements. It supports the concept of quality at the source by doing it right the first time, thereby substantially reducing or eliminating the need for final quality inspections by the supplier or the customer. The primary objective of the certification process is to assure consistent high quality as demonstrated by predictable conformance to our requirements. The basic premise is that we want to identify suppliers that have adequate process controls in place and they *provide legitimate proof* that their products are consistently fit for use, authentic, meet label claims, and are free from contamination or have maximum freedom from contamination.

It is our goal as a medical practice to offer products that meet or exceed all the applicable regulatory requirements, are clinically effective, and safe for our patients, customers, and friends. We feel very strongly about the importance and need for certification and have included it as a major cornerstone of our business philosophy. We seek to identify and do business with natural product suppliers that attain and maintain full compliance with the proposed U.S. Food and Drug Administration Good Manufacturing Practice guidelines for the manufacture of nutritional supplements currently published in the Federal Register.

OBJECTIVES

We are seeking suppliers who:

a. Are interested in making certification a standard part of doing business and we invite you to join us in our pursuit of excellence. Our suppliers have in place or are willing to put in place a documented quality system.
b. Are committed to partnering with us and developing internal programs to assure consistent quality, good communication, timely delivery, and best overall cost.
c. Have or are willing to put in place a comprehensive Quality Assurance testing program that assures raw material and finished product authenticity, label claim potency, freedom from contamination, and stability over the expiration dating period.

Please answer the questions and return the completed audit to: the address at the top of the form. In an effort to protect your IP and confidentiality, you may provide the first and last sheet only for Standard Operating Procedures, Multipage forms, Audit Reports, etc., as proof of proper documentation.

Please answer each question with Yes, No, N/A, or provide further data.

Corporate and Personnel Information

1. Supplier's name:
2. Supplier's address, telephone/fax number, and web address:
3. Manufacturer's name, address, and telephone number (including all manufacturing sites):
4. Name, address, telephone number, and contact person for any/all of your QA/QC Contract Laboratories:
5. Contact personnel: (provide name and e-mail address)
 Plant Manager:
 QA/QC Manager:
 Purchasing Agent:

GMP and Quality of Procedures Information

Check one column or circle one letter for each.	Y	N	N/A
6. Does the company have a Quality Control Unit?			
7. Does the quality unit have the authority to approve/reject the following:			
a. Procedures	a	a	a
b. Specifications	b	b	b
c. Test methods and results	c	c	c
d. Raw ingredients/components	d	d	d
e. Finished ingredients	e	e	e
f. Packaging materials	f	f	f
g. Labels	g	g	g
h. Processing records	h	h	h
i. Forms	i	i	i
j. Instrument/control calibrations	j	j	j
k. Reprocessing operations	k	k	k
8. Do you have a GMP system in place? If so, which do you follow:			
a. Food GMPs	a	a	
b. FDA GMPs for dietary supplements	b	b	
9. Have you ever been independently certified for GMP compliance?			
If so, by whom?			
a. NPA Date of Last Audit: _____	a	a	
b. NSF Date of Last Audit: _____	b	b	
c. USP Date of Last Audit: _____	c	c	
d. TGA Date of Last Audit: _____	d	d	
e. Other: Date of Last Audit: _____	e	e	
10. If independently certified for GMPs, please provide proof that you successfully passed the GMP audit. (Please attach audit report as proof)			
11. Please provide a copy of: The table of contents for your SOP forms (Please attach)			
12. Do written records exist of employee training and education? If yes, please attach an example.			
13. Does a written GMP training program exist for new and veteran employees?			

Raw Materials

Check one column or circle one letter for each.	Y	N	N/A
14A. If you have an in-house laboratory:			
a. Name/e-mail of supervisor:			
b. How many analysts by level of education are in the laboratory?			
GED____BS____MS____PhD____			

14B. If you use contract laboratory personnel are they audited by:
- a. Company personnel — a
- b. A third party — b
- c. Not audited — c
- d. If audited, how often? Yearly. Every 2 yrs. Every 5 yrs. Other — d

15A. When doing in-house or independent testing of "BOTANICAL" raw materials, are they checked for:
(Please provide two examples of test data for each item, a-g)

- a. Identity (To authenticate material or botanical genus and species) — a — a
 - If yes, are SOME or ALL materials tested? (Circle answer)
 - If yes, how often? (Choose one)
 - 1. Each batch received _____
 - 2. Skip lot testing (If so, how often?) _____
 - 3. Other _____
- b. Microbiology Profile (Bacteria, Yeast, and Mold) — b — b
 - If yes, are SOME or ALL materials tested? (Circle answer)
 - If yes, how often? (Choose one)
 - 1. Each batch received _____
 - 2. Skip lot testing (If so, how often?) _____
 - 3. Other _____
- c. Potency (if potency claim exists) — c — c
 - If yes, are SOME or ALL materials tested? (Circle answer)
 - If yes, how often? (Choose one)
 - 1. Each batch received _____
 - 2. Skip lot testing (If so, how often?) _____
 - 3. Other _____
- d. Heavy Metals (Lead, Mercury, Cadmium, Arsenic) — d — d
 - If yes, are SOME or ALL materials tested? (Circle answer)
 - If yes, how often? (Choose one)
 - 1. Each batch received _____
 - 2. Skip lot testing (If so, how often?) _____
 - 3. Other _____
- e. Chemical Solvent Residue — e — e
 - If yes, are SOME or ALL materials tested? (Circle answer)
 - If yes, how often? (Choose one)
 - 1. Each batch received _____
 - 2. Skip lot testing (If so, how often?) _____
 - 3. Other _____
- f. Aflatoxins — f — f
 - If yes, are SOME or ALL materials tested? (Circle answer)
 - If yes, how often? (Choose one)
 - 1. Each batch received _____
 - 2. Skip lot testing (If so, how often?) _____
 - 3. Other _____
- g. Herbicides and Pesticides Residue — g — g
 - If yes, are SOME or ALL materials tested? (circle answer)
 - If yes, how often? (Choose one)
 - 1. Each batch received _____
 - 2. Skip lot testing (If so, how often?) _____
 - 3. Other _____

If your company does not test one or more of these items on every batch of material please provide a detailed rationale for how you prove that omitting the analysis is not missing a quality parameter.

15B. When doing in-house or independent testing of "NON-BOTANICAL" raw materials, are they checked for: (Provide two examples of test data for each item, a-g)

- a. Identity (To authenticate material) — a — a
 - If yes, are SOME or ALL materials tested? (Circle answer)
 - If yes, how often? (Choose one)
 - 1. Each batch received _____
 - 2. Skip lot testing (If so, how often?) _____
 - 3. Other _____
- b. Microbiology Profile (Bacteria, Yeast, and Mold) — b — b
 - If yes, are SOME or ALL materials tested? (Circle answer)
 - If yes, how often? (Choose one)

Continued

1. Each batch received _____
2. Skip lot testing (If so, how often?) _____
3. Other _____

c. Potency (if potency claim exists) — c — c
If yes, are SOME or ALL materials tested? (Circle answer)
If yes, how often? (Choose one)
1. Each batch received _____
2. Skip lot testing (If so, how often?) _____
3. Other _____

d. Heavy Metals (Lead, Mercury, Cadmium, Arsenic) — d — d
If yes, are SOME or ALL materials tested? (Circle answer)
If yes, how often? (Choose one)
1. Each batch received _____
2. Skip lot testing (If so, how often?) _____
3. Other _____

e. Chemical Solvent Residue — e — e
If yes, are SOME or ALL materials tested? (circle answer)
If yes, how often? (Choose one)
1. Each batch received _____
2. Skip lot testing (If so, how often?) _____
3. Other _____

If your company does not test one or more of these items on every batch of material, please provide a detailed rationale for how you prove that omitting the analysis is not overlooking or missing a quality parameter.

16. Do you accept a Certificate of Analysis in lieu of independent testing of raw materials?
17. If you answered yes to the preceding question, please provide a written, detailed rationale for how you quality assure your raw materials at the time of receipt.
18. Metal Detection:
Are all in-process materials metal detected?
If so, by what method? _____
Are finished products metal detected?
If so, by what method? _____
19. How is the effectiveness of metal detection measures evaluated?
(Please attach rationale)

Finished Products

Check one column or circle one letter for each.	**Y**	**N**	**N/A**
20. Are your finished products tested for label claim potency before release for sale? If yes, please provide full test data for three different products If not, please provide a rationale for how you prove you meet the label claim.			
21. Do you put expiration dates or a use by date on your products?			
22. Do you do label claim potency testing (Stability Testing) to verify that the product meets the label claim throughout the expiration dating period? If yes, please provide stability potency assays on three different finished product batches that were tested to verify the expiration date claim. If not, please provide a detailed rationale for how you prove that you have met the label claim through the dated period.			

Thank you

APPENDIX 12 | Vaginal Depletion Pack—Traditional Method

INTRODUCTION

The vaginal depletion pack ("vag pack") was originally developed by the eclectic physicians of the nineteenth century and later modified to its present form by John Bastyr, ND. Over the last 50 years, it has been regularly used by most naturopathic physicians in the treatment of various vaginal disorders.

Although no controlled studies of the clinical efficacy of the vag pack have been published, it has a long, and apparently successful, history of use. Its primary application has been in the treatment of cervical erosions, cervical dysplasia, pelvic inflammatory disease, and pelvic congestion. The mode of action is apparently through its local antibacterial, anhydrous, alterative, and sclerotic activities. These are thought to inhibit local microbial growth, stimulate the body to slough off abnormal cervical cells, and promote lymphatic drainage. However, no research has been done to determine the actual mechanism.

Procedure

Supplies

- Open-mouth 1-lb container with tight-sealing lid
- Anhydrous magnesium sulfate ($MgSO_4$; keep tightly closed)
- Glycerin
- *Hydrastis canadensis* tincture: 0.5 oz
- *Thuja occidentalis* oil (not thuja in oil): 0.5 oz
- *Melaleuca alternifoli*a oil: 0.25 oz
- Bitter orange oil: 0.25 oz
- Vita Minerals 120 (iron sulfate solution): 1 oz
- Cotton: 0.5 in thick, 2 in wide, and 3 in long
- Cotton string (surgical grade): 4 in long (dental floss also works well)

Mixing the Solution

The following steps must be followed carefully. Deviation results in either a runny, inconvenient liquid or a rock-hard, unusable precipitate. Each step requires vigorous stirring before proceeding to the next!

1. Fill the container half full with anhydrous $MgSO_4$.
2. Add glycerin until soupy. Mix until the solution begins to cool.
3. Add oils.
4. Add *H. canadensis.*
5. Add Vita Minerals 120.
6. Stir occasionally over the next 2 to 3 hours until the solution cools. It should have a thick, tar-like consistency.
7. Store in a tightly sealed container in a cool, dry place. The solution will require stirring if not used regularly.

The Tampon

The cotton is folded lengthwise and tied at one end to make a tampon 1 in thick and 3 in long, with approximately 3 in of string hanging from the tied end.

Application

The best time for application is during times of normal uterine drainage—right before or after the menses and during ovulation. The procedure is as follows:

1. Fold 1 tbsp of the formula into the untied end of the cotton tampon (some find it easier to put the solution into the cotton tampon before folding and tying it).
2. Expose the cervix with a vaginal speculum and open it wide enough to insert the tampon.
3. Slide the vag pack, formula-end first, through the speculum until it fits tightly against the cervix. (A uterine forceps can be used to hold the pack and aid its insertion.)
4. Carefully remove the speculum while leaving the pack in place. Avoid touching the sides of the vagina because the fresh pack can cause some irritation. The uterine forceps are used to hold the pack in contact with the cervix as the speculum is removed. Ensure that the string is left exposed in the introitus.
5. Leave the pack in for 24 hours, at which time the patient can remove it by simply pulling on the string.
6. Have the patient douche after an additional 24 hours. A mild vinegar solution is recommended.
7. The procedure can be performed weekly until the desired results are obtained.

CLINICAL APPLICATIONS

Typically, the patient notices an increase in drainage, both while the vag pack is in place and during the following 24 to 48 hours. If she experiences any burning or discomfort, the pack can be removed early, followed by douching. Suggest that she wear a sanitary pad to absorb the typical secretions.

Cervical Dysplasia

When the vag pack is used in the treatment of abnormal cervical cells, inspection of the cervix within a few days of the application reveals a red, eroded appearance where the cells have sloughed off. This typically heals within 7 to 10 days.

The number of applications needed varies with the patient and the condition. This is described in the cervical dysplasia chapter (see Chapter 156).

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